Patient compliance with drug storage recommendations

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Niels Vlieland

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Patient compliance with drug storage recommendations

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1

General introduction

General introduction

Drug quality is a prerequisite for safe and effective drug treatment and requires proper storage and handling of drug products during the entire chain of storage, transport and use. Patients, i.e. the user end of this chain, usually store drugs at home for disease treatment or for later (incidental) use. Drugs should be stored in compliance with specific storage recommendations in order to prevent significant changes in drug quality. Pharmacists advise patients to follow storage recommendations on the drug product label and to discard expired drugs. The manufacturing drug company determines the storage label statement which is included in their application for marketing authorization – i.e. before drug products become available for prescribers and thus for patients. Three important aspects of the drug product should be addressed in this application, namely efficacy, safety and quality [1]. In addition to providing data that supports claims for the drug's efficacy and safety for use in the intended population, the quality of the drug should extensively have been tested and documented. The drug's stability parameters potency, identity and purity should be consistent and within specified limits for every produced batch and during the time period of storage and use. A lower concentration of the active pharmaceutical ingredient and/or the presence of degradation products or other impurities can result in reduced efficacy and/or induce safety problems. Environmental factors such as temperature, humidity and light can affect the stability of the drug depending upon the molecular structure, the formulation and the primary and secondary packaging.

International guidelines for drug stability testing

The joint development of a guideline on drug stability testing, thereby harmonizing stability requirements on an international level, was one of the items discussed at the first International Council for Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) meeting in 1990 [2]. The general principle of the ICH guidelines for stability testing of new drug substances or products is "to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions." [3, 4]. The groundwork for stability test conditions was laid out by Wolfgang Grimm in the 1980's [5, 6]. He performed measurements for temperature and relative humidity at various locations in four climate zones (I – Temperate climate; II – Mediterranean-like and subtropical climates; III – Hot dry climate, dry regions; IV – Hot, humid climate, Tropics) during a whole year. These measurements enabled him to calculate mean temperatures, the mean relative humidity and mean kinetic temperature for each climate zone. The mean kinetic temperature is defined as 'a single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period' [3]. These measurements provided the basis

for determining the stability test conditions. In general, the temperature related chemical degradation of the active pharmaceutical ingredient in solid pharmaceutical dosage forms follows the Arrhenius equation, allowing to predict the degradation level and rate over a certain period of time given the mean kinetic temperature and activation energy of the active ingredient.

Before gaining marketing authorization, each drug should undergo drug product stability tests at two conditions (long-term and accelerated) or three conditions (including intermediate) if a significant change in the drug product at the accelerated storage condition appears (Figure 1). For climate zones I/II, long-term stability test conditions include exposure for 12 months at 25˚C/65% Relative Humidity (RH) or 30˚C/65%RH. Intermediate (if applicable) and accelerated drug stability test conditions are 30˚C/65%RH and 40˚C/75%RH, respectively. Stability data from these test conditions are used to determine the shelf life

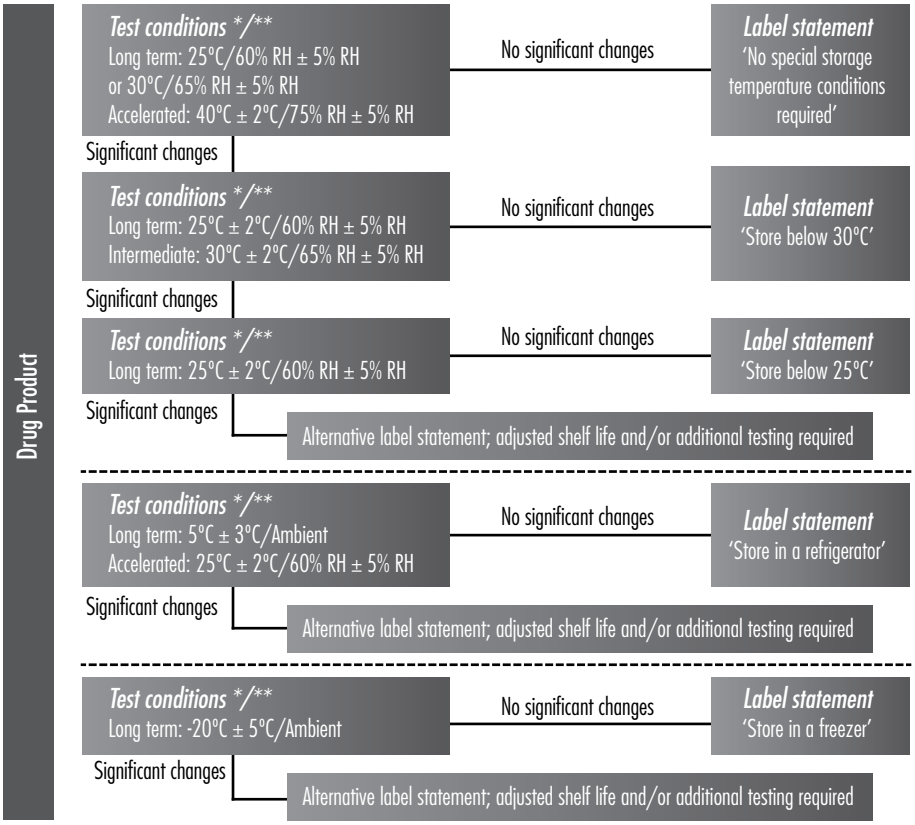

Figure 1. Stability studies, test conditions and intended label statements for new and existing drug products [3, 8]. Drug products require testing on long-term and accelerated conditions to determine the label statement. RH=Relative Humidity. *minimum testing period: long term 12 months, 6 months for existing drug products. Intermediate and accelerated test conditions 6 months. **the drug company decides on long term storage conditions

(e.g. 12 or 24 months) of the drug product and can be used to determine the influence of short time excursions outside the recommended storage conditions [7]. A drug will receive a storage recommendation (e.g. 'store below 30°C') based on its stability test performance for the corresponding conditions [8]. Drug products which fulfill the stability test specification when tested at long-term and accelerated conditions are considered 'stable', i.e. meet all acceptance criteria for potency, purity, appearance and physical properties. These receive the temperature storage label statement indicating no special storage conditions are needed. Several drug products are not stable at room temperature and may require storage between 2-8°C or below -20°C. In case of the first condition, drug products which fulfill the stability test specification when tested at 5°C for twelve months and at accelerated conditions (25°C/60% RH) for six months require the label statement 'store in a refrigerator'. In addition, some drug products require additional statements to emphasize the need for patients to take precautions when storing specific drugs. For example, 'do not freeze' can be added to biologic drug products, that may undergo physical changes after exposure to freezing. Drugs requiring storage at -20°C should be tested for six months at -20°C and should be considered 'stable' at these test conditions before receiving the 'store in a freezer' or 'store and transport frozen' label statement. There are only a few products that require storage in the freezer, e.g. chlormethine hydrochloride gel [9].
Drugs can be exposed to several stress factors other than temperature changes during their production, storage, transportation and handling including humidity, light exposure and mechanical stress. Therefore, results from stress studies, including photostability, form an integral part of the market authorization dossier and are used to determine to what extent these exposures can affect product quality [3].

Figure 2. The pharmaceutical supply chain. Drug storage conditions are monitored in regulatory compliance with the Good Distribution Practice (GDP) until drug dispensing. *Pharmacies do not fall in the scope of the GDP but have distribution standards in place based on the GDP.

Drug storage throughout the pharmaceutical supply chain and after pharmacy dispensing: storage in patients' homes

The pharmaceutical supply chain involves the transport and storage of drugs from production site to patient (Figure 2) [10]. Guidelines to assure that the identity and quality of drugs are unaffected during the different stages of the pharmaceutical supply chain are set out in the Good Distribution Practice guidelines (GDP) [11]. This entails, amongst others, that drugs should be stored in compliance with the drug products' label statement during the entire supply chain in order to maintain their quality and integrity. Drug products should be packed in containers that ensure the stability of the drug product and sufficiently protect against changes in environmental conditions. For drug products requiring refrigeration, cold chain management is essential. Storage of vaccines is a model example indicating the importance of the pharmaceutical supply chain: vaccines are thermosensitive and require refrigeration (2-8°C) from production until the location of use (e.g. physician's office). Breaking the cold chain, by storing these products below 2°C (including freezing temperatures) or above 8°C, can affect the immunological characteristics of the vaccine [12].

In contrast with the tight GDP regulations for drug storage and transport in the first stages of the pharmaceutical supply chain, home storage of drug products is usually not monitored. Although the guideline is not designed for storage in patients' homes, it would be a challenge for patients to be fully compliant with its general principles, such as principle 3.2.1 of the GDP requiring 'suitable equipment and procedures to be in place to check the environment where medicinal products are stored'. Several studies show that a considerable proportion of patients is not able to comply with drug storage recommendations and experiences several other practical problems (e.g. understanding label instructions) when storing drugs in their home [13-15]. Except for specific storage recommendations for drugs requiring refrigeration, few patients generally take into account drug storage recommendations when they store their drugs at home (16). Patients' decisions allocating a drug storage location is often based on its closeness to specific routines (e.g. around mealtimes, daily morning or evening hygiene routines) and using the location as a visual reminder [17].

Consequences of (non-)compliance with drug storage recommendations

Compliance with drug storage recommendations promotes both drug quality and proper use of drugs by patients. First, patient compliance with drug storage recommendations prevents drugs being exposed to unfavorable storage conditions that can reduce their quality. Second, compliance with drug storage recommendations also promotes good use of drugs by disposing of drugs that have passed the expiry date, by having drug information leaflets available and by having no practical problems identifying different drug products and strengths [18]. In addition, drug storage in an accessible and orderly manner requires patient's ability to properly organize their drug stock.

There are numerous examples of how environmental factors, such as temperature, humidity and light, can affect drug quality. Changes in temperature conditions might not only affect the chemical stability of the drug but also affect the physical stability and appearance (e.g.

melting of suppositories or disintegration of tablets). For example, isoniazid should be stored below 25°C and can slowly degrade into hydrazine when exposed to higher temperatures. Hydrazine can be a toxic substance for humans [19]. Moisture can also affect drug integrity; acetylsalicylic acid, the active ingredient of aspirin, can breakdown into salicylic acid and acetic acid when exposed to moisture [20]. Patients are therefore recommended to store drug products containing acetylsalicylic acid in the original packaging to prevent degradation and potency loss. Furosemide solutions, are photosensitive and should therefore always be stored in the original packaging to prevent degradation [21]. Patients are usually unable to determine if a drug has reduced quality, however, a disintegrated or discolored tablet will discourage patients from taking their drug.

How quality of a specific drug product is affected by home storage conditions is highly dependent on its stability profile. Biologic drugs have distinct characteristics that distinguish them from small molecule drugs, and can therefore be more sensitive to temperature changes, light exposure and agitation [22]. While small molecule drugs are manufactured through well-defined and controlled chemical processes, biologics are typically proteins or polypeptides (e.g. synthetic hormones such as insulin or growth hormone, monoclonal antibodies such as tumor necrosis factor-alpha inhibitors) and most are generally larger, more complex and less stable when compared to small molecules. External factors such as vigorous shaking and variable temperature conditions might lead to protein denaturation and may induce formation of protein aggregates [23]. Protein aggregation can increase the immunogenicity, which is the process of a protein being recognized by the human immune system as 'non-self antigen', inducing an immune response against the biologic drug. This results in the formation of antidrug antibodies that may contribute to the risk of adverse drug reactions and decrease effectiveness of the drug product [24].

Evidence on the interplay between (in)adequate home storage conditions, drug product quality and their clinical consequences is scarce. In the 1960's, several investigators reported the association between expired antibiotics, increased drug degradation levels and renal toxicity [25-27]. However, a review in 2004 disputed the involvement of the degraded drug, suggesting the severe adverse events were more likely to be an 'uncommon occurrence outside the use of the expired products' [28]. Reversibility of the renal damage was observed in the majority of cases. For drugs with narrow therapeutic index (e.g. warfarin, levothyroxine), even a small loss in potency may theoretically lead to inadequate drug effectiveness (e.g. warfarin resistance). In 2014, a case of ineffective treatment with levothyroxine possibly related to inadequate home storage conditions for temperature, moisture and light exposure was described [29].

Problems with drug storage by patients are incidentally reported. The Dutch Medicines Evaluation Board issued a warning in 2016, after having received signals that dabigatran capsules were stored by patients outside of the original packaging. They advised patients to not store dabigatran outside of the original package, including in multi-dose dispensing systems, due to risk of drug degradation caused by exposure to moisture [30]. Before these incidents were reported, healthcare professionals already expressed their concerns about

proper use and storage of new anticoagulant drugs, including dabigatran [31]. However, there is no information how more than 27,000 users in the Netherlands store dabigatran at home and how storage practices could affect treatment outcomes [32]. Other problems related to home storage were reported by the Medicines Evaluation Board for methylphenidate controlled-release tablets where patients reported that the tablets burst open upon being exposed to moisture when stored outside of the primary package [33]. In 2013, a change in primary packaging of levothyroxine – bottle to blister – led to an increase of adverse events reports, including heart palpitations, fatigue and headache [34]. The blister package better protects levothyroxine against drug degradation due to environmental factors, such as exposure to moisture and light, suggesting that levothyroxine in the bottle was partly degraded.

More knowledge on home storage of drugs becomes increasingly relevant, as many newly approved drugs are biologic drugs. In 2015, more than 50,000 patients in the Netherlands used biologic drugs, for example Tumor Necrosis Factor-alpha inhibitors, as treatment for chronic inflammatory diseases, such as Rheumatoid Arthritis and Inflammatory Bowel Disease [35]. Currently, biologic drugs represent almost 40% of the entire new drug pipeline [36]. The majority of biologic drugs are available as subcutaneous injection and contrary to the intravenous dosage forms, these are often administered in the domiciliary setting [37]. This brings new challenges to pharmaceutical patient care, as patients need to be counseled on the use of these specific drug products and accompanying storage conditions in their homes. The patient is responsible for proper storage, in an environment that is not controlled, in contrast to the controlled storage environment of the hospital or in the pharmacy. Studies have shown that patients have difficulties in complying with storage recommendations of drugs that require cool storage between 2-8°C, which include most biologic drugs [38, 39].

In conclusion, drug quality is a prerequisite for a drug to remain effective and safe for the complete period of the drugs' intended use. Therefore, adequate storage by patients is essential to ensure safe and effective drug treatment. Patient compliance with drug storage recommendations includes several aspects to prevent drug degradation and promote good use of drugs, such as making sure storage temperature conditions are compliant with label instruction, discarding drugs that have passed the expiry date and having drug information leaflets available to have access to important drug usage instructions. Problems occurring after inadequate drug storage are incidentally reported and larger scale studies are absent. Knowledge on home storage of drugs becomes increasingly relevant, as many newly approved drugs are expected to be biologic drugs, which are generally more sensitive to inadequate storage. In addition, treatment with biologic drugs is expensive and puts a growing burden on national health care budgets. Reduced drug quality as a consequence of inadequate storage by patients is preventable, thereby promoting optimal use of biologic drugs and contributing to the sustainability of our healthcare system.

General aim of this thesis

The general aim of this thesis is to investigate patient compliance with drug storage recommendations. First, this thesis aims to investigate the level of compliance with drug storage recommendations in patient homes. Second, this work will assess specific patient related factors that are associated with compliance with storage recommendations. Third, drug quality attributes and the possible consequences after non-compliance with drug storage recommendations on drug quality attributes will be investigated.

Thesis outline

Chapter 2 of this thesis describes the level of compliance with drug storage recommendations in different patient groups. In **Chapter 2.1** the proportion of patients that comply with home storage temperature conditions of biological disease modifying antirheumatic drugs (bDMARDs) is estimated. Compliance with home storage temperature conditions for oral anticancer drugs that require storage at room temperature is assessed in **Chapter 2.2**. In **Chapter 2.3**, we evaluate compliance with specific drug home storage recommendations, including storage temperature, expiry dates, package integrity and information availability, in the older population.

Chapter 3 focuses on investigating the association between patient related factors and compliance with drug storage recommendations. In **Chapter 3.1**, the association between personality traits of patients and their compliance with different aspects of proper drug storage are assessed. **Chapter 3.2** describes storage practices of patients using bDMARDs and investigates how and where patients store these drugs in their homes.

The consequences of non-compliance with drug storage recommendations are investigated in **Chapter 4**. In **Chapter 4.1**, changes in product quality attributes (aggregate and particle formation) after exposing these products to conditions similar to those observed in patients' homes (chapter 2.1) are investigated for four different tumor necrosis factor-alpha inhibitors. **Chapter 4.2** includes a methodological exploration on the hypothetical impact of inadequate storage conditions of bDMARDs on disease activity in rheumatoid arthritis patients.

Chapter 5 provides the general discussion where results of the aforementioned chapters are discussed and put in a wider context regarding their impact on our views on drug storage by patients as well as on drug development and regulation. Before the final conclusion, the general discussion of this thesis reviews possible clinical implications of non-compliance with drug storage recommendations, discusses future research options and provides guidance on several aspects to consider when assessing the impact storage conditions may have on product quality, drug treatment and clinical outcomes.

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Drug storage by patients

2

2.1

Majority of patients do not store their biological disease modifying antirheumatic drugs within recommended temperature range

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Abstract

Objective

To monitor whether biologic DMARD (bDMARD) home storage temperatures comply with the manufacturers' Summary of Product Characteristics (SmPC) recommendations.

Methods

This observational study included consenting adult patients from eight Dutch pharmacies who received their bDMARDs with a validated temperature logger. Patients were instructed to store their packages according to standard label instructions and to return the temperature logger(s) after use. Primary outcome was defined as the proportion of patients that stored their bDMARDs within the SmPC recommended temperature range. In addition, the proportion of patients storing bDMARDs below 0°C or above 25 °C for longer than two consecutive hours was estimated.

Results

A total of 255 (87.0%) patients (mean age 53.2 (SD; 13.1) years, 51.4% female) returned their temperature logger(s) to the pharmacy. Of these, 17 patients (6.7%) stored their bDMARD within the recommended temperature range. The proportion of the patients that stored their bDMARD for more than 2 h consecutive time below 0°C or above 25°C was respectively 24.3% (median duration: 3.7 h (IQR 2.2 h; range 2.0–1,097.1 h) and 2.0% (median duration: 11.8 h (IQR 44.3 h; range 2.0–381.9 h).

Conclusion

The majority of patients do not store their bDMARDs within the SmPC-recommended temperature range.

Introduction

The introduction of biologic DMARDs (bDMARDs) changed the treatment for patients with inflammatory rheumatic diseases dramatically. In 2013, etanercept and adalimumab were among the best-selling biologic drugs worldwide [1]. Although many patients benefit from using bDMARDs, results from clinical trials suggest that 13–25% of patients discontinue treatment with bDMARDs within 1 year [2–5], which is slightly less than what has been reported in observational studies (15–43%) [6–8].

The formation of antidrug-antibodies (ADAs) to bDMARDs is considered to be one of the possible mechanisms underlying treatment failure [9]. bDMARDs are protein-based drugs and are generally more complex and less stable than traditional small molecule drugs. External factors such as vigorous shaking and extreme temperature conditions can lead to protein denaturation and may induce irreversible formation of protein aggregates [10]. Protein aggregation can increase the immunogenicity, lead to the formation of ADAs and may contribute to the risk of adverse drug reactions and decreasing effectiveness [11–13].

Proper storage and controlled distribution of bDMARDs are essential for ensuring the quality of these drugs. bDMARDs should, according to the summary of product characteristics (SmPC), ideally be stored between 2°C and 8°C [14–18]. In accordance with good distribution guidelines (GDP), drug transport between manufacturer, wholesaler and pharmacy is monitored to guarantee product quality until dispensing [19]. After the drug leaves the controlled environment of the pharmacy, drug transport and storage is taken over by the patient and the drug enters an environment that is often not equipped for storage of temperature-sensitive substances. Patients' home storage of temperature-sensitive drugs has been studied sparsely and only in studies with short follow-up (<30 days) [20, 21]. These observational studies showed that the home storage temperatures of bDMARDs often deviated from the recommended temperature range. None of these studies, however, have monitored home storage temperatures for the complete storage time. Therefore, the aim of this study was to monitor whether bDMARD home storage temperatures comply with SmPC recommendations for one complete dispense period.

Methods

Setting and study population

This prospective multicentre observational follow-up study was conducted in eight Dutch hospitals' (one academic hospital, six general hospitals and one specialized rheumatology clinic) outpatient pharmacies during December 2013 – January 2015. For reimbursement reasons, almost all bDMARDs are dispensed in the Netherlands by the outpatient pharmacy of the hospital where the patient has been treated by his/her rheumatologist. Patients were eligible for inclusion when treated with any of the following bDMARDs: etanercept, adalimumab, golimumab, certolizumab pegol or abatacept. Eligible patients received both

written and verbal information and were asked for a written informed consent. This study was reviewed by the Medical Research and Ethics Committee University Medical Center Utrecht (protocol reference number 14-628/C), which concluded that the study did not fall under the scope of the Dutch Medical Research Involving Human Subjects Act and that ethical approval was therefore not required.

Procedure

Patients who consented received their bDMARDs in the original manufacturer's packaging. Each package dispensed to the patient in a single delivery was put in a closed sealbag including a temperature logger (Supplementary Figure S1). Patients were instructed to store the medication according to label instructions and received care-as-usual, i.e. no additional storage advice was given in the context of this study. Patients were asked to return the temperature logger(s) to the pharmacy when the dispensed medicine had been used. Patients who did not return the temperature logger after three months received a reminder by post including a pre-stamped return envelope to return the temperature logger(s). If needed, second and third reminders were given by telephone at 2 and 4 weeks after the first reminder.

Temperature loggers

The Safe-Rx temperature logger is a small (18 mm × 32 mm × 2 mm), temperature measurement device and is validated according to international standards [22]. The device can store up to 500 000 temperature measurements and was adjusted to measure temperature at least every 10 min. All temperature measurements were automatically stored in a protected online database.

Outcomes

The primary outcome was the proportion of patients that stored bDMARDs within the SmPC-recommended storage range. SmPC-recommended temperature storage was defined as the total storage time between 2°C and 8°C without excursions outside this range for ≥48 h in total or excursions below 0°C or above 25°C for ≥2 h consecutive time. Deviations from the SmPC-recommended temperature storage conditions were defined as: proportion of patients storing bDMARDs below 0°C or above 25°C for ≥2 h; the longest episode duration (consecutive time, hours) below 0°C or above 25°C; and the number of episodes ≥2 h (consecutive time) below 0°C or above 25°C.

Data analysis

Demographic data was presented using means (SD), medians [interquartile range (IQR)] or in percentages of the study population. Total measurement time was the time (in days) between the first and last temperature measurement, and total storage time was defined as the total measurement time minus the final 48 h of temperature measurements. In case the storage temperature changed from below 15°C to 15°C or higher for at least 12 h without subsequent cooling below 15°C for at least 48 h, the total measurement time was right-

censored from the first 15˚C excursion time point. This definition is further illustrated in Supplementary Figs S2–S4. The proportion of total storage time within the SmPC-recommended temperature range (2–8˚C), below 0˚C and above 25˚C was calculated for all patients. Patient characteristics (gender, age and type of bDMARD) of patients lost to follow-up were compared with patient characteristics of those included in the analysis by using the t-test for normally distributed continuous variables and Pearson $\chi 2$ test for differences in proportions. Two-sided P-values < 0.05 were considered to indicate a significant difference. Patient characteristics of those storing bDMARDs within and not within the SmPC-recommended temperature range and of those who store their bDMARD below 0˚C or above 25˚C or not were also compared. All calculations were made with the statistical packages from SAS version 9.2 and SPSS version 21.

Results

A total of 293 patients were included in the study, who received 882 temperature loggers. Of these, 255 patients (87.0%) returned 756 temperature loggers to the pharmacy and were included in our study population. The study population was 51.4% female, with a mean age of 53.2 (SD; 13.1) years (Table 1). More than 95% of patients received treatment with etanercept or adalimumab. The study population did not differ significantly from patients who did not return their temperature loggers to the pharmacy (68.4% female, mean age 52.4 (SD; 14.5) years).

The mean total measurement time was 105.7 days (SD; 45.9). The mean storage time was 82.2 days (SD; 42.6), with 54.8% of the total storage time falling within the SmPC-recommended storage temperature range (Figure 1). The proportion of the total storage time below 0˚C and above 25˚C was 1.7% and 0.04%, respectively. Various patterns of storage

Table 1. Patient characteristics (N=293).

	Patients included in analysis (N=255)		Patients lost to follow up (N=38)		P value
Age (mean, SD)	53.2 (13.1)		52.4 (14.5)		0.74
Gender	N	%	N	%	
Female	131	51.4	26	68.4	0.05
Type of bDMARD					
Etanercept	108	42.4	17	44.7	0.78
Adalimumab	135	52.9	19	50.0	0.74
Golimumab	7	2.7	1	2.6	0.88[a]
Certolizumab Pegol	3	1.2	1	2.6	
Abatacept	2	0.8	0	0.0	

a) Patients using Golimumab, Certolizumab Pegol and Abatacept tested as one group.

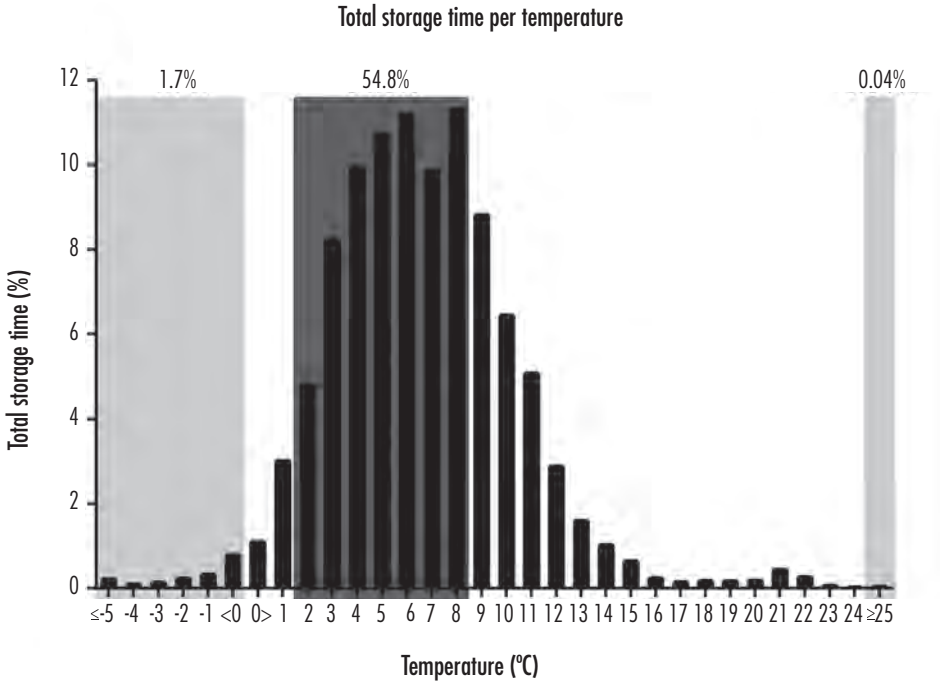

Figure 1. Proportion of total storage time per temperature. The proportion of total storage time between 2°C and 8°C (54.8%) is indicated by dark grey and the proportion below 0°C (1.7%) and above 25°C (0.04%) by light grey.

temperatures were observed (Figure 2). Only 6.7% of the patients stored all bDMARDs packages within the defined SmPC-recommended temperature range, whereas 24.3% of patients stored one or more bDMARD packages for more than 2 h below 0°C. The median duration of an episode where a bDMARD was stored at temperatures below 0°C was 3.7 h (IQR; 2.2 h, range; 2.0–1097.1 h), with a median frequency of 3 episodes (IQR; 14) lasting longer than 2 h. The percentage of patients who stored bDMARDs at above 25°C for episodes >2 h was 2.0%. The median frequency of episodes longer than 2 h with storage temperature above 25°C in these patients was 1 (IQR; 0.5), with a median duration of 11.8 h consecutive time (IQR; 44.3 h, range; 2.0–381.9 h). A total of 35 patients (13.7%) had three or more periods below 0°C for 2 h or longer (median frequency of episodes; 12.5, IQR; 29.3, range; 3.0–211.0). The proportion of patients who stored bDMARDs below 0°C for 24 h or longer consecutive time was 5.9%.

No statistically significant differences were found in gender, age and type of bDMARD of patients who stored bDMARDs within and not within the SmPC-recommended temperature range. The analysis also did not show any statistically significant difference in the gender, age and type of bDMARD in patients who did and did not store bDMARDs below 0°C or above 25°C.

Discussion

This study demonstrates that the majority of patients with inflammatory rheumatic diseases do not store their bDMARDs within the manufacturer's recommended temperature range. In 26.3% of patients, bDMARDs were stored at home at temperatures below 0°C or above 25°C for longer than 2 h (consecutive time). Our findings were similar for males and females, across ages and across type of bDMARD.

Our results are in line with previous publications on home storage conditions for bDMARDs. These (short-term) studies demonstrated that 50–58% of the patients stored their bDMARDs outside the SmPC-recommended storage temperature range [20, 21]. The aforementioned studies report a slightly smaller proportion of patients storing biologics outside the SmPC-recommended storage temperatures than what is reported in our study. However, we used a more strict definition for storing conditions and had a longer follow-up period, which might partly explain the higher percentage of patients storing bDMARDs outside the recommended storage area.

Antibodies against bDMARDs have been found in adalimumab (6–28%) [23–25], but less data is available for the relatively newer bDMARDs abatacept, certolizumab pegol and golimumab [26, 27]. Antibodies against etanercept were all non-neutralizing and only detected in a small proportion of patients or not detected at all, suggesting that immunogenicity may be a less important issue for etanercept [28, 29]. ADAs in reaction to bDMARDs can reduce serum drug levels by directly inhibiting binding of the drug with the target or by formation of drug immune complexes that accelerate drug clearance. This may reduce its effectiveness and might induce adverse events, such as a severe allergic reaction or an immune response to the bDMARD that induces autoimmunity [11].

Storage outside the recommended temperature range could be due to a number of reasons. Patients can store their bDMARD in the refrigerator as instructed, but consumer refrigerators are usually not equipped with a temperature control alarm system and are not solely used for medication storage. Furthermore, older refrigerators or refrigerators with a less advanced cooling system and low airflow could have a greater variation in temperature control [30] (Figure 2A). The bottom and upper shelf of the fridge might be cooler or warmer than other central parts of the refrigerator [31]. Our findings also suggest that bDMARDs are sometimes stored outside a refrigerator for short or longer periods (Figure 2B and C), which is in line with what others have reported [32]. Information regarding the consequences of storage outside the SmPC-recommended temperature range for the product is limited and difficult to obtain for patients and caregivers [33]. It has been widely acknowledged that temperature fluctuations increase the formation of protein aggregates and affect the product quality [34]. We found that 24.3% of patients store bDMARDs below 0°C with a median duration of 3.7 h and with median number of excursions below 0°C of 3, which would expose bDMARDs to very low temperatures for a long time.

To our knowledge, this is the first study that monitors temperature-sensitive drugs for the complete storage time of a single dispensing at home. Patients included were representative

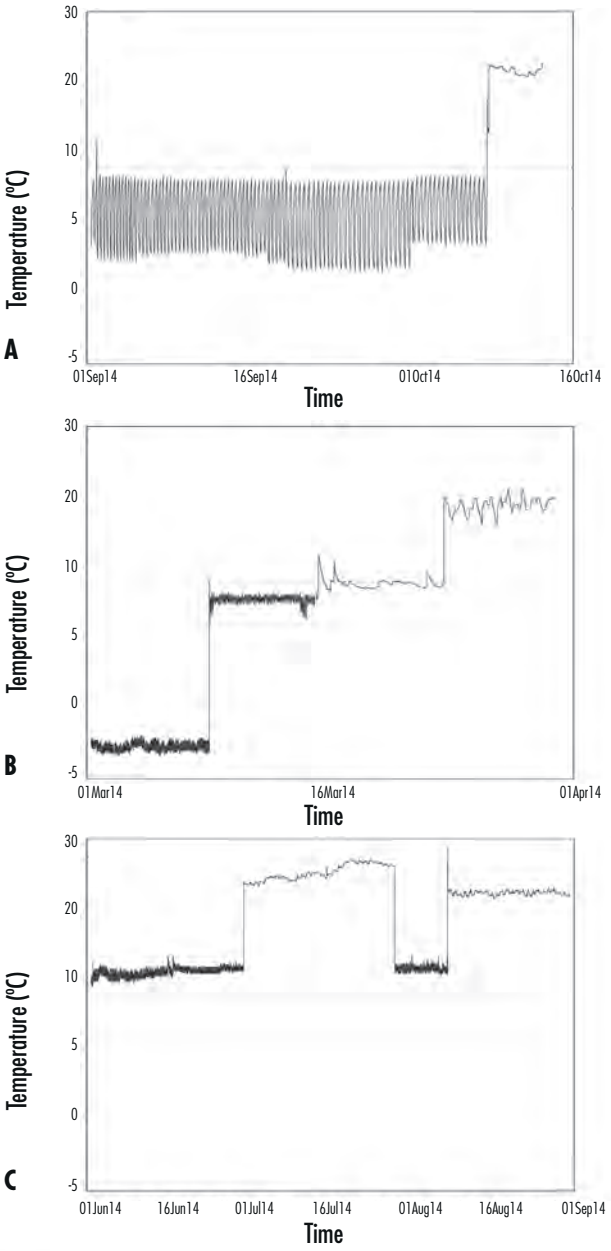

Figure 2. Storage temperature patterns among patients that stored bDMARDs at home. Examples of deviation patterns from the SmPC-recommended temperature range among patients who did not store bDMARDs within the SmPC-recommended temperature range (depicted by the horizontal lines). (A) A saw-tooth graph with multiple cycles of temperature rise and drop. This is in contrast with the examples B and C, which represent longer storage periods below 0˚C (B) and at room temperature or above 25˚C (C) before returning to storage temperatures close to or between 2˚C and 8˚C. bDMARD: biologic DMARD; SmPC: summary of product characteristics.

of the bDMARDs user population because bDMARDS are only dispensed from hospital-based pharmacies in the Netherlands, and only 13% of patients were lost to follow-up. Patient characteristics of those lost to follow-up did not differ from the study population. Limitations of this study were first the lack of information on patients' reasons for storing bDMARDs outside the recommended temperature range, such as due to travelling or accidental storage in the freezer. We also had no information on the exact moment of drug administration. The temperature logger was fixed to the secondary packaging and did not measure temperatures of each individual syringe or prefilled pen. Patients could have taken out one or more syringes or prefilled pens and had these stored elsewhere before injection. This would result in an underestimation of the number of patients who stored bDMARDs outside the SmPC-recommended temperature range. Further, storage time was defined as a period of the whole measurement time. Our definition allowed for less than 48 h outside the 2°C and 8°C temperature range without excursions of 2 h or longer below 0°C or above 25°C. This could have excluded actual storage time for a longer period than 12 h above 15°C. Our definition corrected for a subsequent period of cool storage of at least 48 h, which could have underestimated the duration of storage time outside the SmPC-recommended storage time. Last, the fact that measured temperature changes may not reflect the product temperature inside the package is a limitation. The insulation properties of the package, syringe and prefilled pen protect from short-term exposure to high and low temperatures. To account for possible delay in temperatures becoming equal between package and product, we applied the criterion that the bDMARD had to be stored for at least 2 h below 0°C or above 25°C.

Conclusion

Storage conditions of bDMARDs outside the SmPC-recommended storage temperature range were observed in the majority of patients. To what extent moderate and extreme deviations in storage temperatures could affect product quality and influence efficacy and the occurrence of side-effects of the bDMARDs needs further investigation.

Acknowledgements

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Declaration of conflicting interest

The authors have declared no conflicts of interest.

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Supplementary Information

Appendix 1.

Home storage temperatures of biological disease modifying antirheumatic drugs.

Figure S1.

Appendix 2.

This appendix gives a figurative explanation how total measurement time was censored for the analysis. Total storage time was defined as the total measurement time minus the final 48 hours of temperature measurements. In case the storage temperature changed from below 15˚C to 15˚C or higher for at least 12 hours without subsequent cooling below 15˚C for at least 48 hours, the total measurement time was right censored from the first 15˚C excursion time point.

Below there are three different examples depicting how total measurement time was censored in our study.

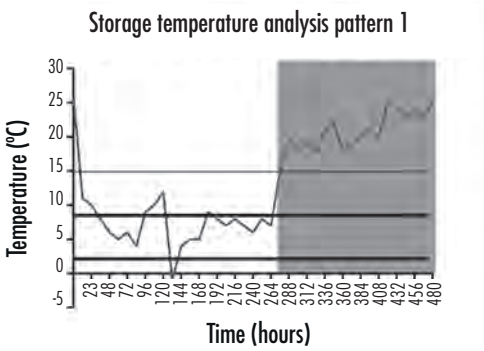

Figure S2. Example 1. At time = 276 hours, temperature measurements change from below 15˚C to above 15˚C and stay above 15˚C for longer than 12 hours without returning to temperature below 15˚C. The temperature measurements during the time highlighted in red are excluded from analysis. Total storage time used in analysis is from t = 0 hours until t = 276 hours.

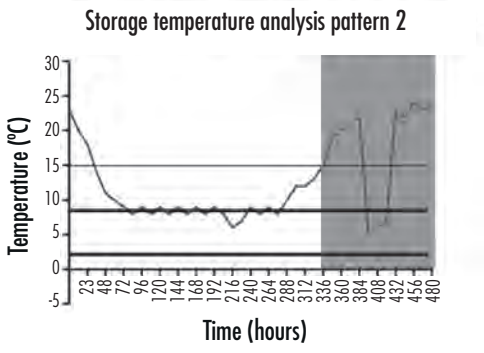

Figure S3. Example 2. At time = 336 hours, temperature measurements change from below 15˚C to above 15˚C and stays above 15˚C for longer than 12 hours. Subsequently, temperature goes below 15˚C for a short period which does not exceed 48 hours. The temperature measurements during the time highlighted in red are excluded from analysis. The total storage time used in analysis is from t = 0 hours until t = 336 hours.

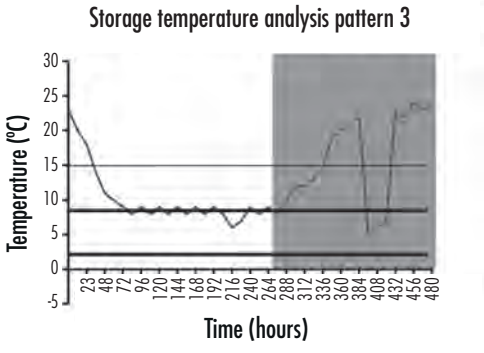

Figure S4. Example 3. The temperature measurements change from below 15˚C to above 15˚C at three time points. The last time point exceeds 12 hours (h=300 until h=336) but is succeeded by a period of temperature measurements below 15˚C for longer than 48 hours. Therefore only temperature measurements belonging to the last 48 hours of the measurement time are excluded from analysis. Total storage time used in analysis is from t = 0 hours until t = 432 hours.

2.2

Actual versus recommended storage temperatures of oral anticancer medicines at patients' homes

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Abstract

Background

Substantial quantities of unused medicines are returned by patients to the pharmacy each year. Redispensing these medicines would reduce medicinal waste and health care costs. However, it is not known if medicines are stored by patients as recommended in the product label. Inadequate storage may negatively affect the medicine and reduce clinical efficacy whilst increasing the risk for side effects.

Objective

To investigate the proportion of patients storing oral anticancer medicines according to the temperature instructions in the product label.

Methods

Consenting adult patients from six Dutch outpatient hospital pharmacies were included in this study if they used an oral anticancer medicine during February 2014 – January 2015. Home storage temperatures were assessed by inclusion of a temperature logger in the original cancer medicines packaging. The primary outcome was the proportion of patients storing oral anticancer medicines as specified in the Summary of Product Characteristics, either by recalculating the observed temperature fluctuations to a single mean kinetic temperature or by following the temperature instructions taking into account a consecutive 24-h tolerance period.

Results

Ninety (81.1%) of the 111 included patients (47.8% female, mean age 65.2 (SD 11.1)) returned their temperature loggers to the pharmacy. None of the patients stored oral anticancer medicines at a mean kinetic temperature above 25°C, one patient stored a medicine requiring storage below 25°C longer than 24 h above 25°C. None of the patients using medicines requiring storage below 30°C kept their medicine above 30°C for a consecutive period of 24 h or longer.

Conclusion

The majority of patients using oral anticancer medicines store their medicines according to the temperature requirements on the product label claim. Based on our results, most oral anticancer medicines will not be negatively affected by temperature conditions at patients' homes for a maximum of three months and are likely to be suitable for redispensing.

Introduction

The increased availability of anticancer medicines allowing for oral administration to treat different types of cancer puts a growing burden on national health care budgets. The costs of oral anticancer medicines were estimated at 173 million Euros in 2015 in the Netherlands, which is approximately one fourth of total expenditure on anticancer medicines [1]. To make better use of current health resources, several suggestions have been made to minimize medicine waste leading to reduced costs and contributing to a sustainable health care for patients with cancer. These include prescribing smaller quantities [2] and redispensing unused medicines [3]. However, for the latter, the quality of medicines needs to be guaranteed and the storage conditions at patients' homes remain a concern. Inadequate storage may negatively affect the medicine and reduce clinical efficacy whilst increasing the risk for side effects.

Some oral anticancer medicines should be dispensed in their original packaging to keep them protected from light and moisture, and require temperature conditions below 25°C or 30°C. Storage claims are defined by the drug companies and based on standardized drug stability test conditions that are outlined in the Q1A International Conference on Harmonisation (ICH) guideline for new drug products [4]. Stability test conditions established by the ICH for climate zone I and II (all European countries) are based on ambient temperature and relative humidity measurements performed in the 1980s [5, 6]. Stability indicating parameters include appearance, assay (potency), impurities, water content, dissolution, particle size and/or other parameters that may be required by the authorities. Stability tests are normally performed at long term, intermediate and accelerated conditions (Table 1). At the time of submission to the regulatory authorities, medicines which fulfil all criteria when tested at long-term and accelerated conditions receive no special storage conditions towards temperature. If a medicine fails to meet the specification after six months accelerated testing, it should be tested at intermediate conditions (30°C/65%RH) as well. When test outcomes at intermediate and accelerated conditions are out of specification, the corresponding storage claims will be to store below 25°C [7]. All product label storage claims should be described in

Table 1. Stability studies and storage conditions for new and existing drug products [5, 8].

Stability study	Storage condition	Minimum time period covered by data at submission
Long term	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH [a]	6[b]/12 months
Intermediate	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

a) The drug company decides whether long term studies are performed at 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH. RH = Relative Humidity.

b) For existing active substances and related finished products.

the European Summary of Product Characteristics (SmPC) or United States Product Insert and correspond with the product labels informing distributors, pharmacies, and patients about the required storage conditions.
Few studies have investigated home storage conditions of medicines. Two studies suggest that medicines are often not adequately stored at home [8, 9], but the studies did not investigate storage temperatures of specific medicines at home over a longer period of time or the influence of ambient temperature. In this study, we investigate the proportion of patients storing oral anticancer medicines according to the temperature instruction in the product label. Furthermore, we investigate the influence of the ambient temperature on the actual storage temperature of oral oncolytics in patient homes.

Methods

Setting and study population

This multicenter observational study was conducted in six outpatient pharmacies in the Netherlands between February 2014 and January 2015. Adult patients (≥18 years) were eligible for inclusion if they were receiving one of the following oral anticancer medicines: imatinib, gefitinib, erlotinib, sunitinib, sorafenib, dasatinib, lapatinib, nilotinib, pazopanib, vandetanib, dabrafenib, everolimus, axitinib, vemurafenib, abiraterone, enzalutamide, and lenalidomide. Patients with obvious cognitive impairments and non-Dutch-speaking patients were excluded. Eligible patients received both written and oral information and were asked for a written informed consent. The study protocol was reviewed and approved by the Medical Ethics Review Board of the University Medical Center Utrecht (protocol reference number 14-628/C).

Study procedure

Patients received their oral anticancer medicine in the original company's primary (e.g. bottles, blisters) and secondary (e.g. cardboard boxes) packaging including a Safe-Rx temperature logger, which was attached to the outer packaging and put in a closed polyethylene seal bag. The Safe-Rx temperature logger is a small (18 mm × 32 mm × 2 mm) temperature measurement device that has been validated according to international standards [10]. The logger was activated upon medicine dispense and device settings were adjusted to have a temperature measurement every 2 min. Patients received standard instructions on adequate storage upon dispensing by the pharmacy's personnel. No extra information was given to those participating in the study. Patients were asked to keep the temperature logger and package in the seal bag and to return the temperature logger(s) when the dispensed medicine had been used. In case the temperature loggers were not returned within four months, a reminder was sent by post including a pre-stamped envelope to return the temperature logger(s). If needed, second and third reminders were given by telephone.

Outcomes

The primary outcome was the proportion of patients storing oral anticancer medicines as specified in the SmPC within the storage tolerances as specified below. We investigated if oral anticancer medicines were stored in accordance with the conditions specified in the SmPC and were not exposed to a mean kinetic temperature (MKT) above 25˚C (sorafenib and everolimus) or above 30˚C (imatinib, lapatinib, nilotinib, vandetanib and abiraterone). The MKT is described in the ICH Q1A guideline as follows:

> *'A single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period.'*[4]

The MKT was calculated for each patient and package over the complete storage period and is generally higher than the mean temperature and takes into account temperature variations and their influence on the medicine based on the Arrhenius equation. Furthermore, we investigated if medicines were stored above 25˚C or 30˚C for a consecutive period of at least 24 h [11, 12] Other oral anticancer medicines (gefitinib, erlotinib, sunitinib, dasatinib, pazopanib, dabrafenib, enzalutamide, lenalidomide, vemurafenib and axitinib) do not require special temperature storage conditions. We investigated whether oral anticancer medicines in this group were stored at a MKT above 40˚C or temperatures that exceeded 40˚C for at least 24 h. The maximum storage temperature of 40˚C was based on accelerated stability test conditions medicines were exposed to [4]. Information on storage temperature requirements were retrieved from the SmPC of each medicine (consulted on 19 October 2015) [13]. We also set the maximum storage period at three months, which corresponds with the maximum dispensing period in the Netherlands. Secondary outcomes were defined as the total storage time for all patients of oral anticancer medicines according to the product label and the relation between storage temperatures and ambient temperature values obtained from hourly measurements from the Royal Netherlands Meteorological Institute in De Bilt, the Netherlands [14].

Data analysis

Demographic data were presented using descriptive statistics. Characteristics (gender and age) of patients lost to follow-up were compared with patient characteristics of those who returned temperature loggers to the pharmacies using t test for normally distributed continuous variables and Pearson chi-square test for differences in proportions. A two-sided p value less than 0.05 was considered to indicate a significant difference. The proportion of storage time at or above 25˚C or at or above 30˚C and the proportion of patients that stored oral anticancer medicines according to the product label were calculated. The mean and 97.5 percentile of daily storage temperatures and mean daily ambient temperatures were calculated and plotted in a line chart. Hourly storage and ambient temperature data were used to visualize individual patient data. The effect of ambient temperatures on daily

storage temperatures was investigated in spring (1 March 2014–31 May 2014), summer (1 June 2014–31 August 2014), autumn (1 September 2014–30 November 2014) and winter (1 December 2014–31 January 2015) and analyzed following a linear mixed effects model. All calculations were made with the statistical package from SAS version 9.2.

Results

Study population

A total of 111 patients were included in the study of which 81.1% (n = 90) returned their temperature loggers to the pharmacy. 'Temperature logger lost or discarded' (n = 3) and 'patient deceased' (n = 4) were reasons for not returning the temperature logger to the pharmacy. Fourteen patients did not respond after the third reminder to return their temperature logger and were considered lost to follow-up. Of our study population, 47.8% (n = 43) was female and the mean age was 65.2 (SD 11.1) years (Table 2). Male patients were more

Table 2. Patient characteristics (N=111).

	Patients included in analysis (N=90)	Patients lost to follow up (N=21)
Age (mean, SD) years	65.2 (11.1)	65.1 (13.5)
Gender	n(%)	n(%)
Female	43 (47.8)	6 (28.6)[a]
Type of oral anticancer medicine		
Everolimus	12 (13.3)	3 (14.3)
Sorafenib	1 (1.1)	1 (4.8)
Abiraterone	9 (10.0)	2 (9.5)
Imatinib	18 (20.0)	2 (9.5)
Nilotinib	10 (11.1)	0 (0.0)
Axitinib	0 (0.0)	1 (4.8)
Dabrafenib	1 (1.1)	0 (0.0)
Dasatinib	6 (6.7)	1 (4.8)
Enzalutamide	3 (3.3)	3 (14.3)
Erlotinib	2 (2.2)	0 (0.0)
Gefitinib	3 (3.3)	2 (9.5)
Lenalidomide	7 (7.8)	3 (14.3)
Pazopanib	4 (4.4)	1 (4.8)
Sunitinib	8 (8.9)	1 (4.8)
Vemurafenib	6 (6.7)	1 (4.8)

a) $p<0.001$.

likely not to return the temperature logger to the pharmacy ($p < 0.001$). Most patients who returned the temperature loggers received imatinib (20.0%) followed by everolimus (13.3%) and nilotinib (11.1%). Thirteen patients (14.5%) used oral anticancer medicines that required storage below 25°C, 37 patients (41.1%) used products that required storage below 30°C and 40 patients (44.4%) used products that required no special temperature conditions. The mean total measured storage time per patient was 64.0 days (SD 25.3).

Primary outcome

Eighty-nine patients (98.9%) met the criteria of the primary endpoint and stored their oral anticancer medicines according to the storage temperature defined in the SmPC (Table 3). One patient stored a medicine that requires storage below 25°C for a consecutive period longer than 24 h above 25°C. None of the patients stored their medicine at a MKT above 25°C or above 30°C and most medicines were stored between 15°C and 25°C. None of the patients using medicines requiring storage below 30°C kept their medication above 30°C for a consecutive period of 24 h or longer.

Secondary outcome

The proportion of measured storage time per temperature for patients using oral anticancer medicines that require storage below 25°C (Figure 1A), below 30°C (Figure 1B) and those that require no special storage temperature conditions (Figure 1C) are presented in Figure 1A to 1C. The proportion of total storage time below 25°C (Figure 1A) for patients using oral anticancer medicines that require storage below 25°C (sorafenib, everolimus) was 642.0 days (71.3%). For patients using oral anticancer medicines that require storage below 30°C (Figure 1B), the proportion of storage time below 30°C was 1143.3 days (93.4%). There was no storage time above 40°C for patients using oral anticancer medicines that required no special temperature conditions (Figure 1C). Mean storage temperatures per day based on all patient measurements are presented in Figure 2 and ranged from 17.4°C (SD 0.56) on 20 February, 2014 to 25.6°C (SD 1.59) on 20 July 2014. Mean daily storage temperature

Table 3. Compliance to drug storage temperature criteria for oral anticancer medicines.

	Sorafenib/ Evrolimus T=25	Imatinib/Lapatinib/ Nilotinib/Vandetanib/ Abiraterone T=30	Gefitinib/Erlotinib/Sunitinib/Dasatinib/ Pazopanib/Dabrafenib/Enzalutamide/ Lenalidomide/Vemurafenib/Axitinib T=40
Patients, n(%)	13 (14.4)	37 (41.1)	40 (44.5)
Patients with at least one package where MKT ≥ T	0 (0.0)	0 (0.0)	0 (0.0)
Patient with at least on package where storage temperature were 24 hours or longer ≥ T	1 (7.7)	0 (0.0)	0 (0.0)

Abbreviations: MKT = Mean Kinetic Temperature.

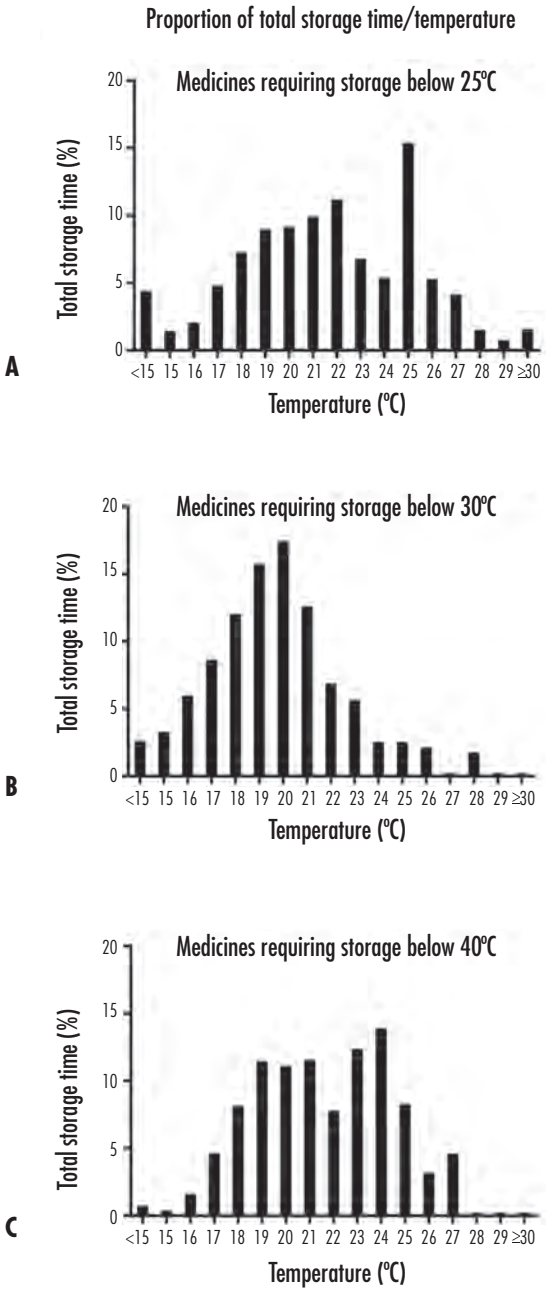

Figure 1. (A) proportion of total storage time per temperature for oral anticancer medicines requiring storage below 25˚C, (B) proportion of total storage time per temperature for oral anticancer medicines requiring storage below 30˚C and (C) proportion of total storage time per temperature for oral anticancer medicines requiring no special temperature conditions.

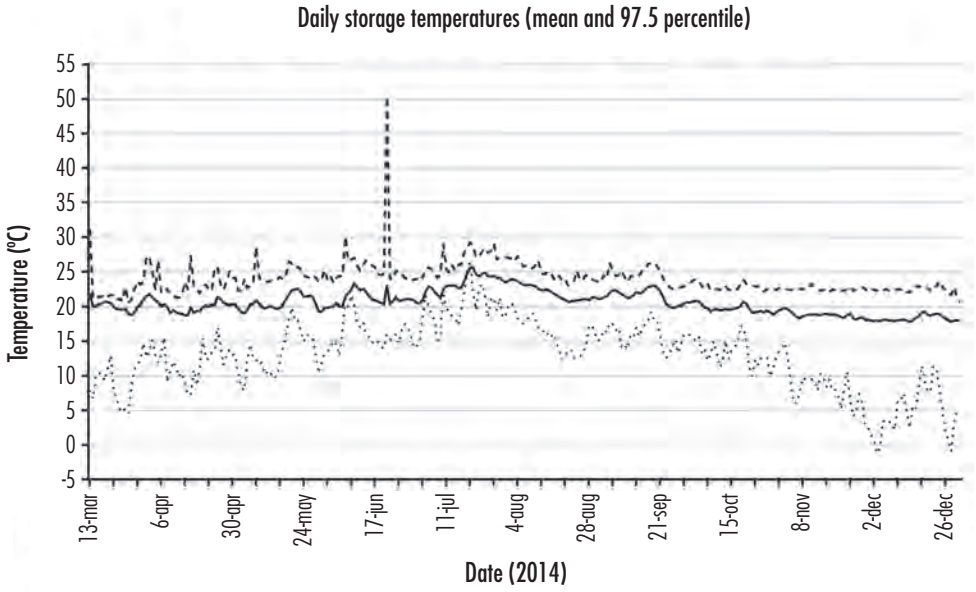

Figure 2. Daily mean (solid line) and 97.5th percentile (dashed line) of storage temperatures from all patients versus daily mean ambient temperatures (dotted line) from 13 March 2014 until 31 December 2014.

in patients using oral anticancer medicines that require storage below 25˚C, below 30˚C or no special temperature storage conditions were 20.6˚C (SD 4.1), 20.7˚C (SD 3.0) and 21.6˚C (SD 3.1), respectively. Maximum and minimum storage temperatures of 58.0˚C (21 June 2014) and 1.9˚C (19 January 2015) were measured. In summer months, an increase of 1˚C ambient temperature resulted in an increase of 0.30˚C storage temperature. This effect was less in the spring (increase of 0.20˚C/1˚C ambient temperature), autumn (increase of 0.20˚C/1˚C ambient temperature) and winter (increase of 0.06˚C/1˚C ambient temperature) period.

Discussion

The majority of patients using oral anticancer medicines store their medicines according to temperature conditions stated on the product label. Most oral anticancer medicines are, therefore, likely to be suitable for redispensing if returned unused to the pharmacy, although for some oral anticancer medicines sensitive to humidity and light, these storage conditions should also be assessed. In the Netherlands, a relationship between actual storage temperature at patient' homes and ambient temperature has been identified, which is the most significant during summer.

Our temperature measurements are in line with what Hewson *et al.* [15] reported on home

storage conditions in New Zealand (climate zone I/II) which showed mean storage temperatures from 18.4°C to 23.6°C with maximum storage temperatures above 25°C. Oral anticancer medicines may be stored at temperatures above 25°C in daily practice, but it is unclear if excursions up to several days above 25°C will affect medicine quality. ICH stability test requirements for authorization of new medicines and existing active substances and their related medicines are based on the MKT, and were investigated by Wolfgang Grimm in 1985 and 1986 [5, 6]. As the MKT value expresses the cumulative thermal stress, it is assumed that temperature excursions (up to 40°C) above 25°C or 30°C induce no significant changes in the medicines' chemical stability [16]. None of the medicines we investigated were stored at MKTs above 25°C, which makes it unlikely that significant chemical degradation of the medicines occurred in our study. For climate zone I in Europe (the Netherlands, Amsterdam), a MKT of 19.3°C and mean temperature of the four hottest months of 20.6°C were measured [6]. These temperatures are slightly lower than mean storage temperatures that we measured in our study (20.6°C–21.6°C). In comparison with the Netherlands, storage conditions in patient homes in climate zone II southern European countries such as Greece and Italy (where mean ambient temperatures in the hottest four months are over 30°C) are likely to be higher and might result in more frequent and longer periods of storage time above 25°C. Furthermore, if patients travel to countries classified as climate zone III or IV, such as India, Israel or Brazil, storage claims based on climate zones I/II stability tests do not longer apply. It is considered that product stability testing in climate zone III and IV would require at least 12 months 30°C/65%RH (long-term conditions) and 6 months 40°C/75%RH (accelerated conditions) [17, 18]. Patients are often not aware of different climate zones and might risk medicine exposure to high temperatures at a specific place at home (e.g. near the heating or window) or abroad.

According to the Public Assessment Report (PAR) documentation, all oral anticancer medicines in our study were tested, according to the ICH Q1A guideline for new medicines, at 25°C/60%RH or 30°C/65%RH long-term/intermediate conditions and at accelerated conditions 40°C/75%RH. The majority of oral anticancer medicines in our study were stable within product specifications at long-term and accelerated conditions. The documentation for two oral anticancer medicines that require storage below 25°C – everolimus and sorafenib – describe a slight increase in impurities at accelerated test conditions [19, 20]. No information is available in the PAR documentation about the possible consequences of inadequate storage.

Unused medicines are returned to pharmacies every day [21]. The possibility of redispensing expensive unused medicines has been discussed in the Netherlands to reduce health care costs and the ambition to create a more sustainable pharmaceutical supply chain [3]. This study investigated important requirements for redispensing and identified medicine quality as one of the main concerns and temperature monitoring as a critical quality parameter. The majority of patients in our study stored oral anticancer medicines according to the storage temperature on the product label. Most medicines were stored at MKTs below 25°C or 30°C and without spikes of 24 h or longer above the defined tolerances. Only for the patients using

medicines that require storage below 25˚C, storage temperatures are often above 25˚C for shorter periods less than 24 h. Although the quality of most oral anticancer medicines can be guaranteed by measuring storage temperatures at home, other storage requirements, such as the ability and willingness of patients keeping the medicine in the original container to protect against moisture and light if stated in the product label are needed to guarantee the medicine quality. If implementing a redispensing system, it should be legally possible, cost beneficial, patients should be willing to participate and accept medicines that have been stored, quality should be assured and there should be clear guidelines (e.g. party responsible for quality of redispensed medicines) [3].

As far as we know, this is the first study that measures home storage temperatures of oral anticancer medicines. Although our sample size was small and there were only six outpatient pharmacies that recruited patients in the study, this study suggests that a large majority of patients store oral anticancer medicines according to recommended storage temperatures. The moment of medicine administration by the patient was unknown and some patients may have started weeks later after the dispensing date or left some of the medicines unused. Therefore, we do not know the exact period of time oral anticancer medicines were exposed to the temperatures measured. We minimized the possible time temperature loggers were not measuring temperature storage data by having a maximum measurement period of three months. By setting the measurement period at three months according to the maximum prescription period, we could have excluded actual storage time. In addition, patients were aware of the study and might have changed their storage practices and locations before starting the measurement period, which might have resulted in an overestimation of the number of patients that store medicines according to the recommended storage temperature on the product label. Ambient temperature measurements were performed at one location only, whereas patients on locations elsewhere might have been exposed to different ambient temperatures which could have influenced the relation between storage temperatures and ambient temperatures. Our results are restricted to climate zone I and II countries, as countries in other climate zones require other test conditions and storage conditions for medicines. Finally, no measurements were performed to assess the relative humidity or light exposure at patient homes. Most oral anticancer medicines are, according to the SmPC, not sensitive to light or moisture and if they are, packages should protect medicines from light exposure and moisture. However, for some oral anticancer medicines that are sensitive to moisture and light, these conditions should be assessed.

Conclusion

The majority of patients using oral anticancer medicines store their medicines according to the temperature conditions stated on the product label. However, if storage below 25°C is required, patients may need additional advice as where to store their medicines at home or when travelling. Before medicines would be suitable for redispensing from a quality perspective, other criteria including light and humidity should be assessed for medicines sensitive to light or moisture. Especially in warmer periods there is a correlation between ambient temperature and storage temperature. As temperatures in the Netherlands rarely are above 25°C, this is not a major issue in The Netherlands. We suggest, however, that this correlation should be further investigated for other climate zone I/II countries with higher daily ambient temperatures.

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2.3

Older patients' compliance with drug storage recommendations

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Abstract

Background

Whereas storage conditions are regulated and closely monitored in every stage of the drug supply chain before drug dispensing, it is unknown if patients store drugs at home according to storage recommendations.

Objective

The objective of this study was to investigate how older patients store their prescription drugs at home and to what extent they comply with drug storage recommendations.

Methods

We conducted a cross-sectional study between October 2015 and March 2016. Forty-four participating Dutch community pharmacies selected four home-dwelling patients (aged ≥ 65 years) using at least one prescription drug. A complete drug inventory at patients' homes was performed. Drugs were considered to fulfill the storage recommendation when these met all drug quality (Q) and information (I) criteria: adequately stored according to drug product label storage recommendations for temperature, light, humidity (Q1); expiry date not passed (Q2); integer primary package (Q3); drug identifiability (I1); drug package insert or information leaflet availability (I2).

Results

One hundred and seventy patients [53.5% female, mean age 74.9 (standard deviation 7.3) years] were included and 1,133 prescription drugs stored at home were registered. More than half of the patients (51.2%) complied with all storage quality and information criteria. Assessment of the individual criteria showed that 76.4% of patients were compliant with criterion Q1 while 90.6, 95.3, 97.1 and 71.2% of patients complied with criteria Q2, Q3, I1 and I2, respectively. 53.2% of drugs that should be kept refrigerated according to storage criterion Q1 were not stored between 2 and 8°C.

Conclusion

This study illustrates that more than half of the older patients comply with general drug storage recommendations.

Introduction

Drug use increases with age, and it is estimated that 25-40% of patients aged above 65 years use at least five prescription drugs [1]. The use of multiple drugs increases the risk for several drug-related problems, such as non-adherence with drugs and storing expired drugs at home [2, 3]. A recent study on home storage conditions of biological drugs showed that only 7% of patients stored these continuously at temperatures specified in the product label [4].
Proper drug storage conditions and practices at home are an important aspect of safe and effective drug treatment. The storage and distribution of drugs are strictly regulated and closely monitored in every stage of the drug supply chain as specified in the Good Distribution Practice guideline [5]. Patients are expected to store their drugs at home according to the storage conditions stated in the Summary of Product Characteristics, such as in the case of drugs requiring refrigeration or storage in the original (outer) packaging to protect from moisture or light, which are provided by the drug companies in the package insert and on the drugs' packaging. In addition to adequate storage conditions, patients should use the drug before the expiry date and keep the drug in an undamaged primary package to ensure drug quality. Furthermore, adequate storage practices also require patients to have access to drug information, by having drugs stored that are identifiable (e.g. for caretakers) and having package inserts available.
Older patients often use multiple drugs and are likely to have more difficulties with drug management at home, including storage, owing to visual or cognitive impairment [6-8]. Increased knowledge on home storage practices could help pharmacists to identify which drug products and aspects of home storage need more attention when counselling patients. This study aims to investigate how older patients store their drugs at home, and to what extent patients comply with drug product storage recommendations.

Methods

Setting and study population

This cross-sectional study was performed between October 2015 and March 2016. The participating pharmacists from 44 Dutch community pharmacies (recruited through the community pharmacist specialist education network) [9] each selected four home-dwelling patients aged 65 years or older who filled at least one prescription drug during the study period. These patients were invited either by telephone or face to face by the community pharmacist to participate. Eligible patients received both written and oral information about the study and were asked for written informed consent to participate.

Ethics

The Medical Ethics Review Committee of the University Medical Center Utrecht (protocol reference number 15-587/C) judged that the Medical Research Involving Human Subjects

Act (WMO) was not applicable to this study. Anonymity of participants was ensured as no research data were traceable by the investigators.

Study procedure

The community pharmacist visited each consenting patient twice at the patients' home. During the first visit, information on home storage of medication was collected using a structured drug inventory assessment (see Appendix S1 of the Electronic Supplementary Material). Patients were asked to present all prescription drugs and show all home storage locations of prescription drugs. The following characteristics were collected for each prescription drug at each storage location on the drug inventory form: drug name, marketing authorisation number (Dutch RVG 'Register Verpakte Geneesmiddelen' or European Union number), Anatomical Therapeutic Chemical (ATC) classification [10], amount (number of packages), use of the drug (chronic/as needed/stopped), storage location, packaging condition (original; intactness), product insert or information leaflet present (yes/no) and the expiry date (month/year). A small temperature logger [11] was placed at each drug storage location to measure storage temperatures. Pharmacists assessed every storage location for possible exposure to light or moisture. Patients received a questionnaire that included questions on socio- and demographic variables. These were collected a week later during the second visit along with the temperature loggers. Date and time of logger placement and collection were registered by the visiting pharmacist.

Outcomes

The assessment of patients' compliance with storage recommendations was performed for each drug based on patients' compliance with five criteria representing (Q) drug quality and (I) drug information availability: (Q1) appropriateness of the storage conditions; (Q2) drug had not passed expiry date; (Q3) primary package integrity; (I1) extent of identifiability of the drug; and (I2) availability of drug information. Patients were considered to comply with appropriate storage conditions (Q1) when storage temperatures for all drugs did not exceed the advised storage temperature range and the drugs were not stored in a humid place or exposed to light when applicable. Drugs not requiring refrigeration were considered to require storage at room temperature defined as temperature below 25°C without excursions above 25°C for 2 h or longer. Refrigerator storage was considered adequate if the temperature was between 2 and 8°C, without excursions outside this range for 2 h or longer. The Dutch G Standard database (a database containing all drug products that are dispensed by or used in the pharmacy in the Netherlands) was used to extract and link the specific drug storage recommendations [12] for each drug. Storage temperatures were assessed for the following storage locations: kitchen, refrigerator, living room, bedroom, bathroom and other (e.g. basement, hallway). Drugs requiring refrigeration stored outside the refrigerator and in use (e.g. insulin pens) were considered adequately stored if this was allowed for the specific drug. With regard to special storage conditions for light and moisture, only drugs (independently of package status) that explicitly required no exposure to light or moisture

were taken into account. Humidity and light exposure, at each storage location, were assessed by the pharmacist and defined as adequate or inadequate. Drugs were considered not expired (Q2) if the expiry dates of all drugs had not passed on the day of the first visit. The drugs' primary package integrity (Q3) was based on the intactness assessment of the primary package (e.g. damaged blister package).
Patients were considered to comply with the criteria of drug identifiability (I1) if drugs stored were identifiable by their primary or secondary packaging as assessed by the pharmacist. Drug storage in multi-dose dispensing systems up to several weeks was considered adequate. Drug information availability (I2) was considered adequate when the patient could present at least one insert for each drug. The primary outcome of this study was the proportion of patients who were compliant with all five criteria mentioned above for all prescription drugs they stored at home.

Covariates

Covariates included the patient characteristics sex, age (65-69, 70-74, ≥75 years), family status (alone, with partner/others), educational level (low, medium, high), number of drugs stored at home (<5, ≥5), and storage locations (1, 2, ≥3).

Data analysis

Demographic data, temperature measurements and compliance with storage criteria were presented using means (standard deviation), medians (interquartile range) or in proportions of the study population. A multivariate logistic regression model was used to assess the associations between the primary outcome (patient compliance with storage conditions) and socio- and demographic variables, number of drugs stored at home, number of home storage locations (excluding 'refrigerator' location) and having drugs that require refrigeration. Results were presented as odds ratios (ORs) with 95% confidence intervals (CIs) and adjusted for all covariates in the model. For the analysis of patient compliance with all storage criteria, only drugs that were in use ('chronic' and 'as needed') were assessed. All statistical analyses were performed using the statistical packages of SAS Version 9.4 (SAS Institute, Cary, NC, USA).

Results

One hundred and seventy patients were included in the study for which 1,133 drug inventory forms were completed (Figure 1). Slightly more than half of the patients were female (53.5%), 47.1% aged 75 years or older and 34.1% of the patients were living alone. 16.5% of the patients had a low educational level. Drugs stored at patients' homes were most commonly agents acting on the renin–angiotensin system (55.0%), drugs used for acid-related disorders (48.5%), antithrombotic agents (47.9%) and lipid-modifying agents (47.9%) (Table 1). Patients stored most drugs in the kitchen (56.2%), the bedroom (37.3%) and the

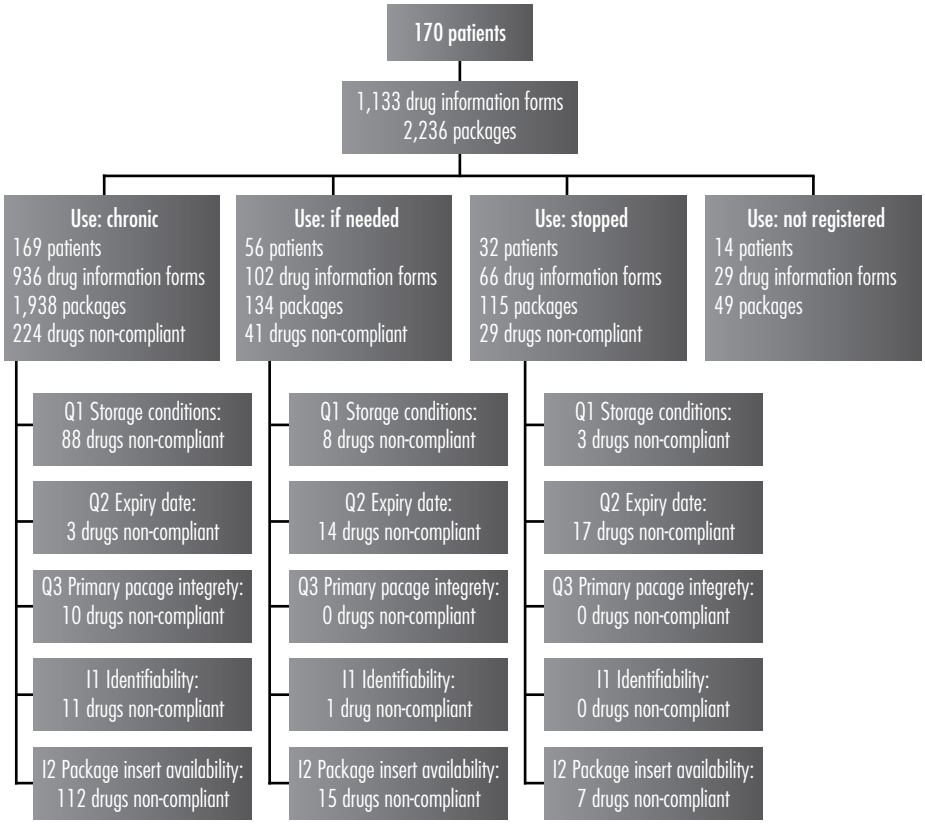

Figure 1. Flowchart of patients, drug information forms and number of packages categorized for actual use.

living room (33.1%). Figure 2 illustrates examples of different storage locations used by patients in the study.

More than half (51.2%) of the patients complied with all storage criteria for drugs they used long term or as needed. 69.4 and 70.0% of patients complied with drug quality criteria and drug information criteria, respectively. Figure 3 presents the level of compliance in proportions of patients, one patient (0.6%) did not comply with the drug quality criteria (Q1–3) (Figure 3a) and three patients (1.8%) did not comply with both drug information criteria (I1–2) (Figure 3b).

One hundred and thirty (76.4%) patients stored all drugs according to the recommended storage conditions for temperature, humidity and light exposure (Q1). Twenty-three (13.6%) patients stored drugs in a humid or light environment when the package label advised otherwise. Only one of these patients did not store a drug in the protective primary or secondary packaging (omeprazole outside primary and secondary packaging stored in

Table 1. Baseline characteristics of the study population (N=170).

Characteristic	Patients n(%)
Sex	
Female	91 (53.5)
Age	
65-69 years	49 (28.8)
70-74 years	41 (24.1)
≥75 years	80 (47.1)
Educational level[a]	
Low	28 (16.5)
Medium	94 (55.3)
High	33 (19.4)
Family type[a]	
Living alone	58 (34.1)
Living with partner/family member/other	110 (64.7)
Drug types (by ATC level 2) most frequently stored[b]	
C09 Agents acting on the renin-angiotensin system	93 (55.0)
A02 Drugs for acid related disorders	82 (48.5)
C10 Lipid modifying agents	81 (47.9)
B01 Antithrombotic agents	81 (47.9)
C03 Diuretics	73 (43.2)
C07 Beta blocking agents	68 (40.2)
C08 Calcium channel blockers	42 (24.9)
R03 Drugs for obstructive airway diseases	35 (20.7)
C01 Cardiac therapy	27 (16.0)
A10 Drugs used in diabetes	26 (15.3)

a) Numbers do not add up to 100% due to missing values.
b) Top-10, in descending order.
ATC = Anatomical Therapeutic Chemical (ATC) classification.

a humid bathroom). There were 17 (9.4%) patients who were using drugs that had already passed the expiry date (Q2). This mostly (82.4%) concerned drugs that were used on an 'as needed' basis. One hundred and sixty-two (95.3%) patients complied with primary package integrity (Q3). Drug information criteria are presented in Figure 3b; 165 (97.1%) patients stored all drugs in identifiable packaging (I1) and 121 (71.2%) patients had the product insert or drug information leaflet (I2) available for all drugs at home.

The mean storage temperature of drugs was highest for drugs stored in the living room

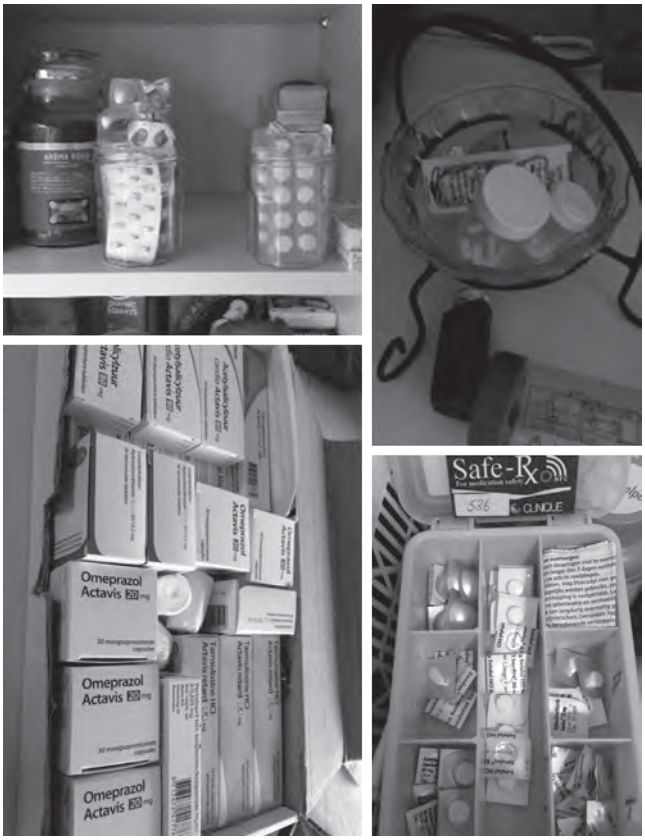

Figure 2. Examples of drug storage in patients' homes.

(mean 20.4°C, range 13.0–27.1°C) and lowest in the bedroom (mean 17.7°C, range 8.4-28.6°C) (Table 2). Drugs requiring refrigeration were stored at a mean temperature of 9.1°C (range – 0.3 to 14.5°C) and 53.2% of these drugs did not comply with the drug quality criteria. Drugs most often not stored according to storage recommendations were calcium/vitamin D preparations, omeprazole and levothyroxine, with 35.5, 34.1 and 33.3% of these drugs, respectively, not stored in compliance with at least one of the five storage criteria.

As presented in Table 3, the number of drugs stored at a patient's home was associated with non-compliance with one or more storage criteria (five or more drugs OR = 2.21, 95% CI 1.08-4.50). Having at least one drug that required refrigeration was associated with non-compliance with one or more storage criteria ($_{adjusted}$ OR = 3.63; 95% CI 1.12-11.74). Furthermore, patients storing drugs at three or more locations at home showed an almost three-fold increase ($_{crude}$ OR = 2.62, 95% CI 1.01-6.82) in non-compliance with one or more storage criteria, but this did not reach significance in the adjusted model ($_{adjusted}$ OR = 2.34, 95% CI 0.82-6.70). Sex, age, family type and educational level were not associated with patients' compliance with one or more storage criteria.

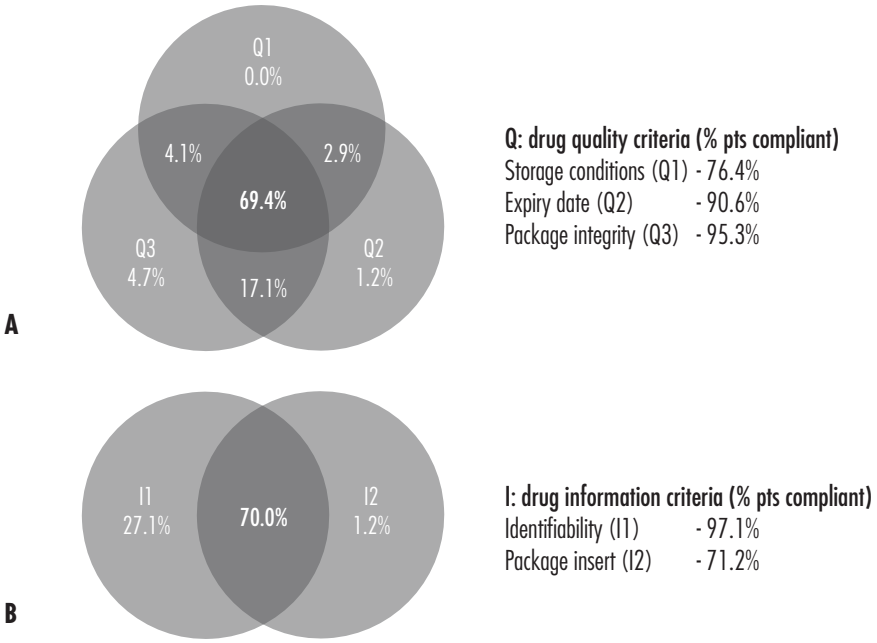

Figure 3. Percentages of patients (pts) compliant with A the Q: drug quality criteria and B the I: drug information criteria (percentages add up to 100%; e.g. 17.1% of patients comply with criteria Q2 and Q3, but not with criterion Q1). Total percentages of pts compliant with each criterion are shown on the right side. Three pts (1.8%) did not comply with both drug information criteria (I1–2) and one patient (0.6%) did not comply with the drug quality criteria (Q1–3).

Table 2. Prescription drugs stored at home including storage locations, compliance with storage criteria and storage temperature.

Storage location	Patients	Number of drugs[a]	Number of drugs non-compliant with storage criteria[b]	Storage temperature
	n(%)	n(%)	n(%)	°C, mean (range)
Kitchen (excluding the refrigerator)	95 (56.2)	383 (40.9)	95 (24.8)	20.2 (7.6 – 30.3)
Refrigerator	22 (13.0)	30 (3.2)	16 (53.2)	9.1 (-0.3 – 14.5)
Bedroom	63 (37.3)	230 (24.6)	38 (16.4)	17.7 (8.4 – 28.6)
Living room	56 (33.1)	253 (27.0)	35 (14.0)	20.4 (13.0 – 27.1)
Bathroom	33 (19.5)	75 (8.0)	21 (28.0)	19.1 (10.1 – 24.4)
Other (e.g. hallway, basement)	38 (22.5)	188 (20.1)	47 (25.2)	19.7 (8.3 – 33.9)

a) Percentages add up >100% due to multiple storage locations for the same type of drug.
b) Percentages of the number of drugs non-compliant/number of drugs total.

Table 3. Associations between patient characteristics and compliance with drug storage criteria

	Patients (170) n(%)	Patients (87) compliant for all drugs n(%)	Patients (83) with ≥1 drug(s) non-compliant n(%)	Drugs n(%)	Drugs non- compliant with storage criteria n(%)	Odds ratio (crude) (95% CI)	Odds ratio (adjusted) (95% CI)
Sex							
Male	79 (46.5)	45 (51.7)	34 (41.0)	439 (44.7)	110 (25.1)	0.65 (0.35-1.19)	0.65 (0.31-1.36)
Age							
65-69 years	49 (28.8)	22 (25.3)	27 (32.5)	242 (24.6)	92 (38.0)	Reference	Reference
70-74 years	41 (24.1)	21 (24.1)	20 (24.1)	251 (25.5)	66 (26.3)	0.78 (0.34-1.78)	0.44 (0.22-1.46)
≥75 years	80 (47.1)	44 (50.6)	36 (43.4)	490 (49.9)	104 (21.2)	0.67 (0.33-1.36)	0.43 (0.21-1.11)
Family type[a]							
Alone	58 (34.1)	31 (35.6)	27 (32.5)	360 (36.6)	76 (21.1)	0.87 (0.46-1.65)	0.68 (0.31-1.48)
Educational level[a]							
Low	37 (21.8)	14 (16.1)	23 (27.7)	268 (27.2)	69 (25.7)	Reference	Reference
Medium	94 (55.3)	48 (55.2)	46 (55.4)	511 (52.0)	141 (27.6)	0.62 (0.26-1.47)	0.73 (0.27-1.94)
High	33 (19.4)	20 (23.0)	13 (15.7)	165 (16.8)	51 (30.9)	0.42 (0.15-1.18)	0.41 (0.13-1.26)
Number of storage locations[b]							
1	76 (44.7)	42 (48.3)	34 (41.0)	425 (43.2)	97 (22.8)	Reference	Reference
2	69 (40.6)	37 (42.5)	32 (38.6)	379 (38.6)	98 (25.9)	1.07 (0.56-2.06)	1.24 (0.60-2.59)
3-5	25 (14.7)	8 (9.2)	17 (20.5)	179 (18.2)	67 (37.4)	2.62 (1.01-6.82)	2.34 (0.82-6.70)
Number of drugs							
≥5	98 (57.6)	41 (47.1)	57 (68.7)	791 (80.5)	215 (27.2)	2.46 (1.32-4.60)	2.21 (1.08-4.50)
Drugs stored in the refrigerator							
Yes	20 (11.8)	5 (5.7)	15 (18.1)	179 (18.2)	69 (38.5)	3.25 (1.12-9.40)	3.63 (1.12-11.74)

a) Numbers do not add up to 100% due to missing values (Family type – 2 values missing, Educational level – 6 values missing).
b) Refrigerators were not taken into account as storage location.
CI = Confidence Interval.

Discussion

This study illustrates that more than half of the older patients store their drugs according to general storage recommendations. 53.2% of drugs requiring refrigeration were not stored according to the recommended storage conditions. Patients with at least five prescription drugs or having at least one drug that requires refrigeration often do not comply with storage recommendations.

The majority of patients in our study population had one or more drugs intended for treating chronic diseases stored at home, such as drugs intended for the treatment of cardiovascular diseases or respiratory diseases. These findings are in accordance with reports on the most commonly dispensed drugs in the Netherlands [1]. Several studies from different countries have investigated home storage of drugs, including Mexico, Malaysia, United Arab Emirates, Belgium and Greece. All identified several problems related to the home storage of drugs [13-17], such as overdue expiry dates and other undesirable storage practices (e.g. storing large quantities of drugs and maintaining drugs that were no longer used). The number of patients storing expired drugs in our study is slightly lower than what others report (5–20%) [16, 18, 19]. This was also observed for the availability of package inserts [16] and might be partially explained by the fact that we included only prescription drugs and the fact that patients stored fewer drugs at home that were used on an 'as needed' basis or that were already discontinued. Having multiple drugs stored at multiple locations has been associated with poor medication storage practices [3, 19]. For older patients, it is thought that their cognitive skills and knowledge to independently manage their drugs are decreased [7]. However, this was not confirmed in our study in which older patients (aged ≥ 75 years) were found, although not statistically significantly so, to be more compliant with the storage criteria.

Based on the temperature measurements performed, most drugs intended for storage in the refrigerator were not stored between 2 and 8°C. This is in line with what has been reported previously regarding storage of drugs that require refrigeration [4]. Pharmacists and pharmacy assistants should explicitly inform patients about adequate cool storage conditions (e.g. central shelf in the refrigerator, away from the back wall) when a drug requiring refrigeration is dispensed at the pharmacy. If drug storage between 2 and 8°C is necessary and there is evidence that drug products degrade rapidly, refrigerators should be equipped with temperature registration or the use of dedicated refrigerators for drug storage should be encouraged.

Few patients (9.4%) stored drugs at home that had passed the expiry date. As one would expect, drugs used 'as needed' or that had been discontinued more often had passed the expiry date than drugs used long term. Good storage practices require patients to check expiry dates of drugs regularly, preventing the use of expired drugs. Although we did not study patients' habits in relation to drug package expiry dates, others have reported that less than half of patients never check the drugs' expiry date before use [7, 20]. More than 28% of patients did not have the package insert and drug information leaflets available for at least

one drug. Many patients stored drug information leaflets and package inserts at a central location. Although the absence of the package insert may not directly affect treatment, accurate information about drugs that patients take long term or may intend to take as needed should be readily available. Primary package integrity is essential for some drugs to protect against light or moisture. Drug identifiability (e.g. storage in recognisable packaging) allows patients and caregivers to identify the drugs and the dosage regimen. In our study, however, only a small number of patients had one or more drugs in a damaged primary packaging (4.7%) or had drugs at home that were not identifiable by the pharmacist (2.9%). The clinical consequences of not complying with storage recommendations are largely unknown. In theory, drugs exposed to inadequate storage conditions can lose efficacy or become toxic. There are few case reports and studies performed on suspected clinical consequences of inadequate drug storage. A physician reported a suspected drug therapy failure owing to inadequate storage of levothyroxine at the patient's home [21]. Several drugs such as tetracycline antibiotics are susceptible to temperature changes and moisture, but there are few cases known where outdated tetracycline antibiotics had clinical consequences likely caused by a degraded product [22]. Furthermore, low humidity storage conditions have been shown to compromise inhalation capsules [23]. In general, drug companies should use protective packaging to protect drugs if they are sensitive to moisture or light. It is therefore improbable that drugs in our inventory that were exposed to light or moisture and stored in the primary or secondary packaging (as most drugs in the inventory) were affected by these conditions.

Only a few studies have investigated different aspects of adequate storage conditions and included home visits by pharmacists to make a complete inventory of prescription drugs. This study provides more insight into storage practices at home and took into account a combination of important storage requirements, such as temperature measurements of storage locations, expiry dates, product insert availability and drug identifiability. However, this study was also subject to some limitations. Participants were aware of the study purpose and might have already discarded unused drugs and reorganized their household before the visit. This might have led to an underestimation of both the number of patients who store drugs inappropriately and the number of drugs not stored appropriately. In addition, there might have been differences in the type and level of questioning used by pharmacists in their attempts to make the inventory of all drugs in the home as complete as possible. Light exposure or relative humidity were also not measured but based on the assessment of the pharmacists. However, to limit variation in the amount of information per patient, pharmacists received protocol training and were required to use a standardized inventory list for each drug they found.

Conclusion

Compliance with storage recommendations was observed in more than half of the older patients. Patients having multiple drugs and having drugs that require refrigeration are often non-compliant with storage recommendations. Manufacturers and pharmacists should emphasize the importance of proper drug storage at home. All patients using multiple drugs may require additional help from their pharmacist, pharmacy technician or caring physician to store drug storage at home appropriately. Extra and repeated information – both written and oral – on drug storage conditions (e.g. middle compartment of the refrigerator or do not store in the bathroom) should be provided to patients as deemed necessary for specific products.

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Nicolaas Vlieland, Bart van den Bemt, Charlotte Bekker, Antoine Egberts, Marcel Bouvy and Helga Gardarsdottir have no conflicts of interest directly relevant to the content of this study.

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Appendix 1 – drug inventory form

Drug inventory form (1) please fill out for each drug				
Drug (use one form for different packages of the same drug) ☐ Drug is not identifiable, please try to fill out as much as you can				
Name/dosage/amount				
Prescription type	☐ prescription drug ☐ OTC ☐ homeopathic ☐ dietary supplement			
Package type* (multiple answers possible)	☐ primary ☐ secondary ☐ unit-dose packaging ☐ drug box organizer ☐ other:			
Storage recommendations on label/package (multiple answers possible)	☐ cool ☐ room temperature ☐ no light ☐ dry ☐ between/below ___˚C ☐ keep away from children ☐ none ☐ keep in original packaging ☐ other:			
RVG/RVH/EU drug number ☐ NA				
Current use according to patient	☐ chronic ☐ as needed ☐ discontinued			
Treatment duration ☐ NA or unknown	_____ week(s) _____ month(s)			
Prescriber ☐ NA or unknown	☐ GP ☐ specialist ☐ dentist ☐ other:			
What is the drug used for (according to patient)?				
General comments**				
Describe all storage locations below separately.				
Storage location				
Number of packages				
Label/packaging text is present and readable ☐ NA	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Nr. (un)opened (s)secondary/(p)primary packages*	☐ Opened, nr. s: p: ☐ Unopenend, nr. s: p:	☐ Opened, nr. s: p: ☐ Unopenend, nr. s: p:	☐ Opened, nr. s: p: ☐ Unopenend, nr. s: p:	☐ Opened, nr. s: p: ☐ Unopenend, nr. s: p:
Expiry date (MM-YYYY)				
Quality (s)secondary/(p)primary packages*	☐ Undamaged, nr. s: p: ☐ Damaged, nr. s: p:	☐ Undamaged, nr. s: p: ☐ Damaged, nr. s: p:	☐ Undamaged, nr. s: p: ☐ Damaged, nr. s: p:	☐ Undamaged, nr. s: p: ☐ Damaged, nr. s: p:
Package insert available ☐ NA	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Drug dosage changed according to patient?		☐ Yes ☐ No		

*primary packaging: packaging with direct contact to the product (e.g. bottle, blister), secondary packaging: encloses the primary packaging (e.g. cardboard box) **e.g. particular organization medicine cabinet, storage of product inserts on a central location, notes on packaging, etc.

Underlying factors of (in)adequate drug storage

3

3.1

Associations between personality traits and adequate home storage of drugs in older patients

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Submitted for publication

Abstract

Objective

To investigate the association between personality traits of older patients and adequate home storage of drugs.

Methods

Forty-four participating Dutch community pharmacists randomly selected each up to four community-dwelling elderly patients (≥65 years) who were using at least one prescription drug. The Big Five Inventory was used to assess the personality traits – 'openness', 'conscientiousness', 'extraversion', 'agreeableness' and 'neuroticism' – of patients. An assessment of adequate home storage of drugs was made. A summed composite score for each patient ranging from zero (adequate storage) to three (inadequate storage) was based on storage criteria representing quality, information and level of storage organization.

Results

51.2% of the patients stored drugs adequately in accordance with all quality (Q) and information (I) criteria. A high level of drug storage organization was found in 70.8% of patients. 43 patients (31.4%) stored their drugs adequately based on all storage criteria (composite storage score 0). No associations between personality dimensions and adequate drug storage were found. Having a lower number of drugs was associated with adequate drug home storage ($OR_{adjusted}$ 0.86; 95% CI: 0.77-0.96).

Conclusion

This study suggests that personality is not associated with adequate home storage of drugs in older patients.

Introduction

Before a new drug is approved and becomes available for patients, stability studies have to be conducted in order to ensure drug quality and thereby safe and effective drug treatment. Drug storage is strictly controlled during several periods of storage and transport before the drug reaches the patient. After dispensing, patients are responsible for adequate storage and they are recommended to store drugs according to the storage label statement provided in the drug information leaflet. Inadequate storage can affect product quality: for example, acetylsalicylic acid is sensitive to moisture, leading to breakdown of acetylsalicylic acid into salicylic acid and acetic acid [1]. This might compromise the drug's efficacy and/or toxicity. The information leaflet states therefore that patients should store drug products containing acetylsalicylic acid in the original packaging and keep below 25°C to prevent degradation and potency loss.

Several observational studies indicate that a considerable number of patients do not store drugs according to the drug product label statement [2, 3]. Older patients often use multiple drugs [4] and may lack the knowledge and capacity to independently manage their drugs [5], making them more susceptible for problems with adequate home storage for drugs. Reasons why patients do not store drugs according to drug label statement are largely unknown. As personality determines for a great deal how patients behave [6], personality traits might also affect the way patients store their drugs. In the field of psychology, personality differences have often been studied using the five-factor model of personality. This model describes differences between people on their behavior, thoughts and feelings based on five broad personality traits: 'extraversion', 'neuroticism', 'conscientiousness', 'agreeableness', and 'openness to experience' [7, 8]. For example, a person who scores high on 'neuroticism' is more vulnerable to stress and more emotionally involved, 'conscientious' people are more punctual, efficient and organized. The five personality traits have been associated with diverse health related outcomes such as drug adherence, quality of life in asthma patients and treatment outcomes of antidepressant drug therapy [9-12].

The association between patient personality traits and adequate home storage of drugs has not been investigated. The aim of this study is therefore to investigate the association between personality traits and adequate home storage of drugs by older patients.

Methods

Setting and study population

A cross-sectional study was conducted between October 2015 and March 2016. Forty-four Dutch pharmacists enrolled in a post graduate community pharmacy training program participated in the study. Each pharmacist received protocol training and selected up to four home-dwelling patients aged ≥65 years who used at least one prescription drug. Eligible patients were invited to participate by telephone or face-to-face at the pharmacy. After

receiving written and oral information, patients that gave written informed consent were included in the study.

Ethics

The Medical Ethics Review Committee of the University Medical Center Utrecht (protocol reference number 15-587/C) judged that the Medical Research Involving Human Subjects Act (WMO) was not applicable to this study. Confidentiality of participants was ensured using anonymized patient codes.

Study procedure

Pharmacists visited each patient twice in their homes. At the first visit, pharmacists used a structured drug inventory made to assess home storage of drugs. Patients were asked to present all prescription drugs that they were currently using (both chronic and as needed) and to show all home storage locations of prescription drugs. The following characteristics were collected for each drug at each storage location on the drug information form: drug identifiability, packaging type (primary and/or secondary) and condition (intactness), presence of drug product information leaflet (yes/no) and the expiry date (month/year). In addition, a small temperature logger [13] was placed at each drug storage location to measure temperatures and patients were asked to complete a questionnaire including a personality assessment using the Big Five Inventory (BFI).

Pharmacists took pictures of and assessed every storage location for possible exposure to light or moisture. If a drug was stored at more than one location, each drug was separately assessed for adequate storage. During the second visit at least one week after the first assessment, pharmacists collected the temperature loggers and the completed personality assessment. Date and time of placement and collection of the temperature loggers were registered by the visiting pharmacist.

Study outcomes

The main study outcome consisted of three aspects of patient's home storage of drugs: storage criteria representing drug quality based on three criteria representing drug quality (Q), storage criteria representing drug information (I) and the level of drug storage organization (O). A composite score for each patient based on these three aspects is described at the end of this section. In addition, patients were asked about their reasons ('storage advice', 'part of a daily/weekly routine', 'as a reminder') to store drugs on a particular location.

Criteria representing drug quality

The quality criteria were assessed for each drug and consisted of the following items: (Q1) drug storage conditions according to label storage statement for temperature, light, humidity; (Q2) the drug's expiry date; (Q3) the drug's primary package integrity (Table 1). Patients were considered to store drugs adequately according to the first quality criterion (Q1) when storage temperatures for all drugs did not exceed the advised storage temperature range as indicated in the drug information leaflet (data extracted from the Dutch G

Table 1. Storage drug quality (Q) and information (I) criteria for drug storage assessment.

Storage criteria	Patient were considered to store drugs adequately when…
Q1 – storage conditions	… storage temperature for all drugs did not exceed the advised storage temperature range as indicated in the drug information leaflet for at least two hours and were not stored in a humid place or exposed to light when applicable.
Q2 – expiry date	… the expiry dates of all drugs had not passed on the day of the first visit.
Q3 – primary package integrity	… all of the drugs' primary packages were intact.
I1 – drug identifiability	… all drug were identifiable (name, strength) by their primary or secondary packaging.
I2 – drug information leaflet	… at least one drug information leaflet could be presented for each drug.

Standard database containing all drug products) [14] for at least two hours and were not stored in a humid place or exposed to light when applicable. Drugs not requiring refrigeration were considered to require storage at room temperature defined as temperature below 25˚C without excursions above 25˚C for two hours or longer. Refrigerator storage was considered adequate if the temperature was between 2˚C – 8˚C, without excursions outside this range for two hours or longer, except when storage outside the refrigerator was allowed for drugs in use (e.g. insulin). For drugs that explicitly require no exposure to light or moisture humidity and light exposure, at each storage location, was assessed by the pharmacist and defined as adequate or inadequate. Patients were considered to store drugs adequately according to the second criterion (Q2) when the expiry dates of all drugs had not passed on the day of the first visit. The drugs' primary package integrity (Q3) was based on the intactness of the primary package (e.g. damaged blister package no longer protective against moisture); patients were considered to store drugs adequately when all of the drugs' primary packages were intact.

Criteria representing drug information availability

The drug information criteria consisted of the following items: the drug's identifiability (I1) and the information leaflet availability (I2) (Table 1). Patients were considered to store drugs adequately when drugs were identifiable (name, strength) by their primary or secondary packaging. Drug storage in a multi-dose dispensing (MDD) system was considered adequate. With regard to the second criterion, patients were considered to store drugs adequately when patients could present at least one drug information leaflet for each drug.

Criteria representing drug storage organization

Drug storage organization (O) was categorized in three organizational levels: high level, intermediate level and low level. Our scale was inspired by scales measuring disorganization and cluttering in households, such as the Clutter-Hoarding Scale [15], but with the primary focus on drug storage locations. High level of drug storage organization was characterized by the extent package sorting, dedicated drug storage location, intact packages,

clear identifiable drugs and neat and well-arranged drug storage locations. An intermediate level of drug storage organization showed partial package sorting, drugs stored with other household belongings and a combination of primary and secondary packages. The lowest level of drug organization was characterized by no package sorting, combination of primary, secondary or no packages, cluttering, multiple storage locations (≥3), difficulties identifying drugs for caregiver (e.g. possible risk of accidental mix-up, errors).
Pictures of storage locations for each patient were rated by five raters (BB, HG, MB, HW, NV). Raters were able to adjudicate pictures of patients as 'not assessable' if they were unable to assess the patients' storage locations (e.g. pictures were vague, zoomed). The final rating was decided based on the agreement of at least four raters. Disagreements were discussed by NV, HG and BB until consensus was reached.

Composite score representing drug quality, drug information availability and drug storage organization

A composite score for adequate storage for each patient was based on storage criteria representing quality (0: adequate; 1: inadequate based on Q1, Q2 and/or Q3), information (0: adequate; 1: inadequate based on I1 and/or I2) and level of storage organization (0: high level, 1: intermediate/low level). This score ranges from zero (adequate storage) to three (inadequate storage).

Personality traits

Patients were asked to fill out the Dutch version of the 44-item Big Five Inventory [16]. The BFI assesses the personality traits – 'openness', 'conscientiousness', 'extraversion', 'agreeableness' and 'neuroticism' – were assessed. 'Openness' refers to a persons' flexibility and their openness to new experiences. 'Extraversion' is characterized by positive emotions and being assertive as well as being energetic whereas 'Neuroticism' is characterized by a person's vulnerability to stress and difficulties controlling impulses and desires. 'Conscientiousness' refers to the level of organization and order. 'Agreeableness' refers to friendliness, being cooperative and accepting. Patients were asked to rate all 44 items (e.g. 'I see myself as someone who does things efficiently' and 'I see myself as someone who tends to be disorganized') of the BFI on 5-point Likert scales (1, strongly disagree; 5, strongly agree). The personality traits 'extraversion' (Cronbach α = 0.79), 'neuroticism' (Cronbach α = 0.78), 'openness' (Cronbach α = 0.77), 'conscientiousness' (Cronbach α = 0.79) and 'agreeableness' (Cronbach α = 0.75) all had sufficiently high internal consistencies. We subjected all BFI items to a factor analysis (varimax rotation) in order to examine whether BFI items measured the corresponding personality traits [7]. The factor loadings observed in the present study were consistent with those presented by Denissen *et al* [16]. Missing values were imputed using multiple imputations [17]. Patients were excluded from the analysis if they omitted more than eight BFI items. For eighteen patients (10.6%) no personality assessment could be made, either because patients did not return (4.5%) or returned an incomplete inventory (6.1%).

Covariates

Covariates included the patient characteristics sex, age, family status (living alone *vs.* with a partner/others), educational level (low, medium, high), use of a multi-dose dispensing system and number of drugs stored.

Data analysis

Demographic data, drug quantities and drug storage quality criteria and information criteria were presented using means (standard deviation [SD]) in case of normal distributions or medians (interquartile range [IQR]) in case of non-parametric distributions or in proportions of the study population. Mean scores (SD, range) for the sum of each of the Big Five personality traits were calculated. Associations between the five patient personality traits of the BFI, patient characteristics (gender, age, education, household size, use of MDD system, number of drugs) and the composite score for adequate drug storage were investigated using an univariate and multivariate logistic regression analysis. A stepwise approach (forward selection), excluding variables (patient characteristics) with $p>0.1$ in the univariate model, was used to build the final model. Results of the logistic regression models were presented as odds ratios with 95% confidence intervals. Patients were considered to store drugs adequately if the composite score was zero. A sensitivity analysis was performed where patients were allowed to violate one of the three storage criteria and still be considered to store their drugs adequately. Additionally, associations between adequate storage quality (Q) and information (I) and the level of home storage organization (O) for drugs were assessed with a separate logistic regression model. Results were presented as odds ratios with 95% confidence intervals. The data was analyzed with the statistical software from SAS version 9.4 (SAS Institute, Cary, North Carolina, USA).

Results

A total of 170 patients were visited at their homes. Of these, 137 patients (80.6%) were assessed on storage quality, information, the level of storage organization as well as their personality and where included in the study. 33 patients (19.4%) could not be assessed on the level of storage organization due to missing/insufficient pictures (8.8%) or because they did not complete their personality assessment (10.6%). More than half of the patients included in the study were female (51.8%), the median age was 74 (IQR: 11) years and 33.6% of the patients were living alone. Most patients had a medium or high educational level (83.2%) (Table 2). The median number of prescription drugs stored was 5 (IQR: 5). One third of the patients (33.6%) used a multi-dose dispensing system to store drugs. Patients' reasons for the use of specific storage locations were most commonly related to aspects of daily routine ('drug intake is part of a (daily) routine', 66.7%) or 'as a reminder to take the drug' (12.3%). 7.1% of patients named 'storage advice' as a reason for storage location, primarily for drugs requiring refrigeration.

Table 2. Baseline characteristics of the study population.

Characteristic	Patients (N=137) n(%)
Age (median, IQR)	74 (11)
Number of drugs (median, IQR)	5 (5)
Sex	
Female	71 (51.8)
Educational level[a]	
Low	23 (16.8)
Medium	75 (54.7)
High	26 (19.0)
Family type[a]	
Living alone	46 (33.6)
Living with others	89 (65.0)
Use of MDD[b]	
Yes	46 (33.6)

a) Numbers do not add up to 100% due to missing values.
b) MDD= multi-dose drug dispensing system.

Figure 1. Examples of storage locations showing different home storage organization levels of drugs. The left pane was rated as high level storage organization, the middle pane as intermediate level storage organization and the right pane as low level storage organization.

66.4% and 69.3% of the patients stored drugs adequately according to quality criteria (Q) and information criteria (I), respectively. The individual storage criteria were as follows: 102 patients (74.5%) stored drugs adequately based on storage conditions (Q1), 123 patients (89.8%) did not store drugs that had already passed the expiry date (Q2) and 129 patients (94.2%) stored drugs adequately by having the drug's primary package intact (Q3). For drug information criteria, 132 patients (96.4%) stored their drugs in an identifiable package (I1) and 97 patients (70.8%) had the drug information leaflet (I2) available for all drugs. Three patients (1.8%) inadequately stored drugs based on both drug information criteria (I1-I2) and one patient stored drugs inadequately based on all drug quality criteria (Q1-Q2-Q3). Representative pictures of home storage locations for drugs are presented in Figure 1. Pictures of location from 79 patients (57.7%) were discussed until consensus was reached. The raters adjudicated 97 patients (70.8%) to a high level of home storage organization (O) for drugs, 34 patients (24.8%) to the intermediate level of storage organization and 6 patients (4.4%) to the lowest level of storage organization.

The mean score of the BFI questionnaire for 'extraversion' in the study population was 27.8 (SD 5.0; range 11-38), for 'agreeableness' 34.6 (SD 4.5; range 18 – 43), for 'conscientiousness' 33.6 (SD 4.7; 16 – 45), for 'neuroticism' 21.7 (SD 4.8; range 9 – 39) and the mean score for 'openness' was 32.6 (SD 5.9; range 15 – 44).

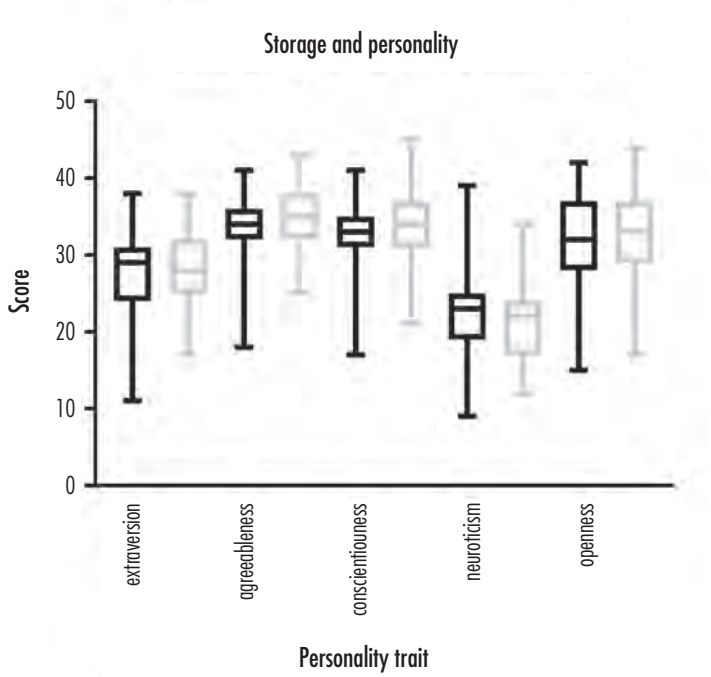

Figure 2. Box plot presenting patient scores on personality traits 'extraversion', 'agreeableness', 'conscientiousness', 'neuroticism', 'openness' and adequate (black) and inadequate (grey) home storage.

Mean scores for each personality trait and the composite storage score are presented in Figure 2. 43 patients (31.4%) stored their drugs adequately based on all storage criteria (composite storage score 0). 54 patients (39.4%), 30 patients (21.9%) and 10 patients (7.3%) stored their drugs inadequately and counted respectively '1', '2' and '3' on the composite score. Personality traits 'extraversion', 'agreeableness', 'conscientiousness', 'neuroticism' and 'openness' were not associated with adequate storage. Having a lower number of drugs stored was associated with adequate storage ($OR_{adjusted}$ 0.86; 95% Confidence Interval: 0.77-0.96) (Table 3). The sensitivity analysis did not result in other significant associations. No associations were found between adequate storage quality (Q) or storage information (I) and the level of drug storage organization (O).

Table 3. Associations between personality traits and adequate home storage conditions for drugs.

	Inadequate storage N=94	Adequate storage N=43	Crude OR (95% CI)	Adjusted OR (95% CI)
Sex*				
Female	53 (56.4)	18 (41.9)	0.56 (0.27-1.16)	-
Age**	73 (11)	76 (12)	1.02 (0.97-1.07)	-
Family type*				
Missing	1 (1.1)	1 (2.3)	NA	-
Alone	32 (34.0)	14 (32.6)	Ref	-
With others	61 (64.9)	28 (65.1)	1.05 (0.49-2.27)	-
Educational level*				
Missing	9 (9.6)	4 (9.3)	NA	-
Low	15 (16.0)	8 (18.6)	Ref	-
Medium	51 (54.3)	24 (55.8)	0.88 (0.33-2.36)	-
High	19 (20.2)	7 (16.3)	0.69 (0.20-2.34)	-
Use of MDD*				
Yes	28 (29.8)	9 (20.9)	0.62 (0.27-1.47)	-
Number of drugs**	6.0 (6.0)	4.0 (4.0)	0.78 (0.68-0.90)	0.86 (0.77-0.96)
Personality traits***				
Extraversion	27.9 (4.8)	27.5 (5.5)	0.99 (0.92-1.06)	1.06 (0.96-1.16)
Agreeableness	35.0 (4.0)	33.5 (4.6)	0.92 (0.85-1.01)	0.94 (0.84-1.04)
Conscientiousness	34.1 (4.3)	32.4 (4.9)	0.92 (0.85-1.00)	0.94 (0.85-1.05)
Neuroticism	21.2 (4.7)	22.6 (5.1)	1.06 (0.98-1.14)	1.05 (0.96-1.15)
Openness	32.8 (5.6)	32.0 (6.3)	0.98 (0.92-1.04)	0.97 (0.91-1.05)

*=n(%). **=median (IQR). ***=mean (SD). -=not included in final model. IQR=Interquartile range. OR=Odds Ratio. CI=confidence interval. MDD=multidose drug dispensing system.

Discussion

In this study in older patients, none of the personality traits, 'extraversion', 'agreeableness', 'conscientiousness', 'neuroticism' and 'openness' were associated with the adequate storage. One-third of older patients were considered to store drugs adequately. A lower number of drugs stored was associated with adequate home storage.

We did not find an association between the five personality traits in older patients and adequate home storage, therefore not supporting the hypothesis that patient's tendency to be punctual and organized ('conscientiousness') promotes adequate home storage. The number of total drugs stored in patients´ homes was lower compared to other studies, which might partly be explained by the assessment of only prescription drugs [18]. The majority of patients had a high level of home storage organization for multiple drugs. The pictures confirmed patient's statements that behavior and daily routines played an important role in their reasons for choosing specific storage locations in their home (e.g. near television or radio as a visual reminder). One-third of patients used multi-dose dispensing systems, which is higher than previously reported [19, 20], possibly due to the high proportion of patient over 75 years of age. We expected patients with the highest level of storage organization would be more likely to store their drugs adequately, however, this was not confirmed in our study. Patients did not mention the drug storage conditions on the product label as a reason for selecting a specific location for storage, except patients having drugs requiring refrigeration. This is consistent with the results of Sanders *et al.*, who found that patients developed individualized behaviors for taking drugs and often adjust these to their daily routines [21]. This fuels our understanding for patients' considerations how and where to store drugs in their homes, suggesting inadequate storage by patients can be non-intentional. In their home setting, patients may not make a rational decision to facilitate adequate drug storage in their homes and can make a different trade-off (e.g. taking drugs out of the refrigerator in case of lack of space or keeping expired drugs for future 'as needed' use) that does not prioritize adequate drug storage.

Adequate storage is a facilitator for good drug use, preventing the use of expired drug products, clear recognition of drug products and thereby minimizing errors or mix-ups, and availability of important drug information in the information leaflet when needed. Improving home storage of drugs requires healthcare professionals to address its relevant determinants. Older patients storing a higher number of drugs store these less adequate. Pharmacists should pay extra attention to the importance of adequate home storage in older patients using multiple drugs, thereby improving home storage conditions, drug quality and facilitating safe use of drugs. In addition to creating more awareness regarding adequate home storage by providing information about drug storage, interventions could promote better storage of drugs. An intervention study aimed to promote adequate drug storage after hospital discharge in older patients showed that having domiciliary visits by the pharmacist can result in better home storage of drugs [22]. Especially those patients with multiple drugs stored in their homes could benefit from a domiciliary visit by the pharmacist or pharmacy

technician with attention for and counselling on adequate drug storage. Our organization scale could be used as a tool to identify disorganization at storage locations for drugs.
The main strength of this study is the assessment of several aspects of home storage of drugs taking into account the quality of storage, information availability and level of storage organization. Older patients were recruited in 44 geographically dispersed pharmacies and home storage characteristics were assessed on site by a trained pharmacist. However, this study was also subject to some limitations. Patients were aware of the study purpose and might have already discarded unused or expired drugs and reorganized their household before the visit. This might have led to an underestimation of the number of patients and drugs that are not stored appropriately. We did not assess if patients were solely responsible for their drug home storage or if they received assistance from their caregiver or partner. Those who have already experienced difficulties with drug storage might have asked for (professional) help or used a multi-dose dispensing system. To limit variation in the amount of information per patient, pharmacists received protocol training and were required to use a standardized inventory list for each drug. No test to assess cognitive functioning was performed. Age associated cognitive decline and incident mild cognitive impairment and dementia are common in older patients [23] and patients with cognitive impairment may already have difficulties storing multiple drugs, possibly interfering with the relation between personality and adequate drug storage. Although the rating of storage locations provides valuable insight in how drugs are stored in patients' homes, its reliability and value needs to be confirmed by others investigators. The limitations mentioned are all likely to increase the type II error rate.

Conclusion

This study suggests that personality is not associated with adequate home storage of drugs in older patients. The majority of patients mentioned daily routines and visual reminders as their main reason considering drug storage locations.

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3.2

Factors associated with (in)adequate storage of tumor necrosis factor – alpha inhibitors in patients' homes

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Abstract

Objective

The aim of this study is to investigate how TNF-α inhibitors are stored in patients' homes and which underlying factors are associated with (in)adequate storage conditions.

Methods

Cross-sectional study performed between December 2016 – December 2017. Patients (aged >18 years) receiving a TNF-α inhibitor from the outpatient pharmacy were included. After giving informed consent, patients were visited once at their home address. An assessment form and a patient questionnaire were used to assess patient knowledge on storage information. Furthermore, patient's storage location characteristics were collected. Storage temperatures were measured for seven days, using a temperature logger, to assess compliance with storage temperature conditions (between 2-8˚C, without periods outside 2-8˚C ≥24 hours). A logistic regression model was used to assess the association between patient characteristics (age, gender, education, household size), storage location characteristics (location in the refrigerator, refrigerator age, density of the refrigerator's packing) and compliance with storage temperature conditions (between 2-8˚C).

Results

70 patients (51.2%) were included in the study (52.9% male, mean age 54.4 [SD 15.2] years). All patients stored their TNF-α inhibitor in the refrigerator. The mean storage temperature in the home refrigerators was 6.3˚C (SD 3.0) and the lowest temperature measured was -7.3˚C in the lower shelf of the refrigerator. About half of the patients (53.3%) stored their TNF-α inhibitor between 2-8˚C. TNF-α inhibitors stored in the lower and middle shelves of the refrigerator were more often stored between 2-8˚C (60.0% of patients) compared to those storing drugs in the upper shelves (38.9% of patients) or the refrigerator door (16.7% of patients). The majority of patients (79.7%) stated that they had received oral and written information about the recommended storage conditions from the pharmacy. Five patients (7.1%) stated they would take their TNF-α out of the refrigerator when there was no space left for their groceries.

Conclusion

More than half of the patients store drugs according to storage recommendations. TNF-α inhibitors kept in the refrigerator door were stored at higher mean temperatures and were more often stored outside 2-8˚C.

Introduction

The introduction of the tumor necrosis factor-alpha (TNF-α) inhibitors have had a large impact on treatment outcomes in patients with immune mediated inflammatory diseases, such as rheumatoid arthritis and Crohn's disease. The first intravenous TNF-α inhibitor that became available on the European market in 1999 was infliximab [1], followed by the first subcutaneous TNF-α inhibitor (etanercept) in 2000 which allowed patients to administer the drug at home [2]. Home administration of these drugs not only increased convenience for the patients due to less hospital visits [3], but also introduced new challenges regarding pharmaceutical patient care. After the medicines have been dispensed from the pharmacy, the responsibility for proper handling and storage is transferred to the patient. The home environment of patients involves storage conditions (e.g. temperature) that are usually less controlled than those applied to storing of medicines in the pharmacy or in the hospital.
Adequate storage of TNF-α inhibitors is important as these consist of large, complex proteins which are generally more susceptible to (quality) changes due to environmental factors than small molecules [4]. In an earlier study we showed that the majority of patients using TNF-α inhibitors do not comply with storage recommendations of the manufacturer ('store between 2-8°C') and around 25% of patients stored these for at least two hours below 0°C [5]. Suboptimal storage conditions could lead to the formation of aggregates which may increase the risk of drug antibody formation [6]. Patients receive information about storage conditions from their pharmacy and this information is also indicated in drug information leaflets and on the drug label. There may be various explanations why storage in patient's home is not in line with the storage conditions recommended by the manufacturer, including insufficient cooling equipment and frequent or accidental opening of the refrigerator door [7]. Consumer refrigerators are generally not equipped to monitor storage temperatures, lack long-term temperature stability and its contents are regularly replaced.
The underlying factors for (non-)compliance with recommended storage conditions remain largely unknown. The aim of this study is to investigate how patients store TNF-α inhibitors and which underlying factors are associated with adequate home storage conditions.

Methods

Setting and study population

A cross-sectional study was performed among adult patients (>17 years) who received a dispensing for either etanercept, adalimumab, golimumab, or certolizumab pegol during December 2016 – December 2017 from the outpatient pharmacy of the University Medical Center in Utrecht (UMCU). The UMCU is one of the largest public health care institutions in the Netherlands [8] and the outpatient pharmacy has over 800 registered users of the aforementioned four TNF-α inhibitors. All eligible patients received detailed information about the study in a patient letter and were contacted by telephone after one week of consideration time. Participating patients were asked for a written informed consent.

Ethics

The Medical Ethics Review Committee of the University Medical Center Utrecht (protocol reference number 16-656/C) judged that the Medical Research Involving Human Subjects Act (WMO) was not applicable to this study. Confidentiality of participants was ensured using anonymized patient codes.

Study procedure

Consenting patients were visited once at their home address by a trained pharmacy master student and were asked to show the location where they store their TNF-α inhibitor(s). Information on storage practices in patients' homes was collected using a structured assessment form for home storage practices (Appendix 1) and a short questionnaire (Appendix 2). The assessment form included detailed questions on storage location and duration of use. In addition, a temperature logger was placed at the storage location and patients received a questionnaire which included questions on socio- and demographic variables and knowledge about drug home storage. Temperature measurements were performed during seven days in the refrigerator. Patients were asked to return the temperature logger and questionnaire using a pre-stamped envelope seven days after the visit.

Storage inventory assessment

Underlying factors that possibly influence storage temperature conditions of TNF-α inhibitors at home were investigated. Factors related to the storage location including equipment and density of refrigerator packing are described in the first section 'storage location characteristics'. Factors related to storage information knowledge of the patient, such as how to store TNF-α inhibitors at home are described in the second section 'storage information knowledge'.

Storage location characteristics

Storage location details were assessed using a structured assessment form and included details on storage location (inside refrigerator yes/no) and if drugs were stored in their primary or secondary packaging. For drugs stored in the refrigerator the following details were assessed: refrigerator type (brand name, freeze compartment presence yes/no), specific location within refrigerator (upper shelves, middle shelves, lower shelves or crisper drawer/door), refrigerator's year of manufacture, and density of the refrigerator's packing. A fully packed refrigerator can increase temperature variation. Photographs were made to assess the level of refrigerator packing, according to standards laid out by Chojnacky *et al.* in 2009: low, medium or high density packing [7]. Low, medium and high density refrigerator packing was defined as follows; low: one or more shelves containing one item or no items; medium: one or more shelves have room left to store at least one item; high: no direct space left to store new items (Figure 1). 'One item' was defined as having at least a volume of 0.5 dm3 (e.g. small bottle soda drink).

Figure 1. Examples of a low density (left pane) packed, medium packed (middle pane) and a high density packed (right pane) fridge.

Storage information knowledge

Storage information knowledge was assessed by questionnaire and included questions on patient knowledge about recommended storage conditions ('I think it is important to store my TNF-α inhibitor according to the product label'), how patients received this knowledge (actively [including oral information] or passively [only written information]) and possible barriers with storage (e.g. 'the drug packages take much space in my refrigerator'). Patients rated how much they agreed on these statements using a five-point Likert scale (0 – strongly disagree to 4 – strongly agree).

Outcome

The main outcome was compliance with storage temperature conditions, defined as drug storage between 2-8˚C, without storage longer than 24 hours consecutive time outside 2-8˚C, with no measurements below 0˚C or above 25˚C longer than two hours (5). Storage temperatures was measured from the time of logger placement in the refrigerator until the return date and time as registered by the patient.

Underlying factors possibly associated with storage

Underlying factors possibly associated with adequate storage temperature conditions included gender, age, household size (alone, ≥2 persons), educational level (low, medium, high), specific location in the refrigerator (lower/middle shelves, upper shelves, door), refrigerator age (<5 years, ≥5 years) and density of the refrigerator's packing (low, medium, high).

Data analysis

Demographic data, temperature measurements and compliance with storage criteria were presented using means (standard deviation [SD]) or in proportions of the study population. Differences in mean temperature were assessed using the student's t test or one-way ANOVA test in case of multiple categories. Uni- and multivariate logistic regression models were used to assess the associations between patient characteristics (gender, age, education, household size) and storage location characteristics (refrigerator location, refrigerator age, density of the refrigerator's packing) and the dependent variable (compliance with storage temperature conditions). A stepwise approach (forward selection), excluding variables with $p>0.2$ in the univariate model, was used to build the final model. Results of the logistic regression models were presented as odds ratios with 95% confidence intervals. To account for frequent fluctuations of storage temperature, a sensitivity analysis was performed where defining adequate storage was based on the proportion of storage time between 2-8°C. Patients with at least 75% of measured storage time between 2-8°C were considered to comply with storage recommendations. All statistical analyses were performed using the statistical packages of SAS version 9.4 (SAS institute, Cary, North Carolina, USA).

Results

In total, 136 patients received a letter with the request to participate in the study. 70 patients (51.2%) were included in the study and were visited at home during the study period and returned a completed questionnaire and temperature loggers. More than half of the patients were male (52.9%), mean age was 54.4 (SD 15.2) years and 18.6% of the patients were living alone (Table 1). Almost half of the patients (45.7%) had a high educational level. The majority of patients (98.6%) were self-responsible for home storage of their medicine and 82.9% of patients had used their TNF- α inhibitors for over two years.

Storage location characteristics

All patients stored their drug in the household refrigerator – one patient using a separate refrigerator solely for drug storage. Twenty-three different refrigerator brands were identified and almost half of the patients (48.6%) had a refrigerator including a freezing compartment. The TNF-α inhibitors were stored in the secondary packaging by 88.6% of patients. Patients most frequently used the lower shelves of the refrigerator to store TNF-α inhibitors (41.4%); the upper shelves, refrigerator door and the middle shelves were less frequently used, by respectively 25.7%, 17.1% and 15.7% of patients (Table 2). Nine patients (12.9%) had a low density packed refrigerator, 32 patients (45.7%) had a medium density packed refrigerator and 14 patients (20.0%) had a high density ('full-packed') refrigerator. Refrigerator packing density could not be assessed for 15 (21.4%) patients.

Table 1. Characteristics of the study population (n=70).

Characteristic	n (%)
Age (Mean, SD) years	54.4 (15.2)
Gender	
Female	33 (47.1)
Educational level*	
Low-Medium	32 (45.7)
High	32 (45.7)
Household size*	
1	13 (18.6)
2	26 (37.1)
≥3	25 (35.7)
Indication	
Crohn's disease	15 (21.4)
Rheumatoid Arthritis	31 (44.3)
Other	24 (34.3)

*do not add up to 100% due to missing values (n=6)

Table 2. Uni- and multivariate logistic regression analysis of patient characteristics, storage characteristics and adequate storage (n=70).

Characteristic	Patients n (%)	Temperature mean ˚C (SD)	Compliant with storage recommendations* n (%)	Univariate analysis Odds ratio (95% CI)	Multivariate analysis Odds ratio (95% CI)
Age					
18-44	24 (34.3)	5.6˚C (2.2)	15 (62.5)	Ref	Ref
45-64	32 (45.7)	7.7˚C (2.6)	11 (34.4)	0.31 (0.10-0.95)	0.31 (0.10-1.02)
≥65	14 (20.0)	6.6˚C (3.2)	7 (50.0)	0.60 (0.16-2.28)	0.91 (0.20-4.01)
Location within refrigerator					
Middle/lower shelves	40 (57.1)	5.7˚C (2.6)	24 (60.0)	Ref	Ref
Upper shelf	18 (25.7)	7.5˚C (2.1)	7 (38.9)	0.30 (0.09-0.97)	0.29 (0.09-1.00)
Door	12 (17.1)	9.2˚C (2.4)	2 (16.7)	0.12 (0.02-0.62)	0.10 (0.02-0.58)

* Storage between 2-8˚C, no longer than 24 hours outside 2-8˚C and no longer than 2 hours below 0˚C or above 25˚C.

Storage information knowledge

72.5% of patients indicated that it was important to store TNF-α inhibitors according to storage conditions as recommended by the manufacturer. The majority of patients (79.7%) stated that they had received oral and written information about the recommended storage conditions from the pharmacy. One patient did not receive information on how to store TNF-α inhibitors at home and six patients (8.6%) could not remember. Twelve patients (17.1%) agreed with the statement that drug packages take much space in the refrigerator. Five (7.1%) patients agreed with the statement that they sometimes removed their drugs from the refrigerator when there is no space available for groceries.

Storage temperature conditions

37 patients (53.3%) stored their TNF-α inhibitor adequately, without storage outside 2-8˚C for longer than 24 hours consecutive time within the seven days observation period. Ten patients (14.5%) stored drugs below 0˚C at least once. One patient stored the drug below 0˚C and passed the two-hour mark, eventually exposing the drug to temperatures below 0˚C for over eleven consecutive hours. Storage above 25˚C was observed in one patient, keeping the drug above 25˚C for over three consecutive hours.

The mean storage temperature in the home refrigerators was 6.3˚C (SD 3.0). The lowest temperature measured was -7.3˚C in the lower shelves of the refrigerator. Refrigerators older than five years had a higher mean temperature (7.4˚C [SD 2.7]; $p<0.01$). The mean temperature in the upper shelves (7.5˚C [SD 2.1]) and the refrigerator door (mean 9.2˚C SD 2.4) were higher ($p<0.01$) compared to the middle shelves (5.6˚C [SD 2.5]) and lower shelves (5.8˚C [SD 2.6]). Low, medium and high packing densities did not have a notable effect on refrigerator temperature.

Associations between storage location characteristics and storage temperature conditions

TNF-α inhibitors stored in the lower and middle shelves of the refrigerator were more often stored between 2-8˚C (60.0% of patients) (Table 2) compared to those storing drugs in the upper shelves (38.9% of patients, adjusted odds ratio 0.29 [95% confidence interval: 0.09-1.00]) or the refrigerator door (16.7% of patients, adjusted odds ratio 0.09 [95% confidence interval: 0.02-0.53]). No associations were found between patient characteristics (gender, age, educational level, household size) or other storage characteristics (refrigerator age, refrigerator packing density) and compliance with storage recommendations. The sensitivity analysis where adequate storage was based on proportion of storage within 2-8˚C did not give different results (35.7% of the patients stored TNF-α inhibitors between 2-8˚C for at least 75% of total storage time).

Discussion

More than half of the patients stored TNF-α inhibitors according to storage temperature recommendations. TNF-α inhibitors kept in the refrigerator door were stored at higher mean temperatures and were more often stored outside 2-8°C. The majority of patients was well informed about proper storage conditions. However, this did not prevent patients exposing TNF-α inhibitors to several unfavorable storage conditions: five patients (7.1%) declared to store TNF-α inhibitors outside the refrigerator when lacking space.

Storage in patients' homes before drug administration is an inevitable part of the drug supply chain. Adequate storage is essential to ensure patients administer a TNF-α inhibitor of expected quality [9]. After dispensing, usually no monitoring of drug storage conditions is performed. Although this study confirms that patients often expose TNF-α inhibitors to temperatures outside 2-8°C [5, 10], there are noteworthy differences with our previous study. More than half of the patients stored between 2-8°C and only one patient stored the drug below 0°C for at least two hours, compared to nearly 25% in the larger study performed in 2015 [5]. This might be due to the short measurement period, taking into account that patients do not continuously expose drugs to temperatures below 0°C, or due to the different definition of adequate storage, allowing patients a longer tolerance period outside 2-8°C (24 hours based on the International Conference on Harmonisation [ICH] guideline on stability testing) [11]. Furthermore, the lowest temperature (-7.3°C) reiterates the large variation consumer refrigerators can have, however, no temperatures reaching -20°C were measured. Refrigerators in this study older than five years had higher mean temperatures but were not more often outside 2-8°C, only partially supporting findings from Cuellar *et al.* [12] that older refrigerators contribute to inadequate storage temperature conditions. Patients seem generally well informed about how to store drugs at home, and all use their refrigerator to provide cool storage and the majority of patients kept the drug in the secondary packaging. However, to prevent extreme low temperatures patients should be recommended to carefully consider the storage location in the refrigerator, possibly by measuring temperature conditions and establishing a dedicated storage location in the refrigerator with the least temperature variation. Patients seem to have no problems with the relatively large secondary packages of some products, only 12% of patients stated that packages of TNF-α inhibitors took much space in the refrigerator. Nevertheless, some patients did take out the TNF-α inhibitors when requiring space in the refrigerator for other items. When expecting a situation when their TNF-α inhibitors would be stored outside the refrigerator (e.g. travelling), the majority of patients anticipated and asked for advice (data not shown). However, when travelling by plane, four patients in our study would carry their TNF-α inhibitors in the check-in luggage, possibly exposing them to extreme low temperatures during the flight [13].

After drug dispensing, the responsibility to provide proper storage for drugs is transferred from the pharmacy to the patient. Pharmacies generally have procedures in place and monitor storage conditions to ensure products are stored according to storage recommenda-

tions. Patient's cooling equipment is important in providing proper storage between 2-8°C. Consumer refrigerators do not provide patients with options to monitor storage conditions, however, pharmacists and patients may reduce temperature variability with simple measures. Pharmacists can perform a pre-check of the storage location at home at treatment initiation. At the first drug dispensing, which is often for a short period (e.g. two weeks), patients may receive the drug's packaging including a logger to measure temperature conditions and allocate a shelf in their refrigerator for drug storage. These measures should be backed by transparent information from drug companies showing reduced shelf life and possible clinical consequences when drugs are stored under aberrant storage conditions. In addition, pharmacists can pay more attention in general as to where patients should specifically place drugs in the refrigerator. Patients should have a dedicated location in the refrigerator for keeping drug packages, preferably at the middle shelves of the refrigerator and not close to the sides, thereby reducing the risk of exposing the drug to large temperature variations. This is, however, dependent on the refrigerator type and quality. Furthermore, there are several commercial options available for patients to continue monitor drug storage and have a notification (e.g. on their smartphone) when the storage location in the refrigerator is too hot or too cold. Third, pharmacies can assist patients giving general tips for good refrigerator use, suggesting not to overpack refrigerators. These measures should preferably be in line with information from drug companies, who can add practical instructions as to how and where their drug should best be placed in the refrigerator.

This study provides valuable insight how patient related factors and how storage locations can influence adequate home storage. The main strength of this study is the evaluation of broad aspects of drug home storage, including temperature measurements, location inventories and patient's level of knowledge concerning drug storage and when confronted with situations outside their home environment. However, this study was also subject to several limitations. First, we had a limited number of patients and were therefore unable to assess the associations between additional storage location characteristics and adequate home storage conditions in a full multivariable regression model. Second, we had only one week of temperature measurements, which does not represent a full prescription period. Furthermore, participants were aware of the study purpose and might have changed storage characteristics before our visit. These limitations might have led to an overestimation of the number of patients who store drugs adequate. In addition, by using a patient questionnaire, patients could be tempted to give socially desirable answers, overstating their awareness and storage information knowledge about adequate drug home storage.

Conclusion

Although the majority of patients store drugs in the refrigerator and are aware of adequate home storage conditions, only half of the patients store drugs according to storage recommendations. Patients can make errors in good home storage practices, thereby exposing TNF-α inhibitors to temperature conditions that compromise drug quality. Drug companies and pharmacists should increase awareness regarding adequate storage temperature conditions and good storage practices in patients' homes.

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Consequences of inadequate drug storage

4

4.1

The impact of inadequate temperature storage conditions on aggregate and particle formation in drugs containing tumor necrosis factor-alpha inhibitors

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Abstract

Objective

To measure aggregate and particle formation in tumor necrosis factor-alpha (TNF-α) inhibitors etanercept, adalimumab and certolizumab pegol product samples after exposure to freezing temperature conditions similar to storage conditions previously observed in patients' homes.

Methods

TNF-α inhibitors in their original primary and secondary packaging were exposed to 32 freeze-thaw cycles (–10˚C for 120min/5˚C for 60 min) or continuous low storage temperature (–20˚C for 96 h) before thawing at 2–8˚C. Non-stressed products were used as controls. The products were analyzed by high pressure size exclusion chromatography (HP-SEC), dynamic light scattering (DLS), nanoparticle tracking analysis (NTA), micro-flow imaging (MFI) and second derivative ultraviolet (UV) spectroscopy.

Results

Ten out of twenty-one stressed product samples (47.6%) showed increased particle numbers in the submicron and micron size range when compared to controls. For each product, DLS, MFI and NTA detected an increase in particle level in at least one stressed syringe (both continuous freezing and freeze-thaw), whereas HP-SEC and UV spectroscopy showed no differences between stressed and non-stressed products.

Conclusion

TNF-α inhibitors are relatively resistant to freezing temperatures similar to storage conditions previously observed in patients' homes. However, almost half of the stressed product samples showed formation of particles in the submicron and micron size range.

Introduction

The introduction of drugs containing tumor necrosis factor-alpha (TNF-α) inhibitors has revolutionized treatments for many inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease [1]. TNF-α inhibitors, and other biologic drugs, differ from the traditional small molecule drugs as these are large complex proteins which are more prone to physical instability processes when exposed to external stress factors such as heat, freeze-thawing and agitation [2]. Due to the specific characteristics of biological drugs, these products need to comply with specific stability test programs and should be assessed regarding their potential immunogenicity [3, 4]. According to the Summary of Product Characteristics documentation of TNF-α inhibitors, it is advised to store these products between 2°C and 8°C, not to expose them to freezing or agitation, and to protect them from light exposure [5,6].

A previous study showed that most patients do not store TNF-α inhibitors within this recommended temperature range; only 7% of patients were able to store TNF-α inhibitors continuously between 2 and 8°C [7]. Almost 25% of patients stored their TNF-α inhibitors below 0°C for 2 h or longer; 5.9% of patients stored their TNF-α inhibitors below 0°C for at least 24 h, with the lowest temperature measured around –20°C. In addition, almost 14% of the patients exposed their TNF-α inhibitors to at least three re-current freeze-thaw cycles with a median duration of almost 4 days. Six patients (2.4%) even exposed their drugs to at least 32 recurrent freeze-thaw cycles [7]. The most common consequence of exposing proteins to freezing temperature conditions is the formation of aggregates [8, 9] which may lead to the development of antidrug antibodies and decreased drug effectiveness, as well as an increased probability of side effects [10, 11].

Experimental data have shown that extreme low temperatures (–80°C) and multiple freeze-thaw cycles can induce formation of antibody aggregates in different non-commercial protein formulations [12, 13]. However, it is unclear if marketed TNF-α inhibitors in their original formulation and primary container will undergo similar structural changes when exposed to less extreme low temperatures or multiple freeze-thaw cycles as observed in consumer refrigerators. The aim of this study was to assess aggregate and particle formation in TNF-α inhibitor product samples when exposed to temperature conditions similar to those observed in patients' homes.

Methods

Materials

The following TNF-α inhibitors were kept in the original primary and secondary packaging and exposed to different temperature conditions as observed in the study by Vlieland *et al.* [7]: adalimumab 40 mg/0.8ml (six product samples Humira® A1-A5), certolizumab pegol 200 mg/ml (six product samples Cimzia® C1-C5), originator/biosimilar etanercept 50 mg/ml

products (seven product samples Enbrel®(originator) E1-E6; six product samples Benepali® (biosimilar) B1-B5 (Table 1). One package of adalimumab and certolizumab pegol contained two product syringes, packages of etanercept (originator and biosimilar) contained four product syringes. The tested TNF-α inhibitors have different characteristics: adalimumab is a human-derived recombinant monoclonal antibody, etanercept is a fusion protein (two TNF-α receptors and a human Fc fragment), certolizumab pegol is a pegylated anti-TNF-α antibody Fab' fragment. We injected all (stressed and control) drug products from the prefilled syringe via the needle through the Teflon lined, pre-slitted screw caps into 1.5 mL sample vials, thereby mimicking as closely as possible a true injection by a patient. Prior to characterization, product samples were prepared with the following corresponding formulation buffers: etanercept: 10mg/ml sucrose, 5.8mg/ml NaCl, 5.3 mg/ml arginine, 3.9 mg/ml $Na_2HPO_4.H_2O$, pH 6.3; adalimumab: 1.3 mg/ml citric acid, 1.5 mg/ml

Table 1. Product samples summary.

Product	Strength	Volume	Lot nr.	Expiry date	Buffer	Control samples	Stressed samples	
Etanercept						2-8°C	Freeze-thaw	Continuous freezing
Enbrel®	50 mg	1.0 ml	N6158 N0062	12/2017 6/2018	10 mg/ml sucrose, 5.8 mg/ml NaCl, 5.3 mg/ml arginine, 3.9 mg/ml $Na_2HPO_4.H_2O$, pH 6.3	1	3 (E1/E2/E3)	3 (E4/E5/E6)
Benepali®	50 mg	1.0 ml	CT0037 CT0026	9/2018		1	3 (B1/B2/B3)	2 (B4/B5)
Adalimumab								
Humira®	40 mg	0.8 ml	61145XD18	12/2017	1.3 mg/ml citric acid, 1.5 mg/ml $Na_2HPO_4.2H_2O$, 0.86 mg/ml $NaH_2PO_4.2H_2O$, 12 mg/ml mannitol, 1 mg/ml polysorbate 80, 6.2 mg/ml NaCl, 0.3 mg/ml sodium citrate, pH 5.2	1	3 (A1/A2/A3)	2 (A4/A5)
Certolizumab Pegol								
Cimzia®	200 mg	1.0 ml	195843	9/2017	0.28 mg/ml (10 mM) sodium acetate, 7.3 mg/ml (125 mM) NaCl, pH 4.7	1	3 (C1/C2/C3)	2 (C4/C5)

$Na_2HPO_4.2H_2O$, 0.86 mg/ml $NaH_2PO_4.2H_2O$, 12 mg/ml mannitol, 1 mg/ml polysorbate 80, 6.2 mg/ml NaCl, 0.3 mg/ml sodium citrate, pH 5.2; certolizumab: 0.28mg/ml (10mM) sodium acetate, 7.3 mg/ml (125 mM) NaCl, pH 4.7.

Applied freezing stress conditions

Temperature conditions were simulated by usage of a Slow Programmable Freezer (Sylab Icecube 1810). This freezer makes use of liquid nitrogen and allows for applying storage temperatures between +5°C and –20°C in a reliable setting with little temperature variation (±0.5°C). TNF-α inhibitors were exposed to temperature conditions based on the lowest continuous temperature and recurrent freeze-thaw cycles observed in patients' homes (Figure 1) and subsequently tested for aggregate and particle formation. In the first stress protocol, three samples from each product (A1-A3; C1-C3; E1-E3; B1-B3) were exposed to multiple freeze-thaw cycles. Products were held at –10°C for 120min and subsequently thawed for 60 min at 5°C. This procedure was performed 32 times for a total exposure time of 96 h. Freezing/thawing speed for both stressing protocols was set to 1°C per minute. In the second stress protocol, samples from each product (A4-A5; C4-C5; B4-B5; E4-E6) were exposed to a continuous low storage temperature (–20°C) for a period of 96 h before thawing at refrigerator temperature (5°C). One sample from each product (stored in a refrigerator between 2°C and 8°C) was used as control. All product samples were stored between 2°C and 8°C before analysis.

Product characterization

The formation of aggregates and particles, and changes in protein conformation was determined by analyzing each stressed and non-stressed product with the methods described below.

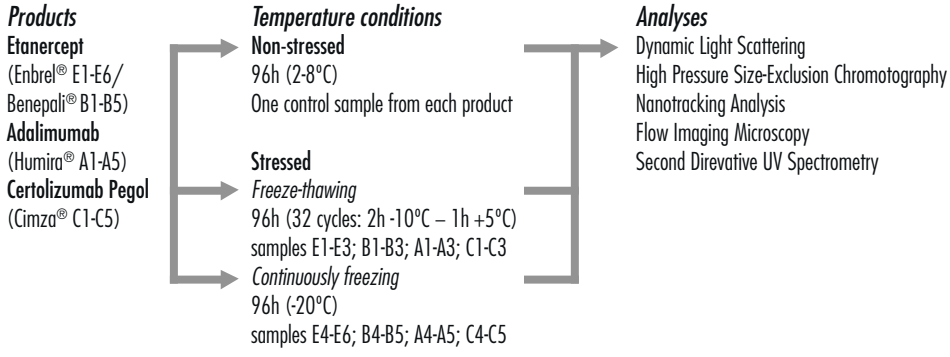

Figure 1. Overview experiments showing four different products, storage conditions and different analyses. h=hours.

Dynamic Light Scattering (DLS)

With DLS aggregates in the size range from about 1 nm to 1 µm can be detected. DLS was performed on a Malvern Zetasizer Nano (Malvern, Herrenberg Germany). 500 µl of the stressed and non-stressed product samples were analyzed in plastic cuvettes at 25°C using the automatic mode for identifying the best number of subruns and measurement time (n = 3). The Z-average diameter and polydispersity index (PdI) were calculated from the correlation function using the Dispersion Technology Software version 7.03 (Malvern, Herrenberg, Germany). All product samples were measured undiluted, except for the certolizumab products, which were diluted 4 fold with 0.28 mg/ml (10 mM) sodium acetate, 7.3 mg/ml (125 mM) NaCl, pH 4.7 due to the high viscosity of the product.

High Pressure Size Exclusion Chromatography (HP-SEC)

With HP-SEC the amount of monomers, dimers and fragments in the products can be detected and quantified. The non-stressed and stressed product samples were analyzed by HP-SEC, using a Yarra 3u SEC-2000 300 × 7.8mm (Phenomenex, Torrance, CA, USA) on an Agilent 1200 chromatography system (Agilent Technologies, Palo Alto, California) combined with a Wyatt Eclipse detector system (Wyatt Technology Europe GmbH, Dernbach, Germany), multi-angle laser light scattering (MALLS) detection with the DAWN® HELEOSTM (Wyatt Technology Europe GmbH) and at a flow rate of 0.5 ml/min. 5 µl of each diluted product sample was injected. All product samples were diluted with formulation buffer to a protein concentration of 1 mg/ml. The mobile phase was composed of 50 mM phosphate, 150 mM arginine and 0.025% NaN_3 at pH 6.5. To quantify aggregation, UV absorption at 280 nm was recorded. From the MALLS signal, the root mean square (rms) diameter was calculated using the Berry Fit in the Astra software version 5.3.2.22 (Wyatt Technology Europe GmbH, Dernbach, Germany).

Nanoparticle Tracking Analysis (NTA)

Particles between 20 and 1000 nm can be detected with NTA. Measurements were performed with a NanoSight LM20, equipped with a sample chamber with a 640-nm laser operating at an angle of 173° with respect to the flow cell. All products were diluted with formulation buffer (Table 1) to a protein concentration of 5 mg/ml. The product samples were injected into the chamber by an automatic pump (Harvard Apparatus, catalog no. 98–4362, Holliston, USA) using a sterile 1-ml syringe (BD Discardit II, Franklin Lakes, New Jersey). For each product a 90 s video was captured with the shutter set at 1495 and the gain at 400. Videos were analyzed by using the NTA 2.0 Build 127 software. The following settings were used for tracking of the particles: background extract on; brightness 0; gain 1.00; blur size 3 × 3; detection threshold 10, viscosity equal to that of water. All other parameters were set to the automatic adjustment mode.

Flow Imaging Microscopy

Micron sized particles up to 25 µm can be detected by MFI. A Micro-Flow Imaging (MFI) system (MFI5200, ProteinSimple, Santa Clara, USA), equipped with a silane coated flow cell (1.41 × 1.76 × 0.1 mm) and controlled by the MFI View System Software version 2, was used for flow imaging microscopy analysis. The system was flushed with 4 ml purified water at 6 ml/min prior to each measurement. The flow cell cleanliness was checked visually between measurements. The background was zeroed by flowing formulation buffer (Table 1) and performing the 'optimize illumination' procedure. 0.3 ml of each product sample (undiluted, only certolizumab pegol was diluted fourfold due to high viscosity) without a pre-run volume because of the limited amount of product was analyzed at a flow rate of 0.17 ml/min and a fixed camera shot rate of 22 flashes per second. The data recorded by the system software was analyzed with MFI View Analysis Suite version 1.2. For each product, stuck, edge, and slow moving particles were removed by the software before data analysis. Because no pre-run volume could be used, the data was recorded from the start of the measurement until the product reached the flow cell. Therefore, data was processed in the time window from 0.7 to 1.7 min, in which the measurement was stable for all products. The equivalent circular diameter (ECD), which is the diameter of a circle that has an area equal to that of the particle imaged by MFI, was calculated and presented as a measure of the particle size (1–100 µm). Numbers of silicone oil droplet-like particles were calculated for each product (only for particles ≥5 um) by visual identification of typical oil droplets, which are round, have a smooth surface and are black with a small whitish spot in the center. In addition, we used the "find similar" procedure in the analysis software to identify particles that have image characteristics similar to those of the selected oil droplet-like particles [14].

Second derivative UV spectroscopy

Second derivative UV spectroscopy was used to detect conformational changes in the products upon stress. Measurements were performed using an Agilent 8453 UV–Vis spectrometer (Agilent Technologies, Waldbronn, Germany) according to the method described earlier (15). The product samples (diluted to 1 mg/ml) were measured in 2 ml half-micro quartz cuvettes (Hellma Benelux, Kruibeke, Belgium) with a path length of 10mm. The absorbance was measured from 240 to 340 nm with intervals of 1 nm using an integration time of 15 s. Background correction was performed with formulation buffer, diluted accordingly in freshly filtered Milli-Q grade water. The second derivatives of the spectra were calculated with UV–Visible ChemStation Software (Agilent Technologies, Walbronn, Germany) using a filter length of 9 nm and a polynomial degree of 4. Thereafter, the second derivatives were splined using 99 data points between the 1-nm measurement points. The vertical distance between the minimum at 283 nm and the maximum at 287 nm is denoted as 'a' and the vertical distance between the minimum and maximum at 290 and 295 nm as 'b' [15]. The ratio a/b is used to determine the exposure of tyrosine residues to bulk solvent, which is sensitive to changes in the tertiary structure.

Results

Temperature stress testing

All products were successfully exposed to the stress protocols mimicking multiple freeze-thaw cycles and continuous freezing temperatures.

Product characterization

Dynamic Light Scattering (DLS)

The Z-average diameter and PdI results for non-stressed and stressed products are summarized in Table 2. Two product samples showed an increase in Z-average and PdI (product sample E3: Z-average 17.48 (SD 0.01)/PdI 0.27 (SD 0.01); product sample B3: Z-average 24.00 (SD 0.03)/PdI 0.27 (SD 0.03) after multiple freeze-thaw stress conditions. In one certolizumab pegol product sample a difference in Z-average and PdI was detected after continuous freezing compared to the non-stressed product C4: Z-average 10.13 (SD 0.02)/ PdI 0.25 (SD 0.02)). Additional peaks in size distribution were detected after both stress conditions; product samples E2, E3, B3 exposed to multiple freeze-thaw stress conditions and product samples E4, C4, C5 exposed to continuous freezing stress conditions show peaks between 4000 nm and 6000 nm.

High Pressure Size Exclusion Chromatography (HP-SEC)

For the non-stressed drug products, monomer content was 97.7% for etanercept (originator), 97.9% for etanercept (biosimilar), 99.5% for adalimumab and 99.6% for certolizumab pegol (Table 2). After both stress test conditions (multiple freeze-thawing and continuous freezing), monomer and dimer content for all drug products did not decrease compared to the non-stressed products (Figure 2). Corresponding molecular weights, based on MALLS data, are presented in Table 2 for the main peak and correspond well with the expected molecular weights for the respective monomeric proteins.

Nanoparticle Tracking Analysis (NTA)

For non-stressed products the following particle concentrations were detected: etanercept (originator) 1.7*108 particles/ml, etanercept (biosimilar) 0.6*108 particles/ml, adalimumab 0.3*108 particles/ml, certolizumab pegol 0.1*108 particles/ml. Two etanercept product samples showed an increase in particle concentration after multiple freeze-thaw cycles (product sample E3: 7.69*108 particles/ml; product sample B1: 9.68*108 particles/ml), which was not observed for the other products exposed to the same stress conditions or continuous freezing. No differences in particle concentrations were measured between non-stressed and stressed (both multiple freeze-thawing and continuous freezing) products of adalimumab and certolizumab pegol (Figure 3). Changes in particle size were detected in etanercept (originator) and etanercept (biosimilar). Mean particle sizes for non-stressed product samples were 259 nm (SD 120) and 294 nm (SD 151), respectively (Table 2). Stressed

samples showed larger mean particle sizes; E4: 335 nm (SD 127), E5: 339 (SD 121), E6: 363 (SD 125), B1: 487 nm (SD 99), B4: 663 nm (SD 345) and B5: 573 nm (SD 261).

Micro Flow Imaging (MFI)

The concentrations of particles ≥2, ≥5, ≥10 and ≥25 μm are shown in Figure 4. Representative images of particles are presented in Figure 5. Non-stressed product sample for etanercept (originator) contained 26,308 particles ≥2 μm/ml and non-stressed product samples etanercept (biosimilar), adalimumab and certolizumab pegol contained respectively 18,168, 5193 and 17,640 particles/ml sized 2 μm or larger. Differences in particle concentrations were observed in etanercept products exposed to multiple freeze-thaw stress conditions: etanercept originator (product sample E3) and etanercept biosimilar (product sample B3). Certolizumab pegol products showed an increased particle concentration (C1, C2) after freeze-thaw stress conditions. Continuous freezing stress conditions also led to an increase in numbers of particles sized ≥2 μm in the following product samples: etanercept E4, E5, E6, B4, adalimumab product sample A5, certolizumab pegol product samples C4, C5.
Besides analyzing the total particle numbers, we used the "find similar" procedure of the MFI software to elucidate whether the increased particle numbers were due to silicone oil droplets, which could be released from the surface of the primary packaging materials, or to proteinaceous particles, or both. This distinction can be made for particles ≥5 μm based on morphological differences between silicone oil droplets and protein aggregates [14]. The results indicated that product samples (E4, E5, E6, B3, B4, A5) contained increased numbers of both silicone oil droplets and other, most likely proteinaceous particles. The percentage of silicone oil droplet-like particles in these product samples varied between 46% and 69% (for particles ≥5 μm; results not shown).

UV Spectroscopy

The a/b ratios for non-stressed etanercept (originator), etanercept (biosimilar), adalimumab and certolizumab pegol products were 0.96, 0.96, 1.48 and 2.64, respectively (Table 1). No changes in a/b ratios between stressed (multiple freeze-thawing and continuous freezing) and non-stressed product samples were detected. Moreover, the peak positions for non-stressed product samples compared to stressed product samples (both multiple freeze-thawing and continuous freezing) were similar (results not shown).

Results summary

A summary of the results of all analytical methods used to detect and characterize aggregates and particles formed in the different stressed products is shown in Table 3. In at least one sample of the four different products tested, to some extent more particles were detected compared to the non-stressed sample. Particles in the submicron and micron size range were detected in ten of the twenty-one TNF-α inhibitor product samples (47.6%), six product samples upon exposure to multiple freeze-thawing and four product samples after exposure to continuous freezing conditions. With HP-SEC and UV spectroscopy no differ-

Table 2. Second-derivative UV spectroscopy, DLS, NTA and HP-SEC results for etanercept (originator and biosimilar), adalimumab and certolizumab pegol drug products under non-stress conditions (2-8°C), freeze-thawing and continuous freezing stress conditions.

Etanercept (originator)								
		Non-stressed 2-8°C	Stressed (E1|E2|E3) 96h FT -10°C/5°C			Stressed (E4|E5|E6) 96h -20°C		
DLS	Z-average in nm (SD)	14.80 (0.01)	15.11 (0.00)	15.54 (0.01)	17.48 (0.01)	15.26 (0.01)	14.56 (0.00)	15.61 (0.02)
	PdI (SD)	0.11 (0.01)	0.09 (0.00)	0.14 (0.01)	0.27 (0.01)	0.01 (0.01)	0.00 (0.00)	0.02 (0.02)
HP-SEC	Monomer (%)	97.7	97.6	97.5	97.6	97.5	97.4	97.3
	Dimer (%)	2.3	2.4	2.5	2.4	2.5	2.6	2.7
	Molecular weight (Da) Monomer	1.3*105	1.3*105	1.3*105	1.3*105	1.3*105	1.3*105	1.3*105
NTA (size estimation)	Mean in nm (SD)	259 (120)	181 (116)	203 (104)	246 (118)	335 (127)	339 (121)	363 (125)
UV spectroscopy	a/b ratio	0.96	0.96	0.96	0.96	0.97	0.93	0.96
Etanercept (biosimilar)								
		Non-stressed 2-8°C	Stressed (B1|B2|B3) 96h FT -10°C/5°C			Stressed (B4|B5) 96h -20°C		
DLS	Z-average in nm (SD)	14.82 (0.01)	15.05 (0.01)	14.80 (0.01)	24.00 (0.03)	14.80 (0.01)	14.91 (0.01)	
	PdI (SD)	0.06 (0.01)	0.09 (0.01)	0.05 (0.01)	0.27 (0.03)	0.08 (0.01)	0.07 (0.01)	
HP-SEC	Monomer (%)	97.9	97.9	97.9	97.4	97.9	98.0	
	Dimer (%)	2.1	2.1	2.1	2.6	2.1	2.0	
	Molecular weight (Da) Monomer	1.3*105	1.3*105	1.3*105	1.3*105	1.3*105	1.3*105	
NTA (size estimation)	Mean in nm (SD)	294 (151)	487 (99)	164 (86)	252 (119)	663 (345)	573 (261)	
UV spectroscopy	a/b ratio	0.96	0.95	0.96	0.96	0.96	0.97	

Table 2 – Continued. Second-derivative UV spectroscopy, DLS, NTA and HP-SEC results for etanercept (originator and biosimilar), adalimumab and certolizumab pegol drug products under non-stress conditions (2-8°C), freeze-thawing and continuous freezing stress conditions.

Adalimumab							
		Non-stressed 2-8°C	Stressed (A1|A2|A2) 96h FT -10°C/5°C			Stressed (A4|A5) 96h -20°C	
DLS	Z-average in nm (SD)	16.28 (0.01)	16.07 (0.01)	15.25 (0.01)	15.82 (0.01)	15.48 (0.01)	15.51 (0.01)
	PdI (SD)	0.03 (0.01)	0.04 (0.01)	0.02 (0.01)	0.03 (0.01)	0.03 (0.01)	0.03 (0.01)
HP-SEC	Monomer (%)	99.5	99.7	99.8	99.8	99.8	99.8
	Dimer (%)	0.5	0.3	0.2	0.2	0.2	0.2
	Molecular weight (Da) Monomer	1.6*105	1.4*105	1.4*105	1.4*105	1.5*105	1.5*105
NTA (size estimation)	Mean in nm (SD)	328 (172)	252 (129)	205 (62)	281 (151)	246 (97)	325 (151)
UV spectroscopy	a/b ratio	1.48	1.48	1.47	1.48	1.48	1.47
Certolizumab pegol							
		Non-stressed 2-8°C	Stressed (C1|C2|C3) 96h FT -10°C/5°C			Stressed (C4|C5) 96h -20°C	
DLS	Z-average in nm (SD)	8.72 (0.01)	8.68 (0.02)	8.81 (0.00)	8.39 (0.01)	10.13 (0.02)	8.70 (0.01)
	PdI (SD)	0.10 (0.02)	0.10 (0.02)	0.11 (0.00)	0.08 (0.01)	0.25 (0.02)	0.21 (0.01)
HP-SEC	Monomer (%)	99.6	99.6	99.6	99.6	99.6	99.6
	Dimer (%)	0.4	0.4	0.4	0.4	0.4	0.4
	Molecular weight (Da) Monomer	5.7*104	5.0*104	5.0*104	5.0*104	5.8*104	5.8*104
NTA (size estimation)	Mean in nm (SD)	527 (176)	304 (122)	398 (137)	335 (162)	415 (177)	455 (240)
UV spectroscopy	a/b ratio	2.64	2.65	2.65	2.65	2.63	2.65

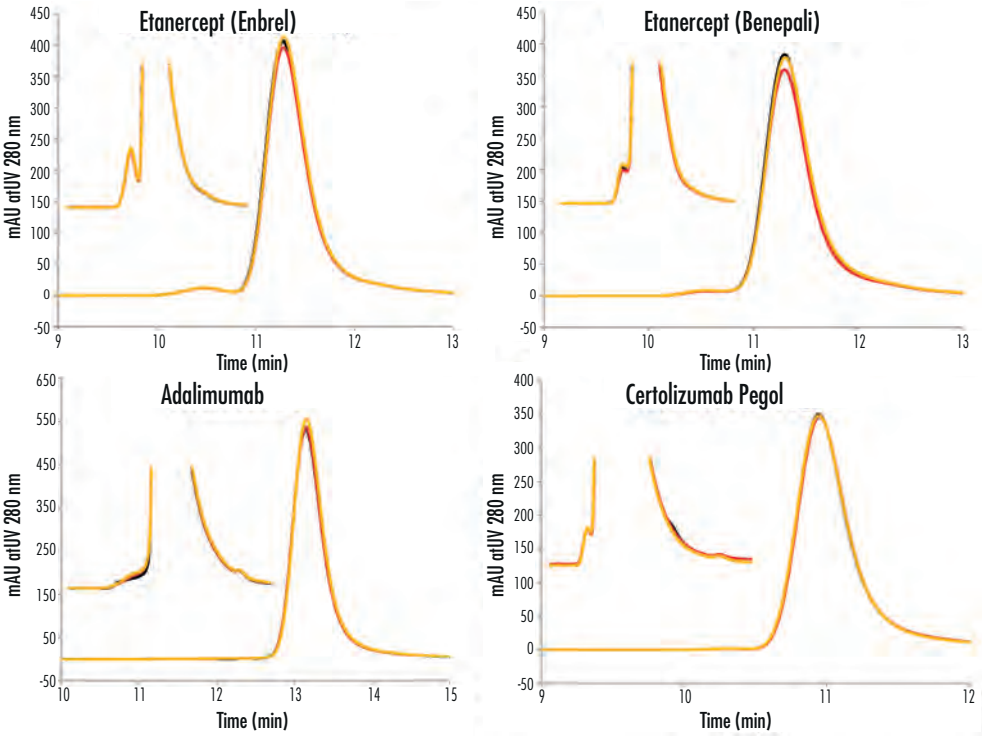

Figure 2. HP-SEC chromatograms. UV detection was performed at 280 nm. Graphs show controls versus two freezing stressed product samples. Black lines represent non-stressed product samples, red lines represent product samples exposed to freeze-thawing and orange lines represent product samples exposed to continue freezing stress conditions.

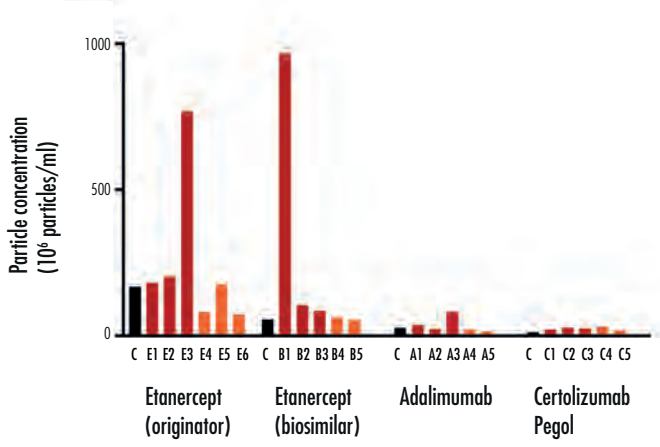

Figure 3. Nanoparticle tracking analysis (NTA). Black bars represent particle concentrations in non-stressed products (C=control sample). Red bars represent particle concentrations in products exposed to freeze-thaw stress conditions, Orange bars represent particle concentrations in products that were exposed to continuous freeze conditions.

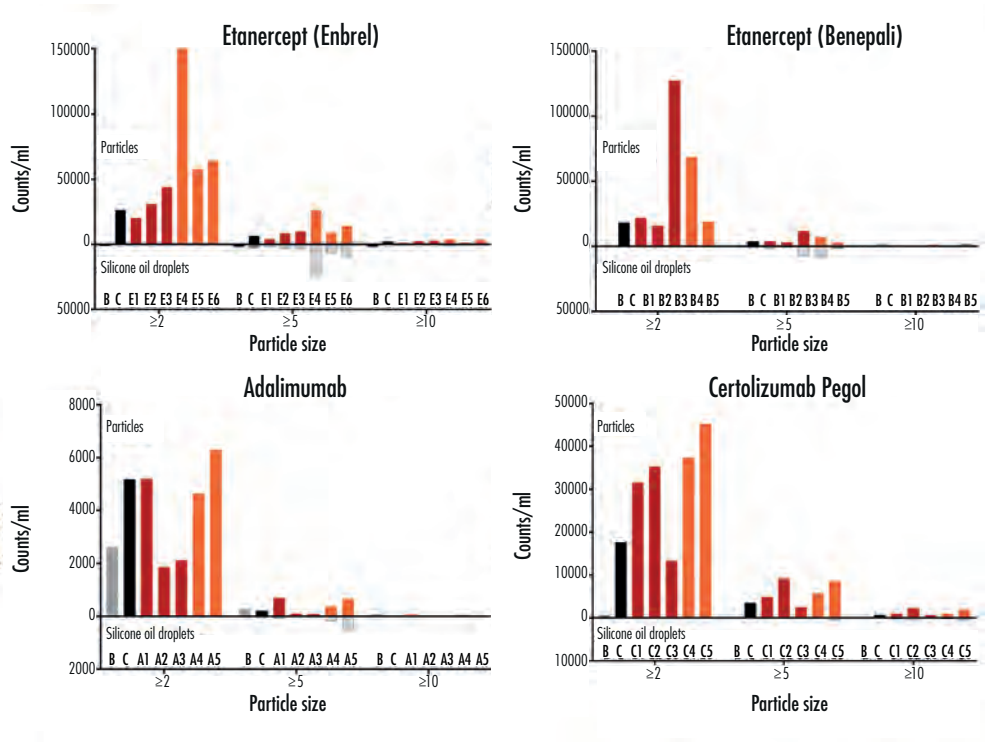

Figure 4. MFI results. Grey and black bars represent particle counts in buffer (b) and control products (c), respectively. Red bars represent particle counts products exposed to freeze-thaw stress conditions, orange bars represent particle counts in products that were exposed to continuous freeze conditions. Silicone oil droplet counts in different products are represented for particles ≥5 µm by light grey bars in the opposite direction.

ences in aggregate formation were detected between stressed (both multiple freeze-thawing and continuous freezing) and non-stressed products. With DLS, differences in aggregate level between one product sample exposed to multiple freeze-thawing and the non-stressed product sample were detected in etanercept originator and biosimilar products. After continuous freezing stress conditions, two etanercept (originator and biosimilar) product samples and certolizumab pegol product sample showed a higher Z-average compared to the non-stressed product. NTA testing showed differences in particle concentration in two stressed etanercept product samples (one originator/one biosimilar) upon freeze-thaw stress conditions compared to the non-stressed products. This result corresponds partially with DLS, for etanercept (originator) product sample E3, where both methods detect increased aggregate levels. Larger particles (>1 µm) were also detected with MFI: etanercept (originator and biosimilar) and certolizumab pegol showed an increased number of particles after freeze-thaw stress conditions. After continuous freezing stress conditions, in at least one product of etanercept (originator/biosimilar), adalimumab and certolizumab pegol an increase in the number of large particles was detected.

Table 3. Overview of product characterization experiments, freezing stress conditions and product samples in which aggregates were detected.

Detection technique	Detection range	Etanercept (originator)		Etanercept (biosimilar)		Adalimumab		Certolizumab pegol	
		96h FT -10°C/5°C	96h -20°C	96h FT -10°C/5°C	96h -20°C	96h FT -10°C/5°C	96h -20°C	96h FT -10°C/5°C	96h -20°C
DLS	Size range: <1 µm	+	0	+	0	0	0	0	+
HP-SEC	Relative amount mono-/dimer/ fragments	0	0	0	0	0	0	0	0
NTA	Size range: <1 µm	+	0	+	0	0	0	0	0
MFI	Size range: >2 µm	+	+	+	+	0	+	+	++
UV spectro-scopy	Structural changes	0	0	0	0	0	0	0	0

FT=Products exposed to freeze-thaw stress (96h); CF=Products exposed to continue freeze stress (96h); 0=no differences in aggregate/ particle level in stressed *vs* unstressed products; +=higher aggregate/particle levels in at least 1 stressed *vs* unstressed product; ++=higher aggregate levels in stressed *vs* unstressed products.

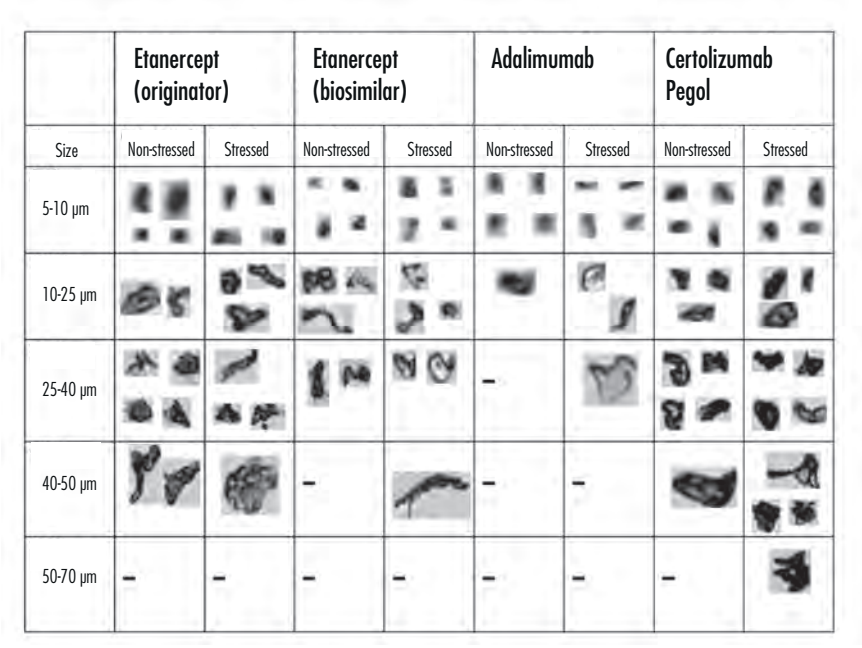

Figure 5. MFI results. Examples of MFI images for all products tested, stressed and non-stressed. Particle size ranges are shown in equivalent circular diameter (ECD). (–)=no particles in size range detected.

Discussion

This study shows that temperature conditions similar to those that occur in patients' homes have minor impact on the level of aggregates and particles in product samples of etanercept (Enbrel® and Benepali®), adalimumab (Humira®) and certolizumab pegol (Cimzia®). Nevertheless, products exposed to these temperature conditions contained more particles in the submicron and micron size range. Almost half of the product samples which were exposed to multiple freezing stress conditions (47.6%; six freeze-thawing and four continuous freezing) showed larger numbers of subvisible particles (>1 μm) compared to non-stressed products.
Our results are qualitatively in line with other studies investigating the formation of aggregates in IgG antibody formulations after exposure to freezing stress conditions, which describe the formation of few aggregates >1 μm [13, 16]. Although others have observed changes in monomer/dimer/oligomer content with HP-SEC and conformational changes with UV spectroscopy [12, 17], we did not find such changes after exposing TNF-α inhibitors to freezing stress conditions. Moreover, not all product samples showed elevated particle levels. For those product samples that did show elevated particle levels by NTA and/or MFI, HP-SEC results indicate that these particles corresponded to a minute fraction of the total amount of protein. This low level of protein aggregation may be due to the fact that in the current study we used marketed products in their original formulation and primary container, whereas the cited studies were done on non-commercial IgG molecules. Moreover, the stress conditions applied in our study were relatively mild when compared to the other studies. With DLS, three product samples (E3, B3, C4) showed an increase in aggregate level after freezing stress conditions. These results were partially in line with the NTA data, showing the formation of particles in one etanercept sample (E3) after multiple freeze-thawing, but not for etanercept (biosimilar) samples and certolizumab pegol. MFI data showed the formation of large aggregates (>1 μm) in at least one sample of all products after both stress conditions (E3, E4, B3, B4, A5, C1, C2, C4, C5), except for adalimumab upon multiple freeze-thawing. In addition, an increase in the number of silicone oil droplets was detected with MFI in some product samples (E4, E5, E6, B3, B4, A5) with the percentages of silicone oil droplets ranging between 46 and 69% [14].
Freeze-thawing has been described as having a smaller impact on the stability of biologics compared to heating or agitation and shows the formation of only few aggregates in the micron and submicron size range [12]. Our observations confirm other findings suggesting that the level of aggregation upon freeze-thaw stress is generally low with particles in the low micron-size range as main degradation product [12, 17-19]. In this study products were exposed to two stress conditions: multiple freeze-thawing and continuous freezing. Although one would expect that multiple freeze-thawing cycles would have more impact than continuous freezing stress, we did not observe such an effect. Subjecting products to continuous low temperatures might increase ice crystal formation or ice texture changes in some of the products, thereby increasing aggregation [20].
In theory, exposing products to inadequate storage conditions as previously reported could

induce the formation of aggregates which could lead to the development of antidrug antibodies and might subsequently affect treatment outcome [10]. Although recent studies have shown that home storage conditions for TNF-α inhibitors are often not adequate [7], there is no evidence that this has resulted in the development of antidrug antibodies or has had other clinical consequences for patients. The relation between inadequate storage, protein aggregation and immunogenicity has not been investigated in humans due to ethical reasons, but a number of experiments in animal models have shown that the amount, size, and nature of aggregates to a certain extent determines the immunogenic potential of a protein drug [10, 19]. A recent post marketing study on peginesatide (an erythropoiesis-stimulating agent) in relation to the occurrence of severe adverse events (49 cases of anaphylaxis, including 7 fatalities) linked these events to a higher concentration of subvisible particles [21]. A prospective study would be needed to investigate the complex relation between storage conditions of TNF-α inhibitors, aggregate formation, immunogenicity and therapy outcomes.
In this study, there were limitations concerning the number of different TNF-α inhibitor products and the number of samples from each product that could be tested. The availability of more samples and products for testing might have enabled us to get a better and more reliable assessment of aggregation risk for different biological drugs that are not stored according to label instructions. We only stressed products for 96 h, whereas patients store products in their refrigerator for up to three months. This difference might have resulted in an underestimation of the number of products that contained aggregates after freezing stress conditions. Extending the stress period would give a better estimation how TNF-α inhibitor products can change during home storage. In addition, we did not assess other important stress conditions that TNF-α inhibitors may be exposed to during transport and long storage periods, such as agitation and light exposure. Exposure to conditions outside the recommended storage conditions might also affect container closure integrity of the drug product, which can have impact on its stability and sterility. As this is one of the first studies in its kind, more research is required in order to investigate the consequences of inadequate storage for product quality and its effect on immunogenicity and clinical response on treatment with TNF-α inhibitors.

Conclusion

The studied TNF-α inhibitors remain relatively stable with regard to the number of aggregates and particles when exposed to temperature storage conditions seen at patients' homes. However, aggregation as a result of freezing stress conditions appears to be probabilistic, as we detected subvisible particles (>1 μm) in almost half of the product samples. Low temperatures (–20°C) and multiple freeze-thaw cycles as observed in consumer refrigerators can induce the formation of few aggregates in different TNF-α inhibitor products.

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4.2

Methodological considerations to assess the impact of storage conditions of biologic disease-modifying antirheumatic drugs on clinical outcomes in patients with rheumatoid arthritis

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Submitted for publication

Abstract

Objective

To evaluate methodological aspects for (1) categorization of storage conditions, and (2) the time relationship in studying the relationship between home storage conditions of biologic disease-modifying antirheumatic drugs (bDMARDs) and clinical outcomes in rheumatoid arthritis patients.

Methods

Drug storage conditions and disease activity between January 2014 – January 2015 were collected from consenting adult patients with rheumatoid arthritis using a bDMARD. Home storage temperature conditions were continuously monitored. Each month of follow up was categorized as adequate or inadequate storage, according two different definitions: (1) less than 70% of time in that month the drug was stored between 2-8˚C and (2) more than 2 hours in that month the drug was stored below 0˚C. For each patient, the follow-up was divided into active disease periods and non-active disease periods. The time relationship between storage conditions and disease activity was defined in two different ways. In the direct effect time scenario, storage conditions at the start of each (non-)active disease episode was used for the analysis. In the delayed effect time scenario, storage conditions from all previous months were used. For each of the four combinations of storage condition categorization and time relationship, the strength of the association between inadequate storage and disease activity was evaluated with logistic regression analysis and expressed as odds ratios (OR) with corresponding 95% confidence intervals.

Results

The mean age of the 33 included patients was 60.1 years (SD 9.6) and more than half were female (54.5%). The average follow-up time was 12 months (range 1 – 13). Eleven patients (33.3%) had one or more active disease periods with a median (IQR) duration of 57 (217) days. 29 patients (87.9%) stored drugs inadequately based on defining inadequate storage as <70% of storage time between 2-8˚C while fifteen patients (45.5%) stored their bDMARD inadequate when using the definition below 0˚C for two hours at least once during follow up. The odds of having an active disease period when storing drugs inadequately (<70% between 2-8˚C) were 0.33; 95% CI: 0.08-1.48 (direct effect) and 0.35; 95% CI: 0.09-1.45 (delayed effect). Odds ratios for the association between inadequate storage as temperature below 0˚C for at least two hours and disease activity could not be calculated as there were zero active disease periods preceded by inadequate storage for both the direct effect and delayed effect time scenarios.

Conclusion
In conclusion, different categorizations for storage conditions greatly influences the number of inadequate storage periods. Although this study did not allow for measuring the impact of inadequate storage categorizations on clinical outcomes, applying different time relationships seems to have a minimal effect on risk estimates. This study shows the methodological complexity when investigating the relationship between storage condition and clinical outcomes.

Introduction

New drugs have extensively been tested in the laboratory setting as well as studied in humans to give patients access to treatments that are likely to have a positive benefit-risk balance [1]. Drug storage according to the product label, which is a reflection of stability studies under various temperature and humidity conditions, is important to guarantee drug product quality during the period of transport, storage and use up to the expiry date. All parties have to follow strict guidelines for Good Distribution Practice (GDP) for drug storage during the entire pharmaceutical supply chain up to dispensing by the pharmacy [2]. After dispensing, the patient becomes responsible for drug storage. Several studies have shown that most patients do not always adequately store their drugs at home [3-6]. The impact of inadequate storage on clinical outcomes is largely unknown. For example, it has been shown that when a container of latanoprost – a prostaglandin analogue used for the treatment of glaucoma – is stored in the sunlight, it could degrade by at least 10% in one afternoon [7]. A small study investigating latanoprost stored in the refrigerator (4°C) and at room temperature (30°C) in healthy volunteers did not find reduced ocular antihypotensive effect in those that received latanoprost stored at 30°C [8]. However, this study did not include an analysis of the level of degradation for drugs stored at these conditions.
In a previous study we showed that the majority of patients do not store biologic disease modifying antirheumatic drugs (bDMARDs) according to the temperature recommendations (store between 2-8°C and not below 0°C) [5]. The vast majority (93.3%) of patients stored bDMARDs outside the recommended 2-8°C for more than 40% of total storage time and around 25% of patients stored these below 0°C for at least two hours. Protein drugs such as bDMARDS are generally more sensitive to temperature changes, light exposure and agitation than classic small molecule drugs [9]. We showed that freezing can lead to formation of protein aggregates in the bDMARD products [10]. It has been suggested that such protein aggregates could induce the formation of antibodies in the patient and thereby lead to a decreased clinical efficacy. It is, however, unknown what the relationship is between inadequate storage, the formation of protein aggregates in the drug product in vitro and a potential clinical effect and detection thereof in vivo. Also, the time relationship

is unknown; inadequate storage might directly lead to a clinical effect or a delayed clinical effect might occur.
Thus, it is unknown how different inadequate storage conditions might impact clinical outcomes. In addition, it is unknown if a direct or delayed clinical effect will occur. Therefore, we aimed in this study to evaluate methodological aspects for [1] categorization of storage conditions and [2] the time relationship between storage of disease-modifying antirheumatic drugs and clinical outcomes in rheumatoid arthritis patients.

Methods

Setting and study population

A selection of patients who participated in a longitudinal multicenter study that assessed whether patients on bDMARDs store their drugs according to manufacturers' Summary of Product Characteristics (SmPC) recommendations (i.e. 'store between 2-8°C' and 'do not freeze') was included. The longitudinal study has been described in detail elsewhere [5]. In short, home storage temperature of patients using bDMARDs was measured continuously using temperature loggers that were included with each dispensing [11]. Patients were included in the present study when they had rheumatoid arthritis (RA) according to the ACR/EULAR 2010 criteria [12] and were treated at the Sint Maartenskliniek. Patients with other immune mediated inflammatory diseases, such as spondylarthropathies, were excluded. The Sint Maartenskliniek is a specialized hospital for rheumatology, orthopedics and rehabilitation in Nijmegen, The Netherlands. Informed consent was obtained from each patient prior to participation.
Patients were included in the study during January 2014 – February 2014 and each patient was followed up until 31 January 2015. Home storage temperature was assessed for each month of follow-up. Clinical information of the included patients was retrieved from medical file. This included data on disease activity (active disease or non-active disease), switch of bDMARD or (temporary) stop, dosage adjustments and adding of comedication. Healthcare professionals in the Sint Maartenskliniek systematically document disease activity and clinically relevant events in the patient medical file system according to treatment protocols, which enabled us to collect reliable retrospective data. Information on dispensed medication was retrieved from the outpatient pharmacy information system of the Sint Maartenskliniek.

Clinical outcomes

For each patient, the follow-up was divided into active disease periods and periods of non-active disease (Figure 1). Start of an active disease period was defined as the first sign of active disease according to the patient medical file. Periods of active disease were characterized by at least one of the following disease related events: disease flare (an increase of Disease Activity Score (DAS28) of at least 0.6) [13], dose escalation of the bDMARD, addition of

flare related co-medication (corticosteroids and/or non-steroidal anti-inflammatory drugs [NSAIDs]) and switching or discontinuation of a bDMARD. If patients already had an active disease period that had started prior to the date of inclusion in the study, the active disease period was set to begin at the month of inclusion. The end of each active disease period was defined as the first mention of non-active disease in the patient medical file. When non-active disease was not reached before the end of follow-up, data was censured on January 31st, 2015. Patients switching to a bDMARD not intended for home administration thus lacking home storage temperature measurements (e.g. infliximab requires intravenous administration) or patients discontinuing their treatment with the bDMARD were censured after switching/discontinuation.

Categorization of storage conditions

Each month was categorized as adequate or inadequate home storage using two definitions based on our previous longitudinal study. According to the first definition, home storage was categorized as inadequate when less than 70% of storage time in that month was between 2-8°C. According to the second definition, home storage was categorized as inadequate when bDMARDs were stored below 0°C two hours or more in that month.

Time relationship

To investigate the time relationship between storage conditions and clinical outcomes, time relationship scenarios representing a hypothetical direct and delayed association between storage and the clinical outcome (Figure 1) were used. According to the direct effect time scenario, storage conditions were assessed in the period up to one month before the period of (non-)active disease. According to the delayed effect time scenario, the whole period before a period of (non-)active disease was assessed. This definition was based on the assumption that inadequate storage at any moment prior to an (non-)active disease period would contribute to a clinical outcome.

Data analysis

Demographic data, temperature measurements and compliance with storage criteria were presented using means (standard deviation [SD]), medians (interquartile range [IQR]) or in proportions of the study population. In the direct effect time scenario, storage conditions were assessed at the start of each (non-)active disease episode (T_n). In the 'delayed effect' time scenario, all previous months of storage temperatures prior to the start of an (non-) active disease period (T_n) were assessed (Figure 1). For each of the four scenario combinations of storage categorization and time relationship, the strength of the association between inadequate storage and disease activity was evaluated with logistic regression and presented as odds ratios (OR) with 95% confidence intervals. The data was analyzed with the statistical package from SAS version 9.4 (SAS Institute, Cary, North Carolina, USA).

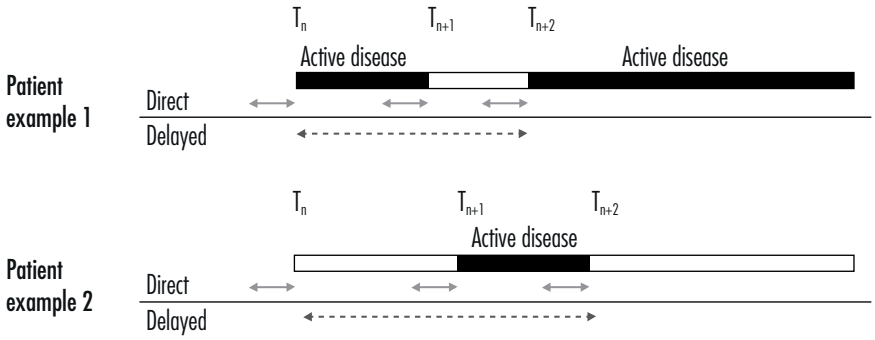

Figure 1. Active and non-active disease episodes of patients and time relationship scenarios. Black indicates a period of active disease and white boxes indicate periods of non-active disease. Solid arrows indicate home storage measurement period of a direct effect, dashed arrows indicate home storage measurement periods for a delayed effect. T_n: start of a (non-)active disease episode.

Results

The mean age of the 33 included patients was 60.1 years (SD 9.6) and more than half were female (54.5%). At baseline, the majority of patients used etanercept (63.6%) or adalimumab (33.3%). During the study period, three patients (9.1%) switched to another subcutaneous bDMARD. Ten patients (30.3%) had been using their bDMARD for less than one year prior to entering the study and 22 patients (66.7%) were treated with their first bDMARD. Storage temperature measurements were measured during 260 months and the mean duration of temperature measurements per patient was 7.9 (SD 2.5) months. The mean disease activity follow-up time for each patient was 12 months (range 1 – 13). In total, 45 periods of active disease and non-active disease were identified in eleven patients (33%). The duration of an active disease period had a median duration of 57 (IQR 217) days. All patients had non-active disease at January 31st 2015.

Impact of the categorization of storage conditions

29 patients (87.9%) stored drugs inadequately at least one month based on defining inadequate storage as <70% of storage time between 2-8˚C. The total number of months inadequately stored according to this definition was 149 (57.3%). Considering the other definition of inadequate storage (below 0˚C for at least two hours), fifteen patients (45.5%) stored their bDMARD inadequate at least once during follow up. The total number of months of inadequate storage according to this definition was 27 (10.4%).

Table 1. Methodological considerations for storage conditions and direct/delayed clinical effect presented in four different scenarios.

Scenario 1A -Inadequate storage <70% between 2-8°C -Direct effect				Scenario 1B -Inadequate storage <70% between 2-8°C -Delayed effect			
Storage	Disease n(%)			Storage	Disease n(%)		
	Active	Non-active	Total		Active	Non-active	Total
Adequate	8 (72.7)	16 (47.1)	24 (53.3)	Adequate	7 (63.6)	13 (38.2)	20 (44.4)
Inadequate	3 (27.3)	18 (52.9)	21 (46.7)	Inadequate	4 (36.4)	21 (61.8)	25 (55.6)
Total	11 (100.0)	34 (100.0)	45 (100.0)	Total	11 (100.0)	34 (100.0)	45 (100.0)
Scenario 2A -Inadequate storage 2 hours below 0°C -Direct effect				**Scenario 2B -Inadequate storage 2 hours below 0°C -Delayed effect**			
Storage	Disease n(%)			Storage	Disease n(%)		
	Active	Non-active	Total		Active	Non-active	Total
Adequate	11 (100.0)	31 (91.2)	42 (100.0)	Adequate	11 (100.0)	29 (85.3)	40 (88.9)
Inadequate	0 (0.0)	3 (8.8)	3 (100.0)	Inadequate	0 (0.0)	5 (14.7)	5 (11.1)
Total	11 (100.0)	34 (100.0)	45 (100.0)	Total	11 (100.0)	34 (100.0)	45 (100.0)

Impact of the definitions of time relationship scenarios

When using the definition of inadequate storage <70% between 2-8˚C, three (27.3%) active disease periods were directly preceded by a month of inadequate storage (Table 1 – scenario 1A). The odds of having an active disease period when considering inadequate storage as storing the bDMARD for less than 70% of the time between 2-8˚C in the direct time scenario was 0.33; (95% CI: 0.08-1.48). When using the same definition of inadequate storage <70% between 2-8˚C but for the delayed effect scenario, four (36.4%) active disease periods were preceded by inadequate storage (Table 1 – scenario 1B). The odds were similar, 0.35; 95% CI: 0.09-1.45, when assessing inadequate storage during in the delayed time scenario. When using the second definition of inadequate storage (below 0˚C ≥2 hours), the direct and delayed time scenarios did not show any active disease period preceded by inadequate storage (Table 1 – scenario 2A/2B). Therefore, odds ratios for the association between inadequate storage and disease activity could not be calculated.

Discussion

This study assessed methodological considerations to assess the hypothetical association between home storage conditions and clinical outcomes. To this end, different categorizations of inadequate storage as well as applying two types of time scenarios – direct or delayed – between inadequate storage and the onset of a clinical event were considered. When the

first categorization of inadequate storage (<70% time between 2-8˚C) was used, similar estimates of the association between inadequate storage and active disease were found for the direct and delayed effect time scenarios. These findings do not support the view that inadequate storage is associated with reduced drug efficacy. Our findings show differences between two definitions used for inadequate storage. When defining inadequate storage as less than 70% between 2-8˚C, almost 60% of storage time was inadequate. However, when storage was defined as below 0˚C for at least two hours, only 10% of storage time was considered inadequate.

In the published literature, there is a lack of scientific data on the clinical implications of inadequate storage of drugs and the mechanisms by which storage conditions affect drug product quality and possible clinical consequences are poorly understood. This might be partially caused by the methodological and ethical complexity of research of this topic. First of all, information about home storage of drugs is rarely available. Secondly, information about the magnitude of quality defects required to induce (if any) a clinical effect is unavailable. Thirdly, the time relationship – direct or delayed – of possible clinical outcomes after inadequate storage is unknown. In order to be able to reliably estimate the influence of inadequate storage on clinical outcomes, data on both the inadequate storing conditions that impact the drug product are needed (duration and severity of exposure), the relevant product changes that occur due to inadequate storage and the type and timeliness of the clinical events that are considered to indicate impact of inadequate storage. The methodological choices to be made when investigating the relation between drug storage and clinical outcomes are dependent on the type of drug and severity of inadequate storage. Our definitions of inadequate storage are not based on evidence how storage temperatures affect different product quality attributes (i.e. changes in monomer content, level of aggregation) but solely based on storage recommendations ('store between 2-8˚C' and 'do not freeze') on the bDMARD product label. Our definitions for inadequate storage might have poorly represented an actual significant reduction in product quality. These definitions should ideally be based on drug stability studies including stress testing considering actual storage conditions reasonably encountered in patients' homes.

The clinical relevance of inadequate drug storage is largely unknown. Although many patients do not store drugs adequately, the expected number of patients to experience adverse clinical effects over time is small, most likely requiring a large study sample size to reliably estimate (if any) a clinical effect. Moreover, there are several patient characteristics and product-related factors influencing drug effectiveness and the occurrence of adverse events, interfering with the relationship between storage conditions and clinical outcomes. For study purposes, a clinical outcome directly related on the level of drug degradation would be a preferred study endpoint. In such a study, one should ideally take blood samples regularly during follow-up to determine the level of antidrug antibodies [14]. In addition, measuring the level of aggregation in the administered drug product would allow investigators to relate product quality to the antibody response. This is most challenging but could possibly be resolved by storing drugs 'in duplo' or the assessment of leftover drugs.

This study was subject to several limitations. The patient sample size was small and limited our options to study multiple methodological considerations in depth, to estimate the risk of inadequate storage and to include covariates in the regression analysis. Temperature measurements were not available during the complete follow up period for each patient. There are several reasons, apart from discontinuation bDMARDs, why patients have no temperature measurements for one or multiple consecutive months. These include a temporary discontinuation because of a planned operation or due to an infection. Other 'gaps' where related to patients not receiving a temperature logger with their bDMARD when dispensed. Furthermore, we based our definition for inadequate storage in this case study only on temperature measurements. Other factors, such as light exposure and agitation, could also affect product quality, but where not included in our study.

Conclusion

Different categorizations for storage conditions greatly influences the number of inadequate storage periods. Although this study did not allow for measuring the impact of inadequate storage categorizations on clinical outcomes, applying different time relationships seems to have a minimal effect on risk estimates. This study shows the methodological complexity when investigating the relationship between storage condition and clinical outcomes.

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5

General discussion

Introduction

New drugs are only accessible for regular patient care when approved by the regulatory authorities. These authorities (e.g. the European Medicines Agency [EMA] or the Food and Drug Administration [FDA] in the US) grant market approval based on documentation showing efficacy, safety and quality of the drug product. This documentation includes studies on drug stability. The active substance, appearance and purity of the drug product should remain within specification during the intended period of storage and use (i.e. up to end of shelf life). In addition, this documentation also indicates the conditions (e.g. temperature and humidity) during transportation and storage of the drug. In general, the international Good Distribution Practice guidelines are used throughout the pharmaceutical supply chain by drug companies, wholesalers and health care professionals and provide guidance on the monitoring of drug storage and transport conditions. However, after dispensing of the drug product to the patient, the patient himself becomes responsible for adequate storage of the drug product at home. Since drug storage conditions are usually not monitored after dispensing, there is little knowledge about the conditions at which drugs are stored in patients' homes.

Adequate drug storage includes several aspects, such as compliance recommended storage temperature conditions, disposal of drugs that have passed the expiry date and having access to important drug usage instructions, e.g. through availability of drug information leaflets. Studies that have investigated home storage practices, show that patients sometimes store drugs beyond the expiry date [(1)] and expose drugs to temperature conditions outside the drug product label recommendations [(2)]. Inadequate storage conditions could impact drug quality, such as in the case of aspirin, where exposure to moisture can lead to breakdown of acetylsalicylic acid, the active ingredient of aspirin [(3)]. Knowledge on home storage of drugs and more importantly the possible consequences thereof is becoming more relevant, as many of the new drugs being marketed are biologic drugs, representing almost 40% of the entire new drug pipeline in 2017 [(4)]. Biologic drugs are generally more complex and might be more sensitive to stress conditions [(5)]. Exposing these biological drugs to stress conditions may lead to protein denaturation and could induce formation of protein aggregates that increases the immunogenic potential of the drug [(6)]. This can result in the formation of antidrug antibodies that may contribute to the risk of adverse drug reactions and decreased effectiveness of the drug product [(7)]. Many of these newly developed biologic drugs are aimed for administration at home, such as in the case of tumor necrosis factor-alpha inhibitors for treating rheumatoid arthritis.

The general aim of this thesis was to investigate patient compliance with drug storage recommendations, the underlying factors of (non-)compliance with storage recommendations and the possible consequences of non-compliance with storage recommendations for drug quality and potential effects on the outcomes of drug treatment.

In this general discussion following three themes related to drug storage will be discussed. The first theme will reflect on drug storage by patients. Second, the next section will reflect

on drug storage in relation to drug development and regulatory implications. The third theme will focus on potential clinical consequences of (non-)compliance with drug storage recommendations.

Reflections on drug storage by patients

Understanding how and where patients store their drugs after dispensing and the underlying factors that are involved is the key element of knowledge needed for designing interventions to improve home storage of drugs.

Drug storage after dispensing and underlying factors contributing to (in)adequate storage

Patients should follow drug storage recommendations as indicated in the drug label, including complying with storage conditions (i.e. temperature, humidity, light), assessing expiry dates regularly and they should guard package integrity. Complying with drug storage recommendations reduces the risk of change in quality of the drug, ascertains that the drugs are identifiable for the patient (and for others living in their household) as well as provides access to drug information (drug information leaflet or package insert). The principles of good storage practices by patients seem relatively straightforward, however, compliance to these recommendations becomes more complex when patients use multiple prescription drugs with various storage recommendations, different expiry dates and complex dosage schemes. These complexities often apply to older patients, whom generally have more prescription drugs stored at home as in this patient group polypharmacy is more common [8]. Several aspects of drug storage after pharmacy dispensing have previously been investigated. These investigations show that patients may store drugs passed their expiry date [1], do not comply with storage recommendations for temperature [9] or moisture [10] or have no drug information leaflets available [11]. Other investigators point out that patients can experience several practical problems related with drug use and storage at home. Patients may keep drugs in unidentifiable packages or bottles [12] and develop their own way to prevent mix-ups (e.g. handwriting on package, store at different location away from other drugs) [13]. In general, these results are in line with our observations described in Chapter 2. In this thesis, we add more depth to the current evidence that is available on drug home storage practices of patients. This was done by continuously monitoring home storage practices instead of performing a cross sectional evaluation as well as performing a detailed home assessment of drug storage practices as well as linking these to patient characteristics. Assessment of home storage temperature for biologic drugs throughout a whole period of the dispensed quantity show that the vast majority of patients (93.3%) do not store biologic drugs between 2-8°C. Around 25% of patients repeatedly expose biologic drugs to temperatures below 0°C, some at temperatures as low as -10°C (Chapter 2.1). Although home storage temperatures for drugs requiring storage at room temperature often exceeded 25°C, this only occurs during

short time periods and within defined stability testing temperature tolerances (Chapter 2.2). A comprehensive analysis including several aspects of drug home storage showed that around half of the older patients does not comply with general drug storage recommendations. In addition, this study (Chapter 2.3) showed that older patients using multiple drugs and those that have drugs requiring refrigeration have more difficulties to comply with drug storage recommendations. This inability to comply with drug storage recommendation does not seem to be related to the patient's personality but seems to be more associated with the number of drugs that are stored at home (Chapter 3.1).

The underlying factors why many patients do not comply with storage recommendations are largely unknown. Patients should be informed by their pharmacy and receive written information about proper drug storage when getting their drugs dispensed. Although most do receive information (Chapter 3.2), they nevertheless expose drugs to several unfavorable storage conditions. Patients are not always capable to ascertain adequate storage in their homes and have problems to independently manage their drugs at home [14]. As an example, drugs requiring protection from light and/or moisture should be kept in the original packaging to protect against light or stored outside a humid location (e.g. bathroom, cellar). The same applies for drugs requiring storage temperature conditions below 25°C or 30°C, where patients should not use storage locations that can reach high temperatures, such as windowsills, dashboard lockers and backpacks. In case patients do not adhere to proper storage conditions, no monitoring takes place to warn patients for potential quality issues. Periods of inadequate drug storage therefore usually go unnoticed. In contrast with (fresh) groceries for which quality can be easily identified before consumption, drugs exhibiting reduced quality are usually not recognizable by patients based on the drug's appearance. It is recommended that patient's (non-)intentional behavior regarding how they store their drugs at home, awareness of inadequate storage and drug stability should be subject of further research.

Storage temperatures of TNF alpha inhibitors were measured continuously for two weeks in patients' homes as described in Chapter 3.2 and confirmed our results that these are often not adequately stores as described in Chapter 2.1. In addition, the exact location of storage in the refrigerator is important for stable storage, as drugs stored in the refrigerator door frequently have a higher mean storage temperature and were more often stored outside 2-8°C when compared to those stored in the middle or lower refrigerator shelves. Also, environmental factors play a role in home storage of drugs. Ambient temperatures influence storage temperatures of drugs that are stored at room temperature in patient homes, especially in the warmer months June, July and August (Chapter 2.2). Although the effect of ambient temperature on storage temperature in the Netherlands was relatively small, this relation could be more significant in other countries with a warmer climate. Storage temperatures in homes generally become warmer in the summer period, increasing the probability storage temperatures are above 25°C or 30°C for a longer time period. In most of these cases, inadequate storage by patients is likely to be non-intentional. In their home setting, patients may not make a rational decision to facilitate adequate drug storage and can make a different

trade-off (e.g. taking drugs out of the refrigerator in case of lack of space or keeping expired drugs for future 'as needed' use) that does not necessarily prioritize adequate drug storage. Patients do not take into account label storage recommendations when considering a proper location to store drugs, except for drugs requiring storage in the refrigerator (Chapter 3.1). Behavior and daily routines play an important role in patients' reasons for choosing specific storage locations in their home. Many patients stated that they stored drugs close to equipment or utensils at home that they often use as 'a visual reminder', such as storing their drugs near radio, their television or toothbrush (Figure 1). We introduced an innovative assessment tool to determine home storage (dis)organization by patients and showed that the level of drug storage organization is relatively high in the older study population. However, organizational level of storage locations and patient compliance with drug storage recommendations was not associated (Chapter 3.1).

Figure 1. Drugs stored in patient's home: 'a visual reminder'.

Backed by evidence regarding personality traits and one's tendency for structure and punctuality ('conscientiousness') [15], we assumed that patients with a higher score on 'conscientiousness' would store drugs better. This was not confirmed by the results in Chapter 3.1. Patients receiving one or more prescription drugs might already be inclined to give storage of drugs more attention compared to storage of other household belongings or may have previously asked for advice on drug storage. Moreover, patients were aware of the study purpose and might have already discarded unused or expired drugs and reorganized their household before the visit.

Improving drug storage by patients

Improving drug storage practices by patients should take into account several storage aspects and be a shared engagement of drug companies, regulatory agencies, pharmacists and patients. Promoting proper drug storage at home can [1] prevent drugs being exposed to inadequate storage conditions that can possibly reduce their quality and [2] benefit appropriate use of drugs, or both. Better compliance with drug storage recommendations can prevent quality loss of drugs. Options regarding how to avoid exposing drugs to inadequate storage conditions include providing better information about adequate storage to patients and offering the possibility of monitoring storage conditions at home. Home innovations in patient households can also contribute to improved drug storage.

The majority of drugs require no special storage conditions (considered stable at accelerated test conditions), thus although these are exposed to inadequate storage conditions will probably not significantly reduce drug quality. However, for drug products that have more strict storage recommendations (e.g. 'store below 25°C', 'keep the container tightly closed') the impact could be larger thus requiring more attention such as additional oral explanations next to the written information in the patient leaflet. Infographics of the key aspects can help patients to better understand the key aspects of effective and safe drug use [16], especially for patients with limited health literacy. In the Netherlands and few other countries, animated drug information is available for a number of drugs, adjusted to user profile (e.g. older patients), in addition to the drug information leaflet [17]. For products requiring special storage conditions, animations could help when instructing patients on how to store drugs in compliance with drug storage recommendations. These animation films could instruct patients on selecting the preferred storage location or show how to properly organize their drug stock. A preferred storage location depends on the drug and can be a location away from sunlight to prevent drugs being exposed to heat or on the middle shelf in the refrigerator for drugs requiring cool storage. To promote proper drug storage organization, patient instructions can include to keep drugs in their identifiable packaging and to keep them properly sorted in one central storage location. To this end, patients using multiple drugs, including drugs that have specific storage recommendations, could benefit from a home visit by the pharmacist to evaluate and promote good drug storage practices.

Our investigations have shown that many consumer refrigerators have a large temperature variation and often expose drugs to temperatures below 2°C or above 8°C. When patients

get a drug dispensed that requires refrigeration for the first time the pharmacists could perform a pre-check of the storage temperature in their refrigerator at home (e.g. having temperature monitored with a simple temperature logger for up to 2 weeks). This would increase awareness for better home storage practices and possibly reduce exposure to storage temperature conditions outside 2-8˚C by identifying a preferred storage location. A temperature logger could also be integrated in the packaging or label of the drug product by the drug company, signaling when storage temperature conditions are out of range. In the supply chain management for other products requiring temperature monitoring (e.g. food products) temperature labels are already used in practice to monitor (real-time) temperature conditions [18]. To avoid distressing patients regarding quality of their drug after short term exposure to conditions not within label recommendations, acceptable tolerance periods for drug products should be determined. Ideally, in case of a long-term excursion outside

Figure 2. Biologic drug products (adalimumab secondary packages on the upper shelf) stored in a refrigerator.

the recommended storage conditions, patients and/or the pharmacist should receive a notification that storage is inadequate. Subsequently, patients can improve drug storage by adjusting storage temperature and/or change location. Including temperature monitoring in drug labels could lead to a large amount of storage information about different drugs, which would allow investigators to study the effects of inadequate storage in a large group of patients. The solutions described above might still be less effective when equipment (e.g. old consumer refrigerators) for drug storage is insufficient. To minimize the duration of home storage by patients, drugs can also be dispensed for a shorter period. For specific biologic drugs requiring administration with long intervals (e.g. every two weeks), these could even be dispensed per injection.

A number of patients reported to temporarily remove biologic drugs from the refrigerator due to lack of space (Chapter 3.2). The relatively large, redundant package size of some biologic drug products might hamper proper storage as these could fill up to half a refrigerator shelf (Figure 2). Around 10% of the patients removed the secondary packaging and one patient used a dedicated refrigerator for storing the biologic drug. Patients might thus benefit from smaller outer package sizes if the drug dosage form allows for. A dedicated drug storage refrigerator or other smaller cooling devices to keep drugs between 2-8°C, would help patients with adequate storage of large secondary packages for drugs with special storage recommendations.

Innovations in patients' households (e.g. home automation) could able patients to monitor and control climate conditions, light and appliances (e.g. home humidifier, air-conditioner). This provides patients with the opportunity to 'extent' the controlled pharmaceutical supply chain to their own homes where they monitor drug storage conditions. For example, if home temperature conditions reach 25°C, sunscreens or air-conditioning can be automatically switched on. Furthermore, home automation could be utilized to help patients properly store drugs by reminding patients to discard drugs that are left unused, monitoring storage conditions (e.g. drugs in the refrigerator) or even more intelligent sensors for temperature, humidity and light used to allocate a preferred storage location for each drug product based on ideal climate conditions. By optimizing storage conditions at home in a controlled manner, patients and pharmacists would be able to assure proper storage conditions at patient homes. This is not only valuable for the patients but also a pre-requisite and a key issue in the discussion on if unused drugs that are returned to the pharmacy might be eligible for re-dispensing [19].

Compliance with drug storage recommendations also benefits appropriate use of drugs. Adequate storage includes identifiability of drugs, the availability of drug information leaflets and drug storage organization. Amongst others, this allows patients and caregivers to easily identify drugs, prevent hoarding of drugs and timely notice and discard those that are beyond their expiry date. Pharmacists and pharmacy personnel can play a key role in promoting good storage practices by providing more active supervision and training of patients. They could make use of the drug storage organization scale introduced in Chapter 3.1 upon a home visit or based on photographic images to identify patients needing such


Safe-Rx
Valsartan
Actavis
accord
INEGY
INEGY
INEGY


DOXYCYCLINE dispergeerbaar
Flo Lys
spaarje

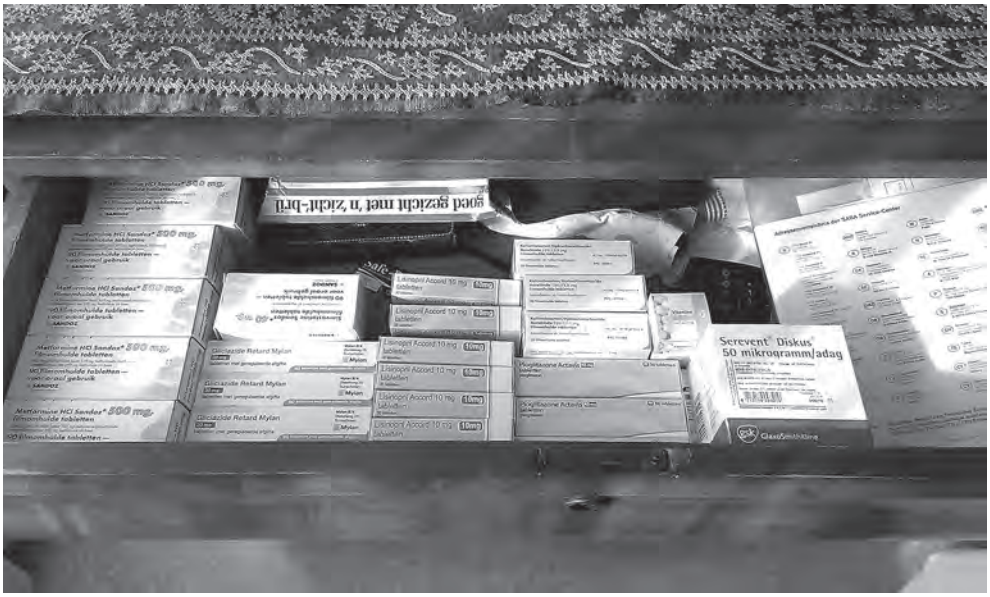

Figure 3 – left and above. Home storage of drugs: drawers with multiple drug packages from three patients illustrating patient's high level of drug storage organization.

assistance. The drug storage organization scale categorizes home storage of drugs in a low, medium or high level (Figure 3) of organization. At (first time) drug dispensing, this would be the preferred moment to provide practical information about drug storage and ask patients how and where they normally store drugs at home, what their rationale is and discuss problems with drug storage they expect or have encountered before. To promote better drug storage, patients might be helped by receiving a medication overview list of all drugs they store at home including expiry dates and (if applicable) special storage conditions. The aforementioned suggested interventions on how to improve drug storage will only be successful when it becomes a shared engagement of drug companies, regulatory authorities, pharmacists and patients. The suggestions described above require investments in training, counseling, guideline development and implementation of home storage innovations that allow patients to better control storage conditions in their homes.

In conclusion, drugs stored in patient's home are often exposed to inadequate storage conditions and recommended storage conditions are not taken into account when patients allocate a storage location for their drugs. Patients do often not comply when using multiple drugs and in case of having drugs that require special storage conditions. There was no difference in the adequacy of drug home storage between those patients that scored higher level of organization than those with lower level of organization. In addition, taking into consideration the pre-defined factors we thought would improve storage (e.g. use of multi-dose dispensing system) did not influence our results. Evidence on drug storage practices by

patients is still scarce, and a combination of qualitative and quantitative research approaches could explore and identify patient related factors promoting or undermining adequate home storage. Insight in successful patient storage practices and strategies may help other patients to improve drug home storage.

Reflections on drug storage in relation to drug development and regulatory implications

Adequate storage is essential to guarantee drug quality. Improved understanding about drug storage by patients could have regulatory implications for drug development. This section further discusses regulatory implications for biologic drugs in more detail.

Drug development and regulatory implications

Drug companies, regulatory authorities and pharmacies aim to provide patients with drug products of good quality. Many drug products do not need special storage temperature conditions and are not sensitive to moisture or exposure to light. Other drugs are less stable and should be stored below 25°C and stored in their original (primary) package to protect against moisture. For new (and existing) drugs with unfavorable stability parameters, drug quality assessments should be made taking into consideration conditions that patients may unintentionally expose these drugs to. As an example, the new anticoagulant drugs dabigatran and rivaroxaban are sensitive to storage conditions (i.e. temperature, moisture), possibly either increasing or decreasing its coagulant effect. Healthcare professionals already expressed their concerns with these products in 2012 [20]. Based on drug stability information known prior to market authorization, a warning should have been issued to keep these drug products in the original packaging. In 2016, the Dutch Medicines Evaluation Board warned patients to not store dabigatran outside of the original package (e.g. in multi-dose dispensing systems) due to risk of losing efficacy caused by exposure to moisture [21].

Placing the patient in the center of drug development has been discussed in reflection papers published by the European Medicines Agency (EMA) [22]. The concept of patient centric drug development intends to consider all elements of drug product design affecting or addressing the specific needs of the target patient population (e.g. older patients or pediatric patients) [23]. Patient centricity should also include patient capacities when considering storage conditions and situations at home. The rationale behind in-use testing is to include actual storage conditions and practices (e.g. opening bottle every day for a month) to determine drug stability when exposed to conditions that exceed or are out-of-scope in standard drug stability testing. Actual storage conditions by patients are a starting point, if reasonably expected to occur on a regular basis. For example, drugs sensitive to moisture are undesirable when patients use an automated multi-dose dispensing system or a weekly dispensing box or similar aids that require storage outside the drug's primary packaging. The new Automated Dose Dispensing guidelines drafted by the European Directorate for the

Quality of Medicines & Healthcare (EDQM) advises authorities to encourage marketing authorization holders to include drug stability information in the Summary of Product Characteristics (SmPC) once they are removed from the protective primary packaging [24]. In line with these guidelines, the Swedish Medical Products Agency only grants permission to market authorization holders to dispense their drug outside of the original packaging, when stability studies include information about in-use stability [25].

The basis for stability testing was laid out in the mid-eighties. We know that drugs requiring storage at room temperature in Chapter 2.2, are for a large part stored at temperatures above 25°C. The stability test guidelines take into account short term exposures above the temperature thresholds during testing but do not specify the frequency or total duration of time. However, the guidelines recommend to further investigate longer excursions in relation to drug stability. Currently it is up to the drug company to decide on the long-term test conditions they choose to apply to their products: 25°C/60% RH or 30°C/65% RH. Based on our measurements of storage temperatures at room temperature, frequent exposure to temperatures above 25°C seem to be 'normal' (almost 30% of total storage time) at patient homes. The yearly mean temperatures in the Netherlands in the past five years are higher than the highest mean temperature in the 1980's, when the standards for drug quality testing where defined by Wolfgang Grimm [26]. Countries in other climate zones could have similar or more profound climate changes. In order to account for changing climate conditions and more frequent extreme temperatures in relation to storage of drugs in patients' homes, changing conditions in which patients store drugs should be taken into consideration for stability testing in drug development. Other factors to consider are better health and increased mobility of patients, thereby increasing the probability of more frequent storage and transportation of drugs outside climate zone I/II. For instance, patients travelling between different climate zones risk their drugs being exposed to high temperature and high humidity climate conditions. In southern European countries, which belong to climate zone II, drugs are possibly exposed to higher temperatures for a more prolonged period of time.

Quality of biologic drugs and regulatory implications

Biologic drugs are generally more complex than small molecule drugs, as they are highly sensitive to formation of structural variants during and after the manufacturing processes. Such variations e.g. fragments, aggregates and changes in glycosylation profiles may have implications for the drugs' effectiveness and immunogenicity [27] and therefore biologic drugs require more complex analytical methods to establish the drug's quality profile. The immunogenic potential of the drug should be investigated in an immunogenicity assay [28]. However, immunogenicity is difficult to predict and depends on many other patient-, disease- and product-related factors [29]. Animal models have been used to predict immunogenicity but these have low validity and little predictive value in humans.

How and if home storage temperature impacts product quality of TNF alpha inhibitors, i.e. by the formation of aggregates, is investigated in Chapter 4.1. All tested products were

relatively resistant to the freezing temperature conditions similar to those observed in Chapter 2.1. However, in half of the tested products larger submicron sized particles were detected. This study also showed that identical product samples from the same production batch exposed to identical temperature conditions can behave differently, suggesting aggregation as a result of freezing stress conditions appears to be probabilistic. To what extent these larger particles are able to induce an immunological response is not known and should be subject of further investigations. A more comprehensive assessment should be made to provide a better risk estimation, where more samples from different batches should be included. These should be exposed to longer duration of stress and should include other relevant stress conditions, such as mechanical stress (shaking) and light exposure.

There are few publications on stability of biologic drugs under different storage temperatures. The work published by Shannon *et al.* investigated storage conditions outside 2-8°C for the TNF-α inhibitor etanercept and showed a satisfactory stability profile for storage conditions for up to four weeks at 25°C and 30°C [30]. Based on their data, a trend of decreased monomer content and increased aggregation level after storage at 25°C for 24 months was reported. How to define adequate storage for biologic drugs is debatable. This largely depends on the specific drug product and tolerated period outside of the recommended storage conditions. With reference to the previous example, it is unknown what level and type of aggregates are required to induce an antibody response. Storage between 8-15°C for at least one month was frequently observed in a majority of patients (Chapter 2.1). Stability for these drugs has not been tested at long-term storage temperatures between 8-15°C, but some of these biologicals can according to the SmPC documentation [31, 32], be stored up to a few weeks (e.g. adalimumab for up to two weeks, etanercept for up to four weeks) below 25°C without losing quality. 'Do not freeze' is often added as an additional labelling statement when temperature below 0°C should be avoided. However, the minimum temperature and duration of stress conditions below 0°C required to induce product quality changes (i.e. formation of aggregates) for these biologic drugs is unknown. In the absence of a clear definition and little information available, drug quality cannot be guaranteed for drugs stored at home outside the recommended temperature range. As our understanding evolves regarding actual home storage conditions for drugs requiring refrigeration, one could argue for more liberal storage conditions possibly allowing patients to store these drugs outside a refrigerator, preventing the exposure of drugs to large temperature variations outside 2-8°C, including temperatures below 0°C. However, more information regarding changes in drug quality, including levels of aggregation, in relation to immunogenicity should first be gathered and made available by drug companies to make a valid risk estimation of different storage temperature conditions.

Clinical consequences of (non-)compliance with drug storage recommendations

Non-compliance with drugs storage recommendations may lead to reduced drug quality and ineffective drug treatment. This section discusses clinical implications of inadequate drug storage and reviews considerations for future research to investigate the relation between drug storage and clinical outcomes.

Clinical implications of inadequate drug storage by patients

The absence of reported cases or larger trials suggests inadequate storage conditions have little effect on clinical outcomes. Further, information on if and to what extent drug storage conditions and reduced drug quality influence clinical outcomes in treated patients is lacking. Although Chapter 2.1 showed that the majority of patients did not store their biologic drugs according to recommended home storage temperatures, it is unlikely that these patients administered ineffective biologic drugs. There is insufficient knowledge of what type of inadequate storage conditions (i.e. duration, severity) affects drug quality. Subsequently, the extent to which drug quality changes affect treatment and clinical outcomes is unknown. The affected drug product might still be potent enough to achieve the desired clinical outcome without safety concerns.

For example, the prostaglandin prodrug latanoprost requires special storage conditions and should not be exposed to light. Patients are recommended to store the drug in the refrigerator until the first use. After opening the drug package patients may store latanoprost up to four weeks at room temperature in the original packaging [33]. Studies show that a container of latanoprost left in the sunlight could degrade by at least 10% in one afternoon [34]. In addition, the Japanese investigators Mochizuki *et al.* investigated use of latanoprost stored under different temperature conditions in two group of healthy volunteers and measured their intra ocular pressure, a hard clinical endpoint [35]. No difference in intra ocular pressure was found between participants receiving latanoprost stored in the refrigerator (4˚C) and those receiving latanoprost stored at 30˚C. Knowledge of how storage conditions impact clinical effect of the drug is very valuable. However, a similar study design may not be useful or ethical in assessing the influence of storage conditions of other drugs. Biologic drugs can undergo structural changes or have formed aggregates that may induce a rare, but severe autoimmune reaction. Nevertheless, this study provides more insight into the influence of storage conditions on product quality and clinical outcomes.

The timeframe of possible clinical implications after inadequate storage is unknown and is dependent on product- and patient-related factors. Drug products with reduced quality may result in a direct or delayed clinical effect. Chapter 4.2 introduces methodological considerations when exploring the relation between home storage conditions and clinical outcomes. Although this study did not aim to estimate the actual effect of inadequate storage on disease activity in rheumatoid arthritis patients, it reviewed relevant scenarios considering how to study such a relationship. Different categorizations for storage conditions greatly influences

the number of inadequate storage periods. Although this study did not allow for measuring the impact of inadequate storage categorizations on clinical outcomes, applying different time relationships seems to have a minimal effect on risk estimates. This study shows the methodological complexity when investigating the relationship between storage condition and clinical outcomes.

Future research considerations

To assess the impact storage conditions may have on drug treatment and clinical outcomes investigators need to collect data on three main components: the drug storage conditions, the relevant product quality parameters and related clinical outcomes. First, precise monitoring of relevant environmental factors including temperature, humidity, light, mechanical stress should be performed. Patients may not continuously expose drugs at home to inadequate storage conditions but can expose drugs to intermittent periods of inadequate storage. Second, the time-relationship between inadequate storage and the effects on drug product quality and subsequently clinical outcomes should be taken into consideration. The mechanisms by which storage conditions affect drug product quality and possible clinical consequences are poorly understood and are dependent on multiple product- and patient-related factors. Clinical outcomes associated with inadequate storage should thus be assessed in the appropriate time window. Patients would probably require a long follow-up period to assess direct and/or delayed clinical effects after inadequate storage.

Third, investigators should make an inventory considering confounding factors: patients who do not comply with adequate drug storage practices and conditions may also be less adherent or have other problems with proper drug management at home [36]. Inadequate storage has been associated with numerous patient related factors that might influence treatment success or other clinical outcomes. Other investigators have shown that a considerable number of patients have limited health literacy [37], which is essential to understand instructions and recommendations for adequate drug storage. For instance, some patients may interpret 'cool storage' other than refrigerator storage and store drugs in the freezer compartment.

Fourth, to assess the relation between drug storage and clinical outcomes, one should preferably use a clinical outcome directly related to reduced drug quality. Although many patients do not store drugs adequately, the expected number of patients to experience adverse clinical effects over time is small, most likely requiring a large study sample size to reliably estimate (if any) an effect. The fifth aspect is most challenging, as it takes into account the assessment of product quality. This could be resolved by storing drugs 'in duplo' or the assessment of leftover drugs. Inadequate storage cannot be investigated setting up a blinded, randomized trial. Investigators are required to measure storage conditions and product quality during or after drug treatment. Depending on the observed storage conditions, relevant product quality parameters should be assessed.

Concluding remarks

Drug storage conditions and practices after dispensing are often inadequate. Patients are non-compliant with drug storage recommendations on temperature and moisture, they store drugs that have passed the expiry date or do not have accompanying drug information. Several underlying factors promoting or undermining storage were identified and interventions to promote better drug storage at home were discussed. Patients reported not taking into account drug storage recommendations when considering a proper location to store drugs, except for drugs requiring storage in the refrigerator. Daily routines and visual reminders play an important role in patients' reasons for choosing specific storage locations in their home. Patient personality traits were not found to be associated with adequate home storage. Drug companies, regulatory authorities and pharmacies need to be aware that for some drugs quality might be compromised before expiry date due to inadequate home storage by patients. Actual storage conditions should, if reasonably expected to be outside drug storage recommendations on a regular basis, be accounted for in stability testing during drug development. In theory, inadequate storage may reduce drug quality and thus could affect drug safety and effectiveness of the drug. In practice, current knowledge gaps limit reliable risk estimation when it comes to linking inadequate home storage of drugs with clinical outcomes. Gathering more knowledge on the consequences of inadequate storage and improving compliance with drug storage recommendations should be a shared engagement between drug companies, healthcare authorities, pharmacists and patients.

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Summary

Summary

Adequate drug storage is essential to guarantee the drug's quality, safety and efficacy. The international Good Distribution Practice guidelines are used throughout the pharmaceutical supply chain by drug companies, wholesalers, pharmacists and other health care professionals and provide guidance on the monitoring of drug storage and transport conditions. After dispensing of the drug product to the patient, the patient himself becomes responsible for adequate storage of the drug product at home. There is little knowledge about the conditions at which drugs are stored in patients' homes, since drug storage conditions are usually not monitored after dispensing.

Adequate drug storage by patients themselves includes several aspects, including compliance with recommended storage temperature conditions, disposal of drugs that have passed the expiry date and having access to relevant drug usage instructions. Studies that have investigated home storage practices, show that patients sometimes store drugs beyond the expiry date and expose drugs to temperature conditions outside the drug product label recommendations. Inadequate storage conditions could impair drug quality, such as in the case of aspirin, where exposure to moisture can lead to accelerated breakdown of acetylsalicylic acid, the active ingredient of aspirin. The same applies to biologic drugs, which are generally more complex and may be more sensitive to stress conditions, where exposure to stress conditions may lead to protein denaturation. This can result in formation of protein aggregates in the drug product which in turn increases the immunogenic potential of the drug as well as in vivo the formation of antidrug antibodies. The latter can increase the risk of adverse drug reactions and decrease the effectiveness of the drug product. Many of the newly developed biologic drugs are aimed for administration at home, such as in the case of tumor necrosis factor-alpha inhibitors for treating rheumatoid arthritis. It is therefore of increasing importance to gather more knowledge on storage conditions at home and possible consequences of inadequate storage.

Chapter 2 describes how patients store different drug products at home. In chapter 2.1, we investigated storage temperature conditions of biologic drugs at patients' home. This study was designed as a prospective observational study and showed that the majority of patients do not store drugs continuously between 2-8°C, and that almost 25% of patients stored biologic drugs for at least two hours below 0°C. In chapter 2.2, drug storage in patients' homes was assessed for oral anticancer drugs that in general require storage at room temperature with some of these drugs requiring storage below 25°C or below 30°C. According to our investigations, the majority of patients stored oral anticancer drugs according to storage recommendations; only one patient stored a drug above 25°C longer than 24 hours. Comparing home storage temperature with ambient temperatures showed that ambient temperature can influence actual storage temperatures inside patient homes. This could be especially relevant for home storage of patients living in warmer regions worldwide.

A cross-sectional study was designed to further investigate storage conditions and practices of patients above 65 years (chapter 2.3). More than half comply with general storage

recommendations which were divided in two domains; storage quality (considering storage conditions, expiry date, package integrity) and storage information (considering identifiability and package insert availability). It was found that older patients storing more than five different drugs at home are more often non-compliant with storage recommendations. Drugs requiring refrigeration were often not stored according to the recommended storage conditions, which was consistent with our findings in chapter 2.1.

Chapter 3 describes two studies investigating the underlying reasons why patients sometimes store drugs at home inadequately. In chapter 3.1, we investigated if patient's personality was related to storage practices. Patients' personality traits could be important determinants of older patients' good storage practices at home, however, our study did not find an association between personality traits and adequate drug storage conditions and practices at home. The majority of patients mentioned daily routines and visual reminders as their main reasons when considering drug storage locations. Around 70% of patients were found to have a high level of drug storage organization at home, based on a new drug storage organization scale developed in this chapter. In chapter 3.2, we specifically asked patients using biologic drugs about their storage locations and underlying reasons for how they stored their biological drugs. Majority of patients were aware of the importance of proper storage conditions and stored their biologic drug in the refrigerator. Biologic drugs kept in the refrigerator door were stored at higher mean temperatures and were more often stored outside 2-8°C. When travelling, patients often take precautions how to store drugs on their vacation (e.g. cool bags, refrigerator).

Chapter 4 describes the possible consequences of inadequate storage conditions and how to measure these. In chapter 4.1, consequences of inadequate storage temperature conditions, as observed in chapter 2.1, were used to stress several biologic drugs and measure drug quality by assessing the level of aggregation. All product tested in this study were relatively resistant to freezing stress conditions, although in almost half of the tested product samples a small number of larger particles was detected, confirmed by different techniques. Chapter 4.2 introduced methodological considerations when exploring the relation between home storage conditions and clinical outcomes. The way temperature storage conditions are defined greatly influences the measured duration of inadequate storage periods. Although this study did not allow for measuring the impact of inadequate storage categorizations on clinical outcomes, applying different hypothetical time relationships to simulate the timeliness of a clinical effect (short term, long-term effects) seems to have a minimal effect on risk estimates. This study showed the methodological complexity when investigating the relationship between storage conditions and clinical outcomes.

The final chapter of this thesis reflected on the following themes related to drug storage; drug storage by patients, drug storage in relation to drug development and regulatory implications, and the potential clinical consequences of (non-)compliance with drug storage recommendations. In conclusion, drug storage conditions and practices after dispensing were often found to be inadequate. Patients are often non-compliant with drug storage recommendations on temperature and moisture, they store drugs that have passed the expiry

date at home or do not have accompanying drug information. Actual home storage conditions and practices should be taken into consideration when defining label statements to safeguard the quality of drugs after dispensing. In theory, inadequate storage may reduce drug quality and thus could affect drug safety and effectiveness of the drug. In practice, current knowledge gaps limit reliable risk estimation when it comes to linking inadequate home storage of drugs with clinical outcomes. Creating more awareness regarding adequate storage practices, investigating consequences of inadequate storage and promoting better drug storage by patients should become a shared effort of drug companies, healthcare authorities, pharmacists and other healthcare professionals and patients.

Samenvatting

Samenvatting

Bewaren van geneesmiddelen volgens de aanbevolen bewaarcondities is essentieel voor de kwaliteit, veiligheid en werkzaamheid van het geneesmiddel. Geneesmiddelenfabrikanten, groothandels en apotheken volgen de internationale richtlijn voor Goede Distributie Praktijken (GDP) als leidraad voor het bewaren en de distributie van geneesmiddelen. Vanaf het moment van uitgifte is de patiënt verantwoordelijk voor het naleven van het bewaaradvies. Er is weinig bekend over de bewaarcondities van geneesmiddelen bij patiënten thuis. Bewaarcondities worden normaal gesproken niet gecontroleerd na uitgifte van het geneesmiddel.

Bewaren van geneesmiddelen omvat verschillende aspecten, waaronder het naleven van het bewaaradvies omtrent juiste bewaartemperatuur, het opruimen van geneesmiddelen waarvan de houdbaarheidsdatum verstreken is en toegang tot de juiste geneesmiddeleninformatie die in de bijsluiter staat beschreven. Echter, verschillende onderzoeken laten zien dat patiënten soms geneesmiddelen bewaren waarvan de houdbaarheidsdatum reeds verstreken is en dat geneesmiddelen buiten de geadviseerde condities worden bewaard. Niet goed bewaren kan mogelijk leiden tot verminderde kwaliteit van het geneesmiddel. Blootstelling aan vocht kan in het geval van acetylsalicylzuur (het actief farmaceutisch ingrediënt van Aspirine®) leiden tot een versnelde afbraak en mogelijk verminderde werkzaamheid. In het geval van biologische geneesmiddelen (biologicals), die in het algemeen meer complex en minder stabiel zijn dan kleine moleculen, en waarbij blootstelling aan stressfactoren mogelijk kan leiden tot denaturatie, speelt dit mogelijk een belangrijke rol. Niet goed bewaren van biologicals kan leiden tot aggregaatvorming en heeft mogelijk klinische gevolgen door de vorming van antilichamen tegen de biological. Dit kan leiden tot bijwerkingen of verminderde effectiviteit. Steeds meer nieuwe geneesmiddelen zijn biologicals en worden veelal thuis door patiënten zelf toegediend. Het is daarom belangrijk om meer te weten te komen over bewaarcondities van geneesmiddelen bij patiënten thuis en om de mogelijke consequenties van het niet goed bewaren van geneesmiddelen in te kunnen schatten.

Hoofdstuk 2 van dit proefschrift beschrijft hoe patiënten verschillende geneesmiddelen thuis bewaren. In hoofdstuk 2.1 is onderzocht bij welke temperatuur biologicals door patiënten thuis worden bewaard. De meerderheid van de patiënten bewaarde biologicals gedurende niet continue tussen de 2-8˚C bewaart en bijna 25% van de patiënten bewaart biologicals minstens 2 uur onder het vriespunt. In hoofdstuk 2.2 werden de bewaarcondities van orale oncolytica – geneesmiddelen die in het algemeen op kamertemperatuur moeten worden bewaard – onderzocht. Dit onderzoek laat zien dat de meeste patiënten orale oncolytica goed bewaren en dat slechts één van de negentig patiënten zijn geneesmiddelen langer dan 24 uur boven de 25˚C bewaarde. Dit onderzoek laat ook zien dat de buitentemperatuur invloed kan hebben op de bewaartemperatuur van geneesmiddelen thuis. Dit zou met name relevant kunnen zijn voor het bewaren van geneesmiddelen door patiënten die reizen door of woonachtig zijn in warmere regionen.

Een cross-sectioneel onderzoek werd opgezet om verder onderzoek te doen naar het thuis

bewaren van geneesmiddelen bij oudere patiënten. Dit onderzoek wordt beschreven in hoofdstuk 2.3. Meer dan de helft van de patiënten voldoet aan algemene bewaaradviezen die werden opgedeeld in bewaarcriteria omtrent kwaliteit (juiste bewaarcondities, houdbaarheidstermijn nog niet verlopen, primaire verpakking nog intact) en informatie (geneesmiddel is identificeerbaar, bijsluiter aanwezig). Oudere patiënten die thuis meer dan vijf verschillende geneesmiddelen bewaren voldoen vaker niet aan een van deze criteria. Daarnaast blijkt dat geneesmiddelen die in de koelkast bewaard moeten worden vaak niet tussen de 2-8°C bewaard worden. Dit bevestigt de resultaten die zijn beschreven in hoofdstuk 2.1.
Hoofdstuk 3 beschrijft twee onderzoeken die onderliggende factoren trachten te identificeren waarom patiënten hun geneesmiddelen niet goed bewaren. De relatie tussen persoonlijkheid – bijvoorbeeld de mate van ordelijkheid – en het bewaren van geneesmiddelen thuis werd onderzocht in hoofdstuk 3.1. In dit onderzoek wordt geen duidelijke relatie gevonden tussen verschillende persoonlijkheidskenmerken ('extraversie', 'vriendelijkheid', 'ordelijkheid', 'emotionaliteit' en 'openheid') en het goed bewaren van geneesmiddelen. De meeste patiënten bewaren geneesmiddelen op een plek gerelateerd aan een dagelijkse routine, of op een centrale plek in de woning waar geneesmiddelen zichtbaar zijn. Daarnaast wordt in dit hoofdstuk een schaal geïntroduceerd waarmee de mate van organisatie voor het bewaren van geneesmiddelen kan worden gecategoriseerd. Ongeveer 70% van de patiënten in dit onderzoek had een hoge mate van organisatie thuis met betrekking tot het bewaren van geneesmiddelen. In hoofdstuk 3.2 worden specifiek patiënten die biologicals gebruiken gevraagd naar onderliggende factoren die mogelijk bijdragen aan (niet) goed bewaren van deze geneesmiddelen. De meerderheid van de patiënten zei op de hoogte te zijn van het belang van goede bewaarcondities en bewaarde de biologicals in de koelkast. Toch gaat het soms ook niet goed. Sommige patiënten gaven aan biologicals soms buiten de koelkast te bewaren vanwege ruimtegebrek. Uit dit onderzoek blijkt dat biologicals in de koelkastdeur op een hogere temperatuur worden bewaard en vaker/langer buiten de 2-8°C worden bewaard. De meeste patiënten gaven aan maatregelen te nemen om te zorgen dat hun biologicals op de juiste temperatuur worden bewaard (onder andere met behulp van een koeltas) wanneer ze langere tijd van huis zijn.
Hoofdstuk 4 beschrijft de mogelijke consequenties van het niet goed bewaren van geneesmiddelen. In hoofdstuk 4.1 onderzochten we de gevolgen van blootstelling aan temperaturen buiten het bewaaradvies, zoals geobserveerd in hoofdstuk 2.1, voor de kwaliteit van biologicals. In deze experimentele studie werden vier verschillende biologicals blootgesteld aan bevriezing en vervolgens werd de mate van aggregaatvorming gemeten. Hieruit blijkt dat alle producten relatief stabiel zijn na blootstelling aan bevriezing. Echter, in bijna de helft van de geteste producten die aan bevriezing werden blootgesteld werden kleine hoeveelheden grotere deeltjes gemeten. In theorie kunnen zulke deeltjes de kans op immunogeniteit van de producten verhogen en daardoor de werking van de producten verminderen. De klinische consequenties hiervan zijn echter onbekend. Hoofdstuk 4.2 introduceert verschillende methodologische overwegingen bij toekomstige onderzoeken van bewaarcondities in relatie tot mogelijke klinische uitkomsten. De gevolgen van het niet goed bewaren van

geneesmiddelen zijn wellicht pas op langere termijn zichtbaar en dat maakt het doen van onderzoek naar de gevolgen moeilijk. Het is daarnaast veelal onbekend bij welke bewaarcondities er een significante verandering in kwaliteit van het geneesmiddel kan optreden. Het laatste hoofdstuk in dit proefschrift gaat in op drie thema's die gerelateerd zijn aan het bewaren van geneesmiddelen; bewaren van geneesmiddelen door patiënten thuis, bewaren van geneesmiddelen in relatie tot de ontwikkeling van (nieuwe) geneesmiddelen en regulatoire implicaties, en onderzoek naar de mogelijke klinische consequenties van het niet goed bewaren van geneesmiddelen.

Uit dit proefschrift blijkt dat geneesmiddelen door patiënten thuis vaak niet volgens de aanbevolen bewaarcondities worden bewaard. Patiënten bewaren daarnaast regelmatig geneesmiddelen waarvan de houdbaarheidsdatum reeds verstreken is of hebben belangrijke geneesmiddeleninformatie niet meer voorhanden. Het niet goed bewaren van geneesmiddelen kan leiden tot een afname in kwaliteit en van invloed zijn op de veiligheid en werkzaamheid van een geneesmiddel. Op dit moment is er weinig kennis over de risico's van niet goed bewaren van geneesmiddelen en de mogelijke klinische gevolgen die dit kan hebben. Meer aandacht voor het goed bewaren van geneesmiddelen, mogelijke interventies om goed bewaren van geneesmiddelen te bevorderen en meer onderzoek naar de gevolgen van het niet goed bewaren van geneesmiddelen wat betreft de kwaliteit, veiligheid en werkzaamheid is een belangrijke volgende stap en vergt de gezamenlijke inspanning van patiënten, apothekers, overheden en fabrikanten.

Dankwoord

Dankwoord

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List of publications

List of publications related to this thesis

Vlieland ND, Gardarsdottir H, Bouvy ML, Egberts ACG, van den Bemt BJF. *The majority of patients do not store their biologic disease-modifying antirheumatic drugs within the recommended temperature range.* Rheumatology (Oxford). 2016;55(4):704-9.

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About the author

Nicolaas (Niels) Dirk Vlieland was born in Amersfoort, The Netherlands, on May 19th, 1985. After graduating secondary school at 'Het Nieuwe Eemland' in Amersfoort he studied molecular life sciences at Maastricht University (graduated with merit) and completed a master in oncology research at the VU University Amsterdam in 2009. Following graduation, Niels worked in the pharmaceutical industry, mainly in the area of clinical trial management. In March 2014, Niels started his PhD research at the hospital pharmacy of the University Medical Center in Utrecht and was enrolled in the postgraduate program of the Graduate School of Life Sciences of the Utrecht University. This PhD project was a collaboration of the University Medical Center Utrecht, Utrecht University and the Sint Maartenskliniek in Nijmegen. In 2015, Niels received a poster prize in the category 'Drug safety and Pharmacoepidemiology' at the FIGON Dutch Medicine Days in Ede, The Netherlands. Niels lives together with Isabel and their two sons, Hidde and Florijn.