Utrecht University

*Department of Pharmaceutical Sciences*

Master Thesis

---

# Meeting patient preferences regarding adverse drug reaction (ADR) information for duration, time to onset and self-management strategies: an observational study

---


[redacted]

[redacted]

[redacted]

[redacted]


*Commissioned by the Netherlands Pharmacovigilance Centre Lareb*

February 4, 2022

## Preface

[redacted]

## Samenvatting

**Achtergrond:** Bijwerkingencentrum Lareb is bezig met de ontwikkeling van een nieuwe website die volledig in het teken staat van bijwerkingen en toegespitst zal zijn op de informatiebehoeften van de patiënt. Er zijn drie domeinen die door patiënten als essentieel worden gezien in de informatievoorziening over bijwerkingen, namelijk: 'duur van de bijwerking', 'tijd tot start van de bijwerking' en 'zelfmanagement strategieën'.

**Doelstellingen:** Ten eerste tracht deze studie te onderzoeken of de huidige informatiebronnen van bijwerkingen in Nederland informatie verstrekken dat is afgestemd op de behoeften van de patiënt. In het tweede van deze studie wordt er gekeken of data van Bijwerkingencentrum Lareb deze gewenste informatie kan verschaffen voor de bijwerkingen 'injectieplaatsreacties', 'infecties' en 'huidreacties' in patiënten met immuungemedieerde inflammatoire aandoeningen die adalimumab of etanercept gebruiken.

**Methode:** Het eerste deel van deze studie bestond uit het selecteren van de huidige informatiebronnen van bijwerkingen die betrouwbaar en *evidence-based* zijn. Vervolgens werden deze bronnen getoetst op de aanwezigheid van informatie over bijwerkingen waar patiënten de voorkeur aan geven. Dit werd gedaan voor de geïncludeerde biologicals in deze studie. Voor het tweede deel van de studie werd zowel de data van de spontane rapportages als data van de Biologische Monitor van Bijwerkingencentrum Lareb gebruikt. In de tweede databron werden patiënten met immuungemedieerde inflammatoire aandoeningen tweemaandelijkse vragenlijsten gestuurd waarin vragen werden gesteld over mogelijke bijwerkingen die zij ervoeren tijdens het biological gebruik. Ook data over de start- en hersteldatum van de bijwerking werd verzameld, dat in deze studie werd gebruikt om de mediane duur van de geïncludeerde bijwerkingen te berekenen. Verder konden patiënten invullen of zij zelfmanagement strategieën toepasten om de bijwerking te behandelen. Patiënten die hier 'ja, namelijk:' invulden, konden de strategie beschrijven in het vrije tekstveld en werden geïncludeerd in de studie. Vervolgens werd er een thematische analyse van deze vrije tekstvelden gedaan. De data van de spontane rapportages werd alleen gebruikt voor het berekenen van de latentietijden voor het domein 'tijd tot start van de bijwerking'.

**Resultaten:** Nederland heeft vijf primaire bronnen die informatie over bijwerkingen verstrekken, namelijk: de website van Bijwerkingencentrum Lareb, de bijsluiter, Apotheek.nl, Farmacotherapeutisch Kompas (FK) en Kijksluiter.nl. De meeste domeinen waren deels aanwezig in deze bronnen. Lareb en Apotheek.nl hadden de hoogste score, gevolgd door de bijsluiter en Kijksluiter.nl. FK had de laagste score. Het tweede deel van de studie had een verschillende patiëntenselectie voor elk domein, waardoor er drie verschillende patiëntenpopulaties ontstonden. Voor het domein 'duur van de bijwerking' werden in totaal 217 patiënten geïncludeerd (73.3% vrouw, gemiddelde leeftijd 52.4 jaar (j) (±13.8 j)), gevolgd door 403 patiënten voor het domein 'start van de bijwerking' (78.7% vrouw, gemiddelde leeftijd 47.5 j (±16.6 j)) en 160 patiënten (68.8% vrouw, gemiddelde leeftijd 53.6 j (±14.8 j)) voor 'zelfmanagement strategieën'. Over het algemeen hadden de meeste patiënten reumatoïde artritis (50.2% voor 'duur van de bijwerking', 40.4% voor 'start van de bijwerking' en 46.3% voor 'zelfmanagement strategieën'). De gevonden mediane duur van injectieplaatsreacties, infecties en huidreacties was respectievelijk 2.25 dagen (*interquartile range (IQR)* 11.0 dagen), 31.0 dagen (*IQR* 63.0 dagen) en 95.5 dagen (*IQR* 174.3 dagen). Daarnaast bestond de mediane start van een bijwerking uit 1.5 maanden (*IQR* 3.9 maanden) voor injectieplaatsreacties, 10.2 maanden (*IQR* 29.1 maanden) voor infecties en 2.0 maanden (*IQR* 6.7 maanden) voor huidreacties. Ten slotte betroffen de meest toegepaste zelfmanagement strategieën de thema's 'verandering in manier van toediening' voor injectieplaatsreacties, 'additionele behandeling van de bijwerking' voor infecties, en 'verandering in zelfzorg' voor huidreacties.

**Conclusie:** Deze studie liet zien dat de huidige bronnen die informatie over bijwerkingen verstrekken in Nederland niet voldoen aan de behoeften van de patiënt, maar dat data van een nationaal bijwerkingencentrum wel kan voorzien in deze informatie.

## Abstract

**Background:** The Netherlands Pharmacovigilance Centre Lareb is developing a new adverse drug reaction (ADR) information tool that accommodates the preferences and needs of the potential end-users, healthcare professionals (HCPs) but especially patients. Patients indicate three domains essential in ADR information provision: 'duration', 'time to onset', and 'self-management strategies' of ADRs.
**Objectives:** First, this study aims to assess whether the current ADR information provision sources in the Netherlands provide information in line with the domains that patients prefer. Second, if data collected by pharmacovigilance centres can provide information on the domains 'duration', 'time to onset', and 'self-management strategies' was examined for the ADRs injection site reactions, infections, and skin reactions in adalimumab and etanercept users.
**Methods:** The first part of this study consisted of selecting primary ADR information sources in the Netherlands that were reliable and evidence-based. Subsequently, the availability of ADR information preferred by patients in these sources was considered for the included biologics. For the second part of the study, both the spontaneous ADR report registry and Dutch Biologic Monitor (DBM) data were used. In the DBM, patients were handed bimonthly questionnaires, which included questions about ADRs that they experienced. Also, questions about the start/recovery date of the ADR were asked and used in this study to calculate the median duration of the included ADRs. Besides, patients could fill in whether they applied self-management strategies or not. Patients who filled in 'yes' could describe the applied strategy in the open-ended text fields and were included in this study. Subsequently, a thematic analysis was conducted for the open-ended text fields. Furthermore, the spontaneous ADR report registry data contained information about latency periods of the included ADRs and was used to calculate the median time to onset.
**Results:** The Netherlands has five primary ADR information sources: the website of the Netherlands Pharmacovigilance centre Lareb, the patient information leaflet (PIL), Apotheek.nl, Farmacotherapeutisch Kompas (FK), and Kijksluiter.nl. Most domains were partially available at these sources. Lareb and Apotheek.nl had the highest score, followed by the PIL and Kijksluiter.nl. FK had the lowest score. The second part of the study included a different selection of patients for each domain, which resulted in three different patient populations. For the domain 'duration', a total of 217 patients (73.3% female, mean age 52.4 years (y) (±13.8 y)) met the inclusion criteria, 403 patients (78.7% female, mean age 47.5 y (±16.6 y)) for 'time to onset', and 160 patients (68.8% female, mean age 53.6 y (±14.8 y)) for 'self-management strategies'. Also, in all three patient populations, patients mostly had rheumatoid arthritis (50.2% for 'duration', 40.4% for 'time to onset', and 46.3% for 'self-management strategies'). The calculated median duration of injection site reactions, infections and skin reactions was 2.25 days (interquartile range (IQR) 11.0 days), 31.0 days (IQR 63.0 days), and 95.5 days (IQR 174.3 days), respectively. Besides, the median calculated time to onset of the included ADRs was 1.5 months (IQR 3.9 months) for injection site reactions, 10.2 months (IQR 29.1 months) for infections, and 2.0 months (IQR 6.7 months) for skin reactions. Furthermore, the most frequently applied self-management strategies for injection site reactions, infections, and skin reactions involved the themes 'changing methods of administration', 'additional treatment for the ADR', and 'change of personal care', respectively.
**Conclusion:** This study showed that the current ADR information provision in the Netherlands does not comply with the patient preferences and needs regarding ADR information and that data of a pharmacovigilance centre can provide in this.

***Keywords:*** *Adverse drug reaction, ADR information, Duration, Time to onset, Self-management strategies, Biologics, Pharmacovigilance centre, Injection site reactions, Skin reactions, Infections.*

## Table of Contents

## List of abbreviations

| | |
|---|---|
| **ADR** | Adverse drug reaction |
| **ATC** | Anatomical Therapeutic Classification |
| **bDMARD** | Biological disease-modifying antirheumatic drug |
| **DBM** | Dutch Biologic Monitor |
| **FK** | Farmacotherapeutisch Kompas (English: Pharmacotherapeutic Compass) |
| **GP** | General practitioner |
| **HCP** | Healthcare professional |
| **HLGT** | High Level Group Term |
| **HLT** | High Level Term |
| **IMID** | Immune-mediated inflammatory disease |
| **IQR** | Interquartile range |
| **LLT** | Lowest Level Term |
| **MedDRA** | Medical Dictionary for Regulatory Activities |
| **PIL** | Patient information leaflet |
| **PT** | Preferred Term |
| **Q1** | Quartile 1 |
| **Q3** | Quartile 3 |
| **RA** | Rheumatoid Arthritis |
| **RWD** | Real World Data |
| **SmPC** | Summary of Product Characteristics |
| **SOC** | System Organ Classes |
| **SpA** | Spondyloarthritis |
| **TNF-α** | Tumour Necrosis Factor-alpha |
| **WHO** | World Health Organization |

# 1. Introduction

An adverse drug reaction (ADR) is defined by The World Health Organization (WHO) as (1):

*"Any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or the modification of physiological function.''*

ADRs are slowly becoming a public health problem due to their growing clinical and economic impact (2,3). Therefore, patients and healthcare professionals (HCPs) must have sufficient information about ADRs. Furthermore, information about ADRs is patients' most frequently requested type of drug-related information. They state that sufficient information about this topic can contribute to making better-informed decisions about their treatment and that the needs for reliable ADR information sources are high (4–6). Besides, a study by Leporini et al. showed that ADRs belong to one of the major impediments to patients' medication use and that accurate and understandable information about this topic is needed (6).

Today, information about ADRs is limited to the patient information leaflet (PIL) or several informative websites, which mostly do not accommodate the patients' information needs and are often not read (4). Misjudgement of ADRs is a common problem in healthcare because it may lead to non-adherence to the drug treatment, which has clinical and economic implications (7–9). Furthermore, the list of ADRs in the PIL deters some patients and evokes emotional reactions such as fear or anxiety. Therefore, patients may decide not to take the medicine at all (10,11). For that reason, ADR information provision must suit the patients' preferences to understand ADRs better, reduce fear and anxiety towards a medicinal treatment, and improve drug adherence.

Kusch et al. composed seven domains in a systematic review regarding ADR information needs and preferences of patients that comprise: frequency, severity, time to onset of ADRs (i.e., at the beginning of treatment vs prolonged effects), duration of ADRs, prevention strategies, monitoring of ADRs, and self-management strategies on how to treat (the burden of) the ADR/when to visit a physician. This information helps compose ADR information tools (12).

The Netherlands Pharmacovigilance Centre Lareb (hereinafter: Lareb) generates knowledge about pharmacovigilance, including information about aspects of ADRs. Their job is to disseminate this information to HCPs and patients. Therefore, they are developing a new ADR information tool, which will be elaborated on in the following subheading.

## 1.1 Background information: the Bijwerkingwijzer

To meet patients' individual needs regarding ADR information, Lareb is developing the Bijwerkingwijzer (https://www.bijwerkingwijzer.nl). This online tool encloses patient-reported

information on ADRs and will be developed especially for patients but can also be used by HCPs. It will be the first website in the Netherlands to entirely focus on ADRs. Since patients find different information about ADRs important compared to HCPs, Lareb will use patient preferences regarding ADR information as the foundation of this website (13,14).

The pilot version of the Bijwerkingwijzer was tested with fictitious data before and contained: ADR prevalence, ADR prevalence when the medication is used for other conditions, the gender ratio of an ADR, age differentiation of patients with the ADR, course and burden of the ADR. However, this tool needed to be optimised according to patient preferences. Moreover, involving these preferences contributes to more patient-centred care, improving individual health outcomes and giving financial benefits (15).

Lareb is currently developing this tool for patients using biologics to treat immune-mediated inflammatory diseases (IMIDs) as the use of biologics has been rapidly increasing during the past years (16). Besides, optimising pharmacovigilance is essential due to these medicines' relatively new and expensive character. Lareb will expand the usefulness of this tool for patients with other conditions and medicines in the future.

## 1.2 Research context

As described before, Lareb is developing a new ADR information tool containing different topics about ADRs. The previously mentioned domains of Kusch et al. are a solid foundation of subjects, as patients prefer them. Furthermore, Lareb has several data sources containing real-world data (RWD) about ADRs, such as spontaneous reports of ADRs and reports from cohort event monitoring studies (i.e. the Dutch Biologic Monitor (DBM)), which could be used to provide information on the Bijwerkingwijzer. However, it is unknown if this data may provide information aligned with the previously mentioned domains.

To assess whether these sources provide information preferred by patients, the two most frequently used biologics in the DBM were studied, adalimumab and etanercept, and the three most commonly reported ADRs, namely: injection site reactions, infections and skin reactions (17).

### 1.2.2 Included domains

Not all seven domains can be analysed in this study. However, only domains that can be extracted from the included data sources, and are relevant to use on the Bijwerkingwijzer, are included. The included domains in this study are ‘duration’, ‘time to onset’ and ‘self-management strategies’ of ADRs. The domains ‘frequency’, ‘prevention strategies’, ‘appropriate monitoring’ and ‘severity’ of ADRs are not included. Frequencies and appropriate monitoring of ADRs can be found in other sources such as the

PIL and protocols, respectively. Furthermore, HCPs should give information on the severity of ADRs without deterring patients and prevention strategies require different methods than used in this study.

## 1.3 Objectives

This study consists of two parts. The first part of the study aims to assess whether the current information on ADRs in the Netherlands fulfils the previously identified domains regarding information needs and preferences of patients.

The objective of the second and central part of the study consists of examining to what extent pharmacovigilance centre data sources contain information about duration, time to onset and self-management strategies of injection site reactions, infections and skin reactions of patients with IMIDs using adalimumab or etanercept.

# 2. Methodology

The previous chapter emphasised the importance of this study and introduced the objectives. This section will give more information about the study design, including data sources and analysis used to obtain the results for objectives one and two in this study.

## 2.1 Study design

First, an assessment of available ADR information sources in the Netherlands was conducted and compared with the domains identified by Kusch et al. For each biologic included in this study was looked at whether the seven domains were addressed at the source (objective one).

Second, an observational study was conducted using different approaches to determine whether RWD collected by pharmacovigilance centres could fulfil patients' information needs and preferences regarding ADR information provision. For the domains duration, time to onset, and self-management strategies were looked at whether the included data sources could provide this information. This method was applied for the three most frequently reported ADRs of adalimumab and etanercept, namely: injection site reactions, infections and skin reactions (objective two).

## 2.2 Comparison of ADR information sources in the Netherlands

The methodology for the first objective of this study will be presented in the following sections.

### 2.2.1 Search strategy

Several sources were included to assess whether the current ADR information sources in the Netherlands provide ADR information preferred by patients. This study included a source if it was publicly available for patients and if the information was reliable and evidence-based. Information was seen as reliable if HCPs or the government had compiled it. Evidence-based information meant that the presented ADR information was supported by scientific research.

### 2.2.2 Testing availability of ADR information

The included sources were tested on the availability of ADR information of adalimumab and etanercept. The availability of frequency, severity, time to onset, duration, self-management strategies, appropriate monitoring, and prevention strategies was considered. If a domain was available at the source, a ‘+’ sign was given. Domains could also be partially available, which meant it was present for one ADR but not for all ADRs presented at the source. If this was the case, a ‘±’ sign was assigned. A ‘-’ sign indicated that the domain was not available at the source.

## 2.3 Obtaining ADR information from pharmacovigilance centre data sources

The second objective of this study focussed on obtaining information on the three included domains from pharmacovigilance centre data sources. Information on the included data sources and analysis of this data is presented in the following sections.

### 2.3.1 Data sources

On behalf of completeness, two types of data sources from Lareb were included in this study. The first included data source was a cohort event monitoring database that included data collected during the DBM, held from 2017-2020 (18). Patients eligible for participation in the DBM were biologic users with IMIDs. In the DBM, patients had to fill in bimonthly questionnaires about possible ADRs that occurred during the use of their biologic. A total of 9370 questionnaires were completed at the end of the DBM. As a result, the DBM included data on the burden of ADRs, ADR course, start/recovery dates of ADRs, self-management strategies, and other types of information concerned with ADRs attributed to treatment with biologics in patients with IMIDs (19).

The second data source included spontaneous reported ADRs, which could either be reported by the patient or HCP on the website of Lareb (20). This data source included data on ADR reports, start date, seriousness, burden and outcome of the ADR.

Thus, these two pharmacovigilance centre data sources provide data to acquire knowledge on ADRs and will be included in this study to test whether they meet patients' information preferences and needs regarding ADR information provision.

### 2.3.2 Data processing

Professional pharmacovigilance assessors of Lareb coded the ADRs in the included databases. The used codes come from the Medical Dictionary for Regulatory Activities (MedDRA), version 20.1 (21). MedDRA is a dictionary for medical terminology and exists of five levels, ranging from specific to broad terminology: Lowest Level Terms (LLTs), Preferred Terms (PTs), High-Level Terms (HLTs), High-Level Group Terms (HLGTs) and System Organ Classes (SOCs). SOCs consist of grouped HLGTs merged on aetiology, manifestation site or purpose (22). For infections and skin reactions, the SOCs ‘infections and infestations’ and ‘skin and subcutaneous tissue disorders’ were used, respectively, to select ADRs because it retrieves the data most widely. The SOC in which injection site reactions are classified is called 'general disorders and administration site conditions' that also includes other types of conditions and therefore is too broad for this study. Therefore, The HLGT 'administration site reactions' was used for injection site reactions to select the ADRs. The medicinal products used in this study are classified according to the WHO Anatomical Therapeutic Classification (ATC) system (23).

### 2.3.3 Data analysis

The three included domains were analysed using SPSS version 22.0 and Microsoft Excel 2019. It is important to clarify that different selection criteria were applied for each domain to meet the objectives. This resulted in the selection of three different patient populations, all of which were analysed differently, as described in the following sections. Furthermore, the analysis of each domain started with descriptive statistics to generate patient characteristics.

#### 2.3.3.1 Duration

The duration of an ADR indicates how long the ADR lasts. Only data from the cohort event monitoring system (DBM) could be used to meet this definition. Therefore, this data source was used to calculate the duration of the three included ADRs. Patients who participated in the DBM had to fill in the start date of the reported ADR. Besides, they were asked to mark their ADR as ‘recovered/resolved’, ‘recovering/resolving’, ‘not recovered/not resolved/ongoing’, and ‘not recovered/not resolved/got worse’. If a patient indicated that the relevant ADR was recovered/resolved, they were asked to fill in the specific recovery date of the ADR. This date could later be used to calculate the duration of the ADR. Also, patients could use the open-ended text fields to add additional information about the course of their ADR. Some patients used these fields to describe the duration instead of giving an accurate recovery date. Therefore, open-ended text fields were leading in calculating the duration of an ADR because some patients found it challenging to understand what date to fill out in the 'recovery date '-section.

Furthermore, if a patient mentioned that the ADR lasted ‘a couple of’, ‘some’ or ‘a few’ minutes/hours/days, a duration of 2.55 minutes/hours/days was filled in because these words are often interpreted as two or three, so the mean was taken (24). Instead of using 2.5, 2.55 was used to recognise these reports in the data easily. Also, when a patient mentioned that the ADR lasted two to three days, for example, the mean was calculated.

Patients were included for the domain ‘duration’ if they filled in the start and recovery date of their ADR and/or clarified the duration of the ADR in the open-ended text fields. Conversely, patients who did not meet these criteria or who indicated that the recovery date of the ADR was previously to the start date were excluded (figure 1).

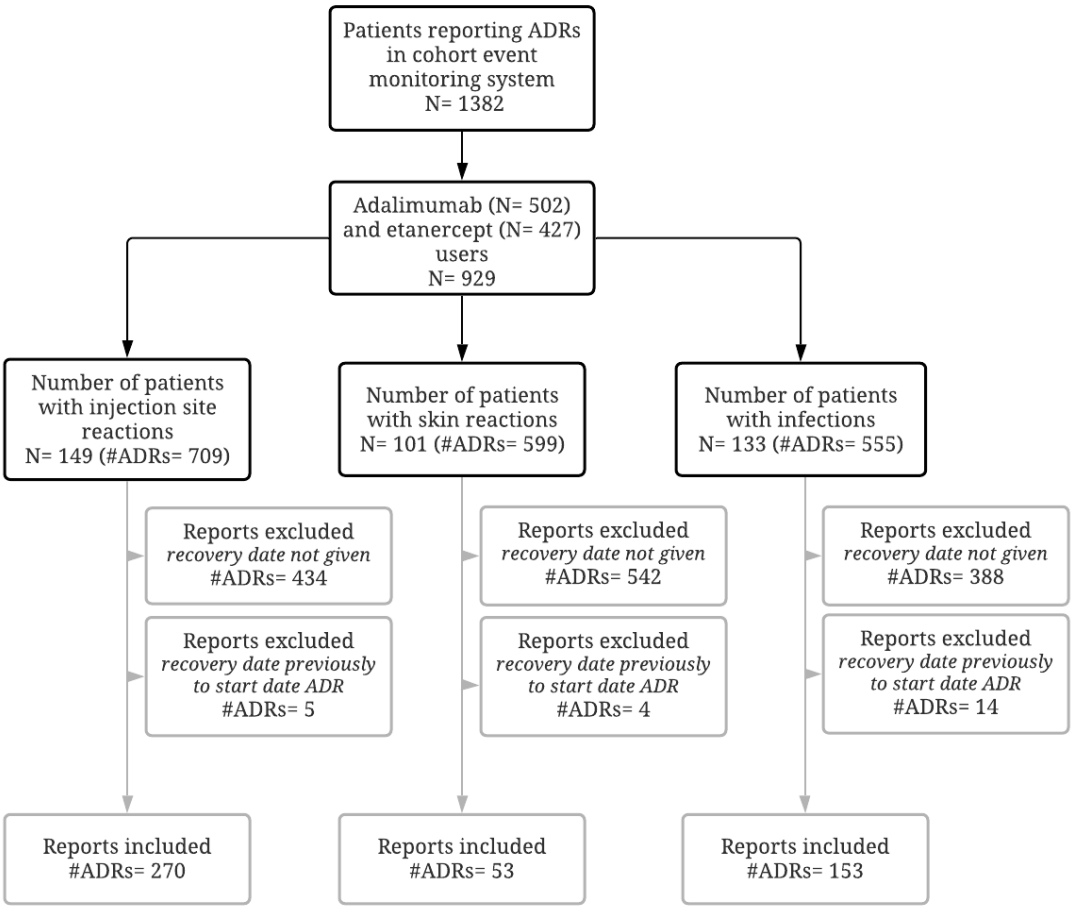


**Figure 1.** Flowchart of the patient and adverse drug reaction (ADR) report selection to meet the inclusion criteria of the domain 'duration'.

*Note: N= number of patients, #ADRs= number of adverse drug reactions (ADRs).*

For each included report was calculated what the average duration was in days. The following formula was used:

$$Recovery\ date\ of\ the\ ADR\ -\ start\ date\ of\ the\ ADR\ =\ duration\ of\ the\ ADR$$

As mentioned before, patients participating in the DBM had to fill in multiple questionnaires to report several ADRs, which were either different or the same as before. Therefore, one patient could have multiple reports considering one ADR. All the reports were taken into account, and if one patient reported the exact ADR multiple times, the duration of these reports was averaged (figure 2). Therefore, the number of reports was expressed in #ADRs (number of ADRs).

Finally, the duration could not be calculated for the spontaneous report registry because the recovery date of the ADR was not requested in this data source, and no open-ended text fields were present to describe the course of the ADR. The spontaneous reports only illustrated the course of the ADR concisely, i.e., whether it was ‘resolved,’ ‘ongoing,' or ‘status unknown.’

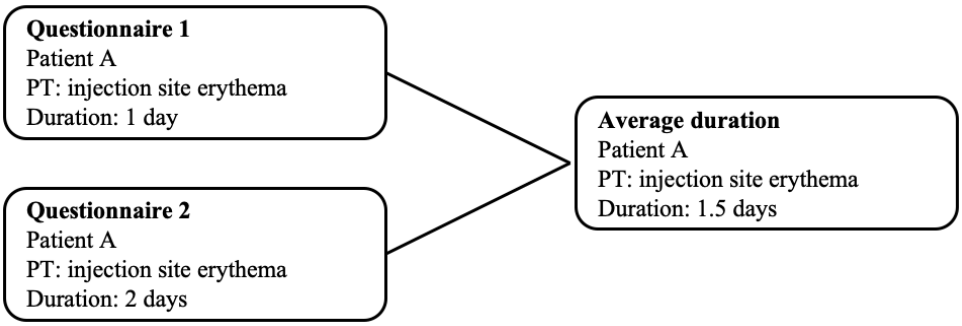


**Figure 2.** Example of calculating the average duration of the same adverse drug reaction (ADR) report from one patient.

*Note: PT = preferred term.*

#### 2.3.3.2 Time to onset

The time to onset describes how long it takes for an ADR to occur after starting the treatment, also known as latency time. For example, if an ADR occurs several hours after the start of therapy or if it is a long-term effect. Latency periods were calculated in months to examine the time to onset of an ADR by using the following formula:

$$ADR\ start\ date\ -\ medicine\ start\ date\ =\ latency\ period$$

Both the spontaneous ADR report registry and the cohort event monitoring system contained information about the latency periods of ADRs. However, the spontaneous ADR report registry was the most useful source to calculate latency periods. Therefore, only this data source was used to calculate latency periods and describe the onset of an ADR.

To calculate latency periods, patients with IMIDs who used adalimumab or etanercept and reported injection site reactions, infections or skin reactions were selected. Reports were excluded if the start date of the biologic or ADR was not given or if the start date of the ADR was previously to the start date of the biologic (figure 3).

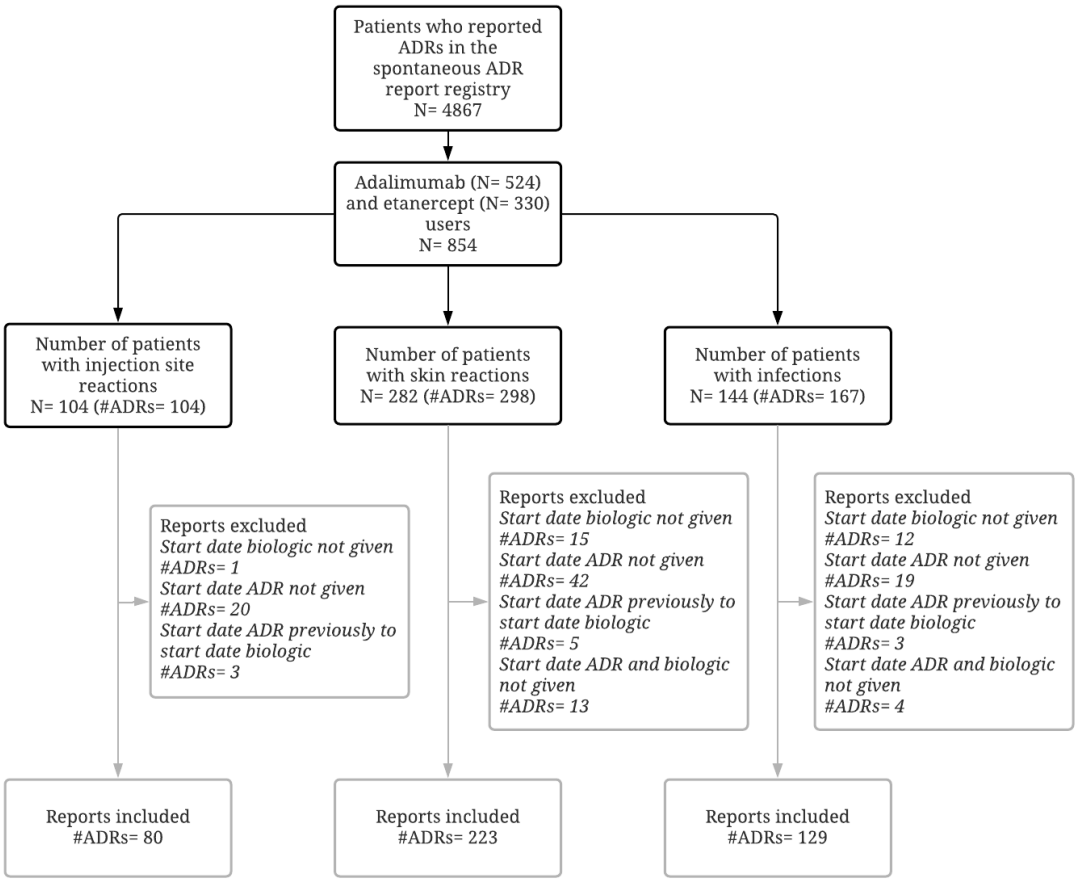


**Figure 3.** Flowchart of adverse drug reaction (ADR) report selection in the spontaneous ADR report registry to calculate the time to onset of the included ADRs.

*Note: N= number of patients, #ADRs= number of adverse drug reactions (ADRs).*

#### 2.3.3.3 Self-management strategies

Self-management strategies include all patient-initiated actions to handle an ADR. In the cohort event monitoring database (DBM), patients could mention if they carried out specific actions to reduce the burden of their ADR. Patients filling in 'yes, namely:' were included in this study. Patients who filled in 'no' were excluded (figure 4). Open-ended text fields could be used to describe the self-management strategy they applied. The spontaneous report registry did not contain a field where self-management strategies could be filled out, so this database could not be used for this domain.

Subsequently, after selecting the patients who were eligible for inclusion, a thematic analysis was conducted. The open-ended text fields were read and coded, resulting in several subthemes emerging. These subthemes were ultimately merged into overarching themes. Finally, the included ADR reports were categorised according to their theme. For example, if patients reported multiple self-management strategies in one open-ended text field, they were split up and categorised into several themes. Furthermore, suppose a patient used a prescribed medicinal treatment to cure the ADR. In that

case, it could also be seen as a self-management strategy because the doctor's visit was on the patient's initiative.

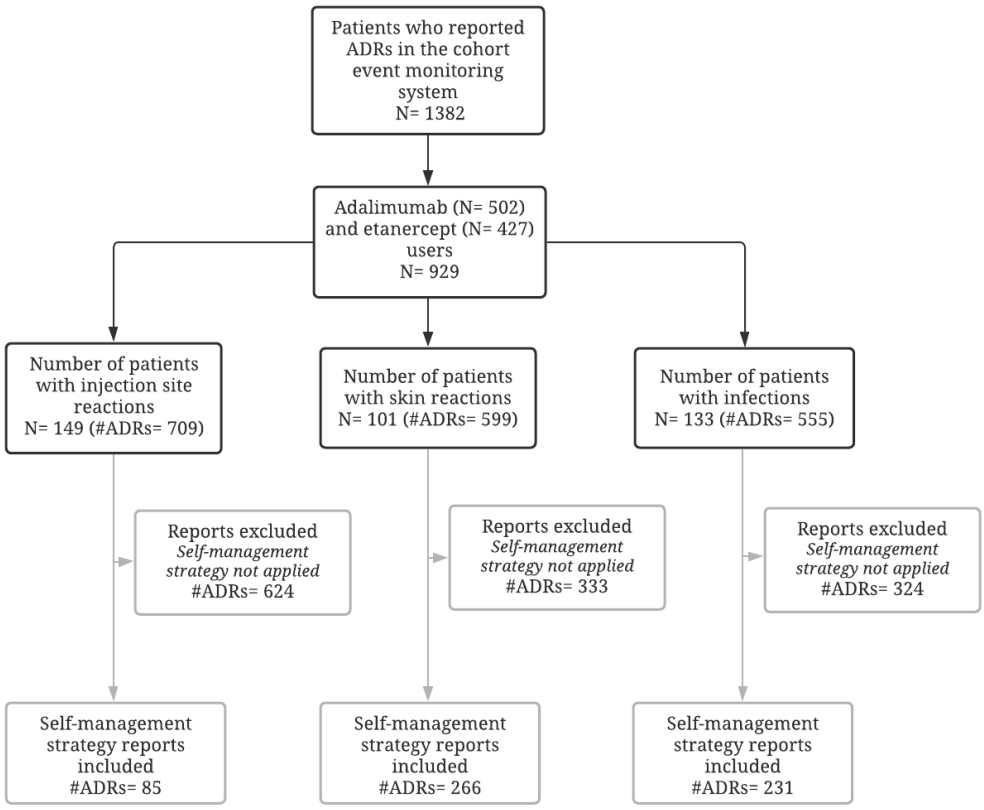


**Figure 4.** Flowchart of the adverse drug reaction (ADR) report selection regarding self-management strategies from the cohort event monitoring system.

*Note: N= number of patients, #ADRs= number of adverse drug reactions (ADRs*).

## 3. Results

This chapter will present the obtained results for objectives one and two of this study. In addition, relevant results will be supported and clarified by using tables and figures presented in the following sections.

### 3.1 Comparison of ADR information sources in the Netherlands

Five reliable and evidence-based sources containing ADR information in the Netherlands were found and included in this study. First, the website of Lareb was included, which mainly consists of information or notifications about ADRs for both patients and HCPs (25). The second source is the PIL, which is available for each patient as it is added to the packaging of a registered medicine. Besides, patients can also search for the PIL online (26). Another source included is Apotheek.nl, a website compiled by pharmacists containing information about medicines for patients (27). Furthermore, Farmacotherapeutisch Kompas (FK) (in English: Pharmacotherapeutic Compass) is included, a book and website specially made for HCPs. Nevertheless, this source is publicly available, reliable, and evidence-based, thus included in this study (28). The final source is Kijksluiter.nl, the visualised PIL for patients who cannot read (29). In order to see whether these sources enclose the seven previously mentioned domains, the presented information about the biologics included was screened. Table 1 presents the results of this screening.

**Table 1.** Screening of five primary adverse drug reaction (ADR) information sources in the Netherlands for containing seven ADR information domains that patients prefer.

| Sources | Domains | | | | | | |
|---|---|---|---|---|---|---|---|
| | Frequency | Severity | Time to onset | Duration | Self-management strategies | Appropriate monitoring | Prevention strategies |
| Lareb | + | + | ± | ± | ± | - | - |
| PIL | + | ± | - | - | ± | - | - |
| Apotheek.nl | + | ± | ± | ± | ± | - | - |
| FK | + | - | - | - | - | - | - |
| Kijksluiter.nl | + | ± | - | - | ± | - | - |

*Note: '+' sign= domain available at the source, '±' sign= domain partially available at the source, '-' sign= domain not available at the source, Lareb= the Netherlands Pharmacovigilance Centre Lareb, PIL= Patient information leaflet, FK= Farmacotherapeutisch Kompas.*

This screening showed that Lareb and Apotheek.nl have the highest score. The PIL and kijksluiter.nl have an equal score, followed by FK with the lowest score. In addition, the domains 'severity', 'time to onset', 'duration', and 'self-management strategies' were partially available at the website of Lareb, the PIL, Apotheek.nl, and Kijksluiter.nl. A domain was marked as partially available when the relevant domain was present for one ADR but not for the other. For example, on Apotheek.nl, the duration of

injection site reactions was given, but the duration of skin reactions was not. Furthermore, the self-management strategies that were given only included information on when to consult a physician, but no other self-management strategies were described.

## 3.2 Obtaining ADR information from pharmacovigilance centre data sources

The following subheadings present the results of the data extraction regarding the three included domains: duration, time to onset, and self-management strategies.

### 3.2.1 Duration

The duration was calculated using the previously mentioned formula in section 2.4.1 of the Methodology chapter. The following subheadings present what the calculated duration was per ADR. The duration is expressed by the median, interquartile range (IQR), quartile 1 (Q1) and quartile 3 (Q3) for all the ADRs because the data was skewed. Moreover, some patients filled in an extremely low or high duration of an ADR, so the mean duration was not representative for the majority of the data.

#### 3.2.1.1 Patient characteristics

Table 2 presents the patient characteristics of the included patients for this domain. The total number of included patients was 217. Most patients were female (73.3%), and the mean age was 52.4 years (y) (± 13.8 y). All patients suffered from IMIDs, with rheumatoid arthritis as the most common condition (50.2%), followed by psoriatic arthritis (17.5%) and Bechterew's disease/axial spondyloarthritis (SpA) (10.1%). The distribution of adalimumab and etanercept users was nearly equal, 51.2% vs 48.8%, respectively.

**Table 2.** Patient characteristics of included patients for the 'duration' domain.

| *Patient characteristics, N= 217* | |
|---|---|
| **Gender,** N (%) | |
| Female | 159 (73.3) |
| **Age,** mean (SD) | 52.4 y (±13.8 y) |
| **Indication,** N (%) | |
| RA | 109 (50.2) |
| Psoriatic arthritis | 38 (17.5) |
| Bechterew’s disease and RA | 2 (0.9) |
| Bechterew’s disease/axial SpA | 22 (10.1) |
| Bechterew’s disease/axial SpA and psoriasis | 2 (0.9) |
| Bechterew’s disease/axial SpA and psoriatic arthritis | 1 (0.5) |
| Crohn’s disease | 21 (9.7) |
| Ulcerative colitis | 3 (1.4) |
| Psoriasis | 5 (2.3) |
| Other[a] and RA | 3 (1.5) |

| | |
|---|---|
| Other[b] and psoriatic arthritis | 1 (0.5) |
| Other[c] | 10 (5) |
| **bDMARD,** N (%) | |
| Adalimumab | 111 (51.2) |
| Etanercept | 106 (48.8) |

[a]Rheumatoid arthritis-associated lung disease (n=1), systemic lupus erythematosus (n=1), systemic scleroderma (n=1).

[b]Peripheral spondylitis (n=1).

[c]Uveitis posterior and panuveitis (n=2), ADA2 deficiency (n=1), birdshot chorioretinopathy (n=1), hemochromatosis (n=1), hidradenitis suppurativa (n=1), juvenile idiopathic arthritis (n=2), sarcoidosis and uveitis (n=1), vasculitis and uveitis (n=1).

*Note: N= number of patients, SD= standard deviation, y= years, RA= rheumatoid arthritis, SpA= spondyloarthritis, bDMARD= biological disease-modifying antirheumatic drugs.*

#### 3.2.1.2 Injection site reactions

The cohort event monitoring system showed 709 ADR reports of injection site reactions from 149 patients using adalimumab or etanercept. A total of 270 reports met the inclusion criteria and were included in this study. The other 439 reports were excluded for not meeting the inclusion criteria (figure 1). After averaging to gain unique PTs, a total of 165 reports were left to analyse. The included injection site reactions consisted of injection site pain (26.7%), pruritus (23.0%), erythema (14.5%), inflammation (13.3%), haematoma (10.9%), swelling (6%), irritation (3.0%), rash (2.4%), induration (1.2%), vesicles (1%), and discomfort (0.6%) according to the MedDRA PTs.

Figure 5 shows that 18% (#ADRs= 29) of the reported injection site reactions lasted shorter than a day, ranging from thirty seconds (#ADRs= 1) to twelve hours (#ADRs= 4). Of that 18%, seventeen reports (58.6%) indicated that the ADR lasted 'zero' days by filling in the same start as recovery date. Patients explained in the open-ended text fields that this either meant that the ADR was present during injection (#ADRs= 6) or that the ADR resolved the same day (#ADRs= 1). The other ten reports did not clarify the duration of 'zero' days in the open-ended text fields. Additionally, most reports (61%) stated that the ADR lasted three days or less. Thus, 39% reported that the ADR lasted longer than three days.

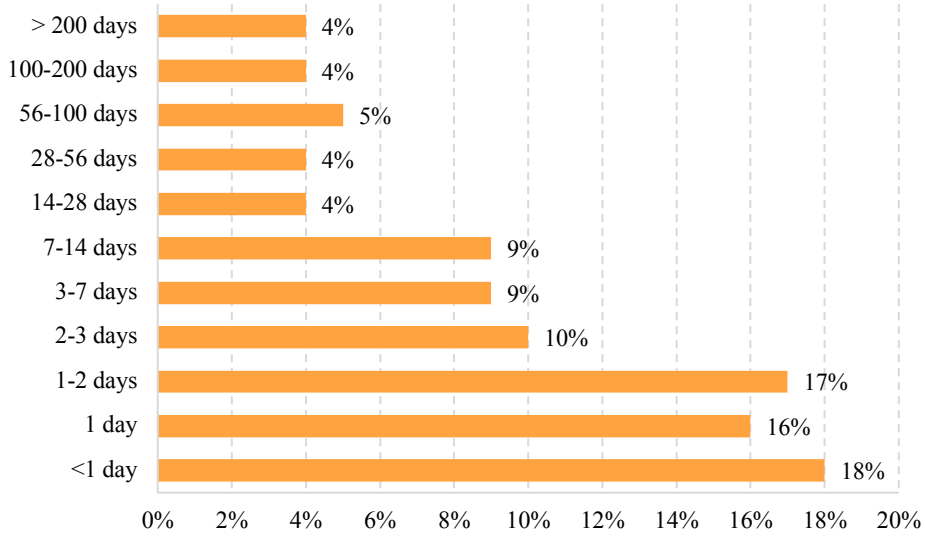


**Figure 5.** Frequencies of different durations for injection site reactions (x-axis) presented in days (y-axis).

Injection site pain (#ADRs= 44), pruritis (#ADRs= 38) and erythema (#ADRs= 24) were the most frequently mentioned PTs of injection site reactions. The median duration of these ADRs gave the most accurate representation of the data and was respectively 1.0, 2.0 and 2.1 days. Table 3 shows the corresponding IQR, Q1 and Q3.

**Table 3.** The median duration and corresponding interquartile range (IQR), quartile 1 (Q1) and quartile 3 (Q3) of the most frequently mentioned injection site reactions: pain, pruritus and erythema.

| Injection site reaction | Duration (days) | | | |
|---|---|---|---|---|
| | #ADRs | Median (IQR) | Q1 | Q3 |
| Pain | 44 | 1.0 (11.8) | 0.0 | 11.8 |
| Pruritus | 38 | 2.0 (3.2) | 1.0 | 4.2 |
| Erythema | 24 | 2.1 (14.9) | 1.0 | 15.9 |

*Note: #ADRs= number of adverse drug reactions.*

#### 3.2.1.3 Infections

For infections, 133 patients reported 555 ADRs, of which 153 met the inclusion criteria (figure 1). After averaging similar PTs from one patient, 126 reports were analysed. These 126 reports included 39 unique PTs. Nasopharyngitis (12.7%), pneumonia (11.9%), and cystitis (11.1%) were the three most frequently mentioned infections. The most prolonged median duration was 60.8 days of nasopharyngitis, followed by pneumonia with a median duration of 31.0 days. Cystitis lasted the shortest, with a median duration of 10.2 days. The reported duration of the three most frequently mentioned ADRs was diverse, as displayed by the IQRs (table 4).

**Table 4.** The median duration and corresponding interquartile range (IQR), quartile 1 (Q1) and quartile 3 (Q3) of the most frequently reported infections: cystitis, pneumonia and nasopharyngitis.

| Infection | Duration (days) | | | |
|---|---|---|---|---|
| | #ADRs | Median (IQR) | Q1 | Q3 |
| Cystitis | 14 | 10.2 (32.5) | 7.8 | 40.3 |
| Pneumonia | 15 | 31.0 (44.0) | 11.0 | 55.0 |
| Nasopharyngitis | 16 | 60.8 (97.1) | 2.7 | 99.8 |

*Note: #ADRs= number of adverse drug reactions.*

The fourteen reports of cystitis infections included two reports (14.3%) that described a duration of three days. However, five reports indicated that the ADR lasted 34 days or longer, of whom two explained in the open-ended text fields they had to receive two antibiotic treatments to resolve the condition. Also, in one of these five reports, the patients stated that the ADR resolved after antibiotic treatment of three months. Furthermore, the remaining reports indicated a duration between 7-30 days (#ADRs= 7), of which two reports explained that the patient suffered from several cystitis infections a year.

In addition, six of the fifteen reports (40%) from patients who suffered from pneumonia indicated that the ADR had a duration of three weeks or less, with one patient reporting that the ADR resolved within three days. The infection lasted longer than a hundred days in two reports (13.3%), of which one person had to use antibiotics permanently. The remaining seven reports (46.7%) ranged from 25-92 days.

Furthermore, in six nasopharyngitis reports (37.5%), patients indicated the infection lasted fifteen days or less. Four reports (25%) showed a duration longer than a hundred days. The remaining reports ranged from 31-96 days (#ADRs= 6).

Concluding, out of the 126 reports, 48 infections (38%) resolved within two weeks (figure 6). One patient reported a duration of ‘zero’ days. The open-ended text field did not clarify the course of this ADR, but due to lack of argumentation to reject this report, it was included in the analysis. In addition, 28 reports (22%) had a duration of 4-8 weeks. Infections lasting over a year (#ADRs= 7) ranged from 426 days to 966 days. One report of 937 days indicated that the patient suffered from an increased infection susceptibility during the use of adalimumab. Also, one patient with a vulvovaginal mycotic infection described that the infection was recurrent. The remaining five reports did not clarify the duration in the open-ended text field.

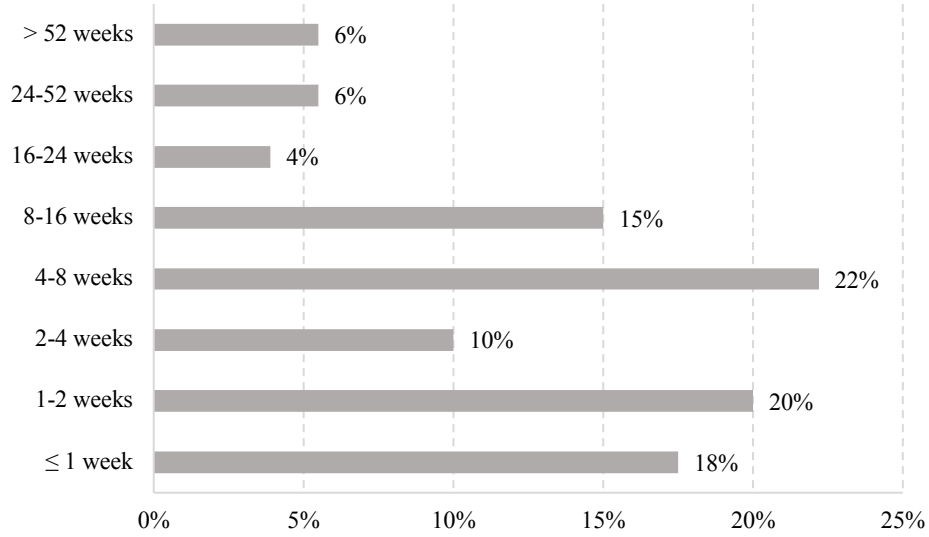


**Figure 6.** Frequencies of different durations for infections (x-axis) presented in weeks (y-axis).

#### 3.2.1.4 Skin reactions

The total number of reports considering skin reactions from patients using adalimumab or etanercept was 599. A total of 53 reports of skin reactions met the inclusion criteria (figure 1). After calculating the average duration of similar PTs per patient, 44 reports were analysed. These 44 reports included 25 unique PTs. The most frequently reported skin reactions were pruritus (20.5%) and pruritic rash (11.4%). The median duration of these ADRs was seven and 196 days, respectively (table 5). Five reports were made concerning pruritic rash, of which one report had a duration of 1219 days. The patient explained that the rash was expanding in the open-ended text fields and made an appointment with the general practitioner (GP). The remaining four reports indicated that the rash was over but gave no explanation about the course of the ADR. Furthermore, nine reports were made of pruritus, in which three reports indicated that the ADR occurred during or right after injecting. Three reports had a duration of 97-238 days but did not explain the course of the ADR.

**Table 5.** The median duration and corresponding interquartile range (IQR), quartile 1 (Q1) and quartile 3 (Q3) of the most frequently reported skin reactions: pruritus and pruritic rash.

| Skin reaction | Duration (days) | | | |
|---|---|---|---|---|
| | #ADRs | Median (IQR) | Q1 | Q3 |
| Pruritus | 9 | 7.0 (108.5) | 1.0 | 109.5 |
| Pruritic rash | 5 | 196.0 (747.0) | 117.5 | 864.5 |

*Note: #ADRs= number of adverse drug reactions.*

Looking all the included reports of skin reactions, the majority of skin reactions (54%) lasted either ≤ 1 week (27%) or 12-26 weeks (27%) (figure 7). Four out of twelve reports from ≤ 1 week (33.3%)

indicated that the ADR occurred during the administration of the biologic. Furthermore, 16% (#ADRs= 7) of the reports indicated a longer than one-year duration. Two of these reports reported 'dry skin' and 'psoriasis' and described that the infection was recurrent. One patient indicated that the pruritic rash was expanding, as explained earlier. The remaining four reports did not clarify the duration of their ADR.

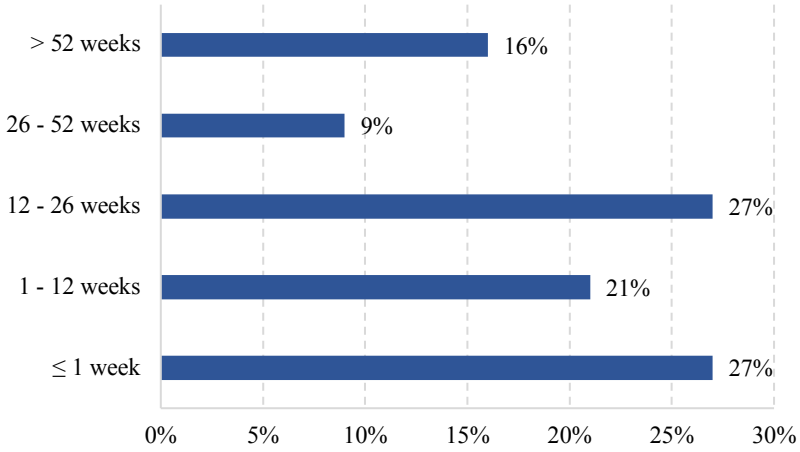


**Figure 7.** Frequencies of different durations for skin reactions (x-axis) presented in weeks (y-axis).

#### 3.2.1.5 Duration of adverse drug reactions compared to each other

The subheadings above present the calculated durations for the three included ADRs. This section shows the durations compared to each other. These median durations of injection site reactions, infections and skin reactions were 2.25, 31.0, and 95.5 days, respectively. The corresponding IQR, Q1, and Q3 are presented in table 6.

**Table 6.** The median duration and corresponding interquartile range (IQR), quartile 1 (Q1) and quartile 3 (Q3) of injection site reactions, infections and skin reactions.

| Adverse drug reaction | Duration (days) | | | |
|---|---|---|---|---|
| | #ADRs | Median (IQR) | Q1 | Q3 |
| Injection site reactions | 165 | 2.25 (11.0) | 1.0 | 12.0 |
| Infections | 127 | 31.0 (63.0) | 11.0 | 74.0 |
| Skin reactions | 44 | 95.5 (174.3) | 7.0 | 181.3 |

*Note: #ADRs= number of adverse drug reactions.*

The spread of durations is further specified in figure 8 and shows the duration of injection site reactions, infections, and skin reactions compared to each other. This figure shows that injection site reactions mostly (70%) lasted shorter than or equal to a week, infections mostly lasted 2-8 weeks (32%). Most skin reactions lasted shorter than or equal to a week (27%) or 16-26 weeks (21%).

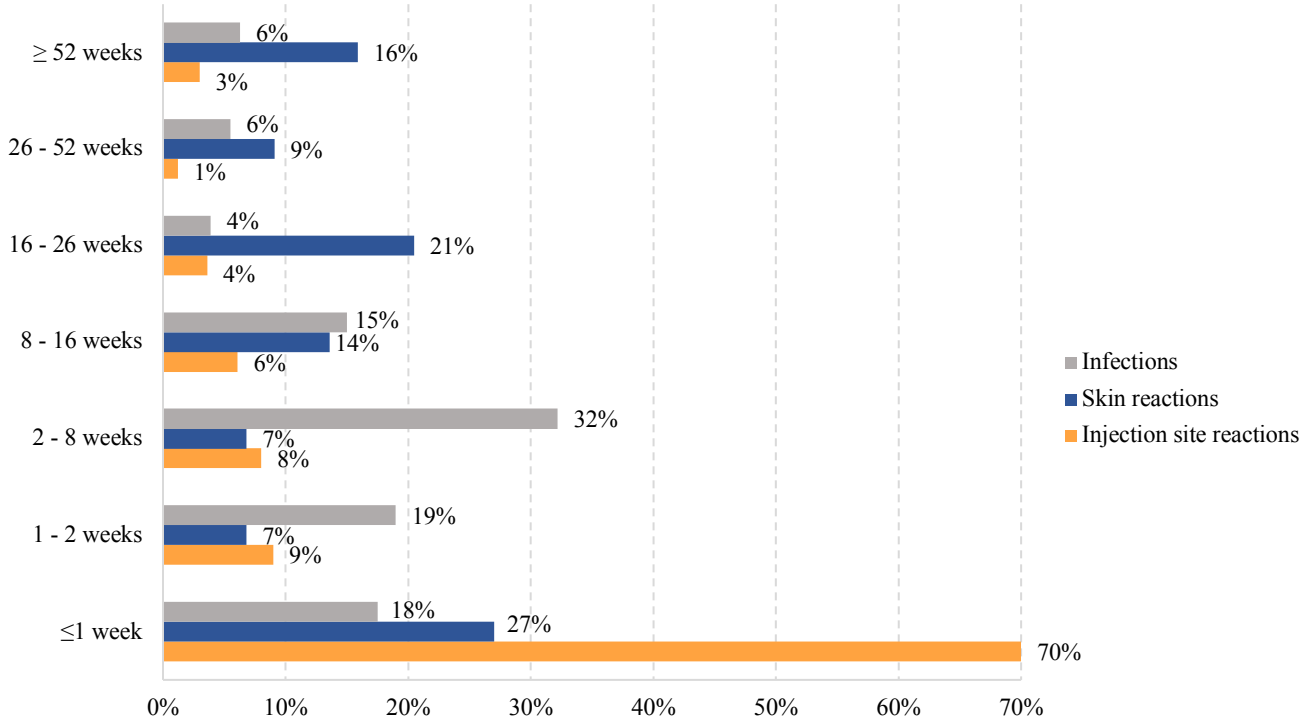


**Figure 8.** Frequencies of different durations for infections, skin reactions and injection site reactions (x-axis) in weeks (y-axis) compared to each other.

### 3.2.2 Time to onset

For the 'time to onset' domain, the total amount of reports included was 432. Out of these reports, 167 were made by physicians, 87 by pharmacists, 148 by patients or other non-healthcare professionals, 29 by other healthcare professionals and one reporter was unknown. Therefore, the calculated latency periods of the ADRs were skewed, thus presenting the median with the corresponding IQR, Q1, and Q3 was the best way to present the data.

#### 3.2.2.1 Patient characteristics

Table 7 presents the patient characteristics of the included patients for this domain. The total amount of included patients was 403, of which 78.7% was female. The mean age was 47.5 y (±16.63 y). Most of the patients suffered from rheumatoid arthritis (40.4%), followed by Crohn's disease (15.9%). Many reports belonged to the indication 'Other' because reporters often forgot to fill in the indication and were labelled as NULL (n=52). Also, most patients (64.5%) used adalimumab.

**Table 7.** Patient characteristics of the included patients for the 'time to onset' domain.

| *Patient characteristics, N= 403* | |
|---|---|
| **Gender,** N (%) | |
| Female | 317 (78.7) |
| **Age,** mean (SD) | 47.5 y (±16.63 y) |
| **Indication,** N (%) | |
| RA | 163 (40.4) |
| Ankylosing spondylitis | 29 (7.2) |
| Psoriatic arthropathy | 25 (6.2) |
| Rheumatic disorder | 14 (3.5) |
| Juvenile idiopathic arthritis | 6 (1.5) |
| Arthritis | 8 (2.0) |
| Crohn's disease | 64 (15.9) |
| Ulcerative colitis | 10 (2.5) |
| Psoriasis | 13 (3.2) |
| Other[a] | 71 (17.6) |
| **bDMARD,** N (%) | |
| Adalimumab | 260 (64.5) |
| Etanercept | 143 (35.5) |

[a]Acute febrile neutrophilic dermatosis (n=1), autoimmune disorder (n=2), hair disorder (n=3), hidradenitis (n=3), inflammatory bowel disease (n=1), polyarthritis (n=1), spondylitis (n=3) spondyloarthropathy (n=1), uveitis (n=2), product used for unknown indication (n=2), NULL (n=52).

*Note: N = number of patients, y = years, SD = standard deviation, RA= rheumatoid arthritis, bDMARD = biological disease-modifying antirheumatic drug.*

#### 3.2.2.2 Injection site reactions

A total of eighty reporters notified eighty injection site reactions that met the inclusion criteria and were included in calculating the latency periods (figure 3). Most reported PTs were injection site reaction (26.3%), pain (23.8%), and erythema (12.5%). According to the MedDRA terminology, the PT 'injection site reaction' classified: reaction injection site (NOS), injection site maceration, injection site muscle reaction, injection site reaction NOS, delayed injection site reaction following multiple administrations (30). The median time to onset of injection site reactions was 1.5 months, with an IQR of 3.9 months. Injection site pain and erythema had nearly the same onset with a median of 1.3 and 1.6 months, respectively. Injection site reaction had the lowest median with 0.4 months (12 days) (table 8).

#### 3.2.2.3 Infections

One hundred fourteen reporters notified the 129 spontaneous reports regarding infections that were eligible for inclusion. Out of these reports, herpes zoster infections (6.2%), pneumonia (10.1%), and respiratory tract infections (5.4%) were the three most frequently reported infections. The median onset of infections was 10.2 months with an IQR of 29.1 months. Pneumonia and herpes zoster infections had an equal median of 5.4 months. The IQR of pneumonia was greater in comparison with the IQR of

herpes zoster infections, 45.7 and 16.0 months, respectively. Respiratory tract infections had the longest time to onset with a median of 6.1 months (IQR= 19.1 months) (table 8).

#### 3.2.2.4 Skin reactions

Skin reactions were the most frequently reported of all three ADRs, with 223 reports by 215 reporters. The majority of reports included alopecia (13.5%), rash (12.1%), and pruritus (9.9%). The median time to onset of skin reactions was 2.0 months with an IQR of 6.7 months. Alopecia, rash and pruritis had a comparable median time to onset of 1.1, 0.7 and 1.9 months, respectively (table 8).

**Table 8.** The onset of injection site reactions, infections, skin reactions and the most frequently reported preferred terms (PT) presented in months.

| ADR | Time to onset (months) | | | |
|---|---|---|---|---|
| | #ADRs | Median (IQR) | Q1 | Q3 |
| Injection site reactions | 80 | 1.5 (3.9) | 0.08 | 3.9 |
| Injection site reaction | 21 | 0.4 (3.3) | 0.0 | 3.3 |
| Injection site pain | 18 | 1.3 (4.7) | 0.4 | 4.7 |
| Injection site erythema | 9 | 1.6 (2.2) | 0.2 | 2.3 |
| Infections | 129 | 10.2 (29.1) | 1.7 | 30.8 |
| Pneumonia | 13 | 5.4 (45.7) | 0.7 | 46.4 |
| Herpes zoster infections | 7 | 5.4 (16.0) | 1.0 | 17.0 |
| Respiratory tract infections | 7 | 6.1 (19.1) | 3.2 | 22.4 |
| Skin reactions | 223 | 2.0 (6.7) | 0.4 | 7.1 |
| Alopecia | 30 | 1.1 (6.3) | 0.5 | 6.7 |
| Rash | 27 | 0.7 (10.1) | 0.1 | 10.2 |
| Pruritus | 22 | 1.9 (7.7) | 0.03 | 7.8 |

*Note: ADR= adverse drug reaction, #ADRs= number of adverse drug reactions, IQR= interquartile range, Q1= quartile 1, Q3= quartile 3.*

### 3.2.3 Self-management strategies

The following section presents the results of the domain ‘self-management strategies’.

#### 3.2.3.1 Patient characteristics

Table 9 shows the patient characteristics of the included patients for self-management strategies. A total of 160 patients reported 588 ADRs, of which 649 self-management strategies were identified—most patients filled in multiple strategies to cope with the ADR. The majority of these patients (68.8%) were female, and the most common indications were rheumatoid arthritis (46.3%), psoriatic arthritis (20.6%) and Bechterew’s disease/axial spondyloarthritis (SpA) (11.9%). The adalimumab and etanercept user distribution was nearly equal, 52.5% vs 47.5%, respectively.

**Table 9.** Patient characteristics of the included patients for the 'self-management strategies' domain**.**

| *Patient characteristics, N= 160* | |
|---|---|
| **Gender,** N (%) | |
| Female | 110 (68.8) |
| **Age,** mean (SD) | 53.6 y (±14.8 y) |
| **Indication,** N (%) | |
| RA | 74 (46.3) |
| Psoriatic arthritis | 33 (20.6) |
| Bechterew's disease/axial SpA | 21 (13.2) |
| Bechterew's disease/axial SpA and rheumatoid arthritis | 2 (1.2) |
| Crohn's disease | 17 (10.6) |
| Ulcerative colitis | 3 (1.9) |
| Other[a] and RA | 4 (2.4) |
| Other[b] | 6 (3.8) |
| **bDMARD,** N (%) | |
| Adalimumab | 84 (52.5) |
| Etanercept | 76 (47.5) |

[a]Rheumatoid arthritis-associated lung disease (n=1), systemic scleroderma (n=1), Bechterew's disease (n=1), Crohn's disease (n=1).

[b]Uveitis posterior and panuveitis (n=1), birdshot chorioretinopathy (n=1), hemochromatosis (n=1), hidradenitis suppurativa (n=1), juvenile idiopathic arthritis (n=1), psoriasis (n=1).

*Note: N= number of patients, y= years, RA= rheumatoid arthritis, SpA= spondyloarthritis, bDMARD= biological disease-modifying antirheumatic drug.*

#### 3.2.3.2 Thematic analysis

A thematic analysis of the open-ended text fields considering self-management strategies was conducted to obtain the results for this domain. The reading and coding of these fields resulted in several themes emerging, which are presented in figure 9.

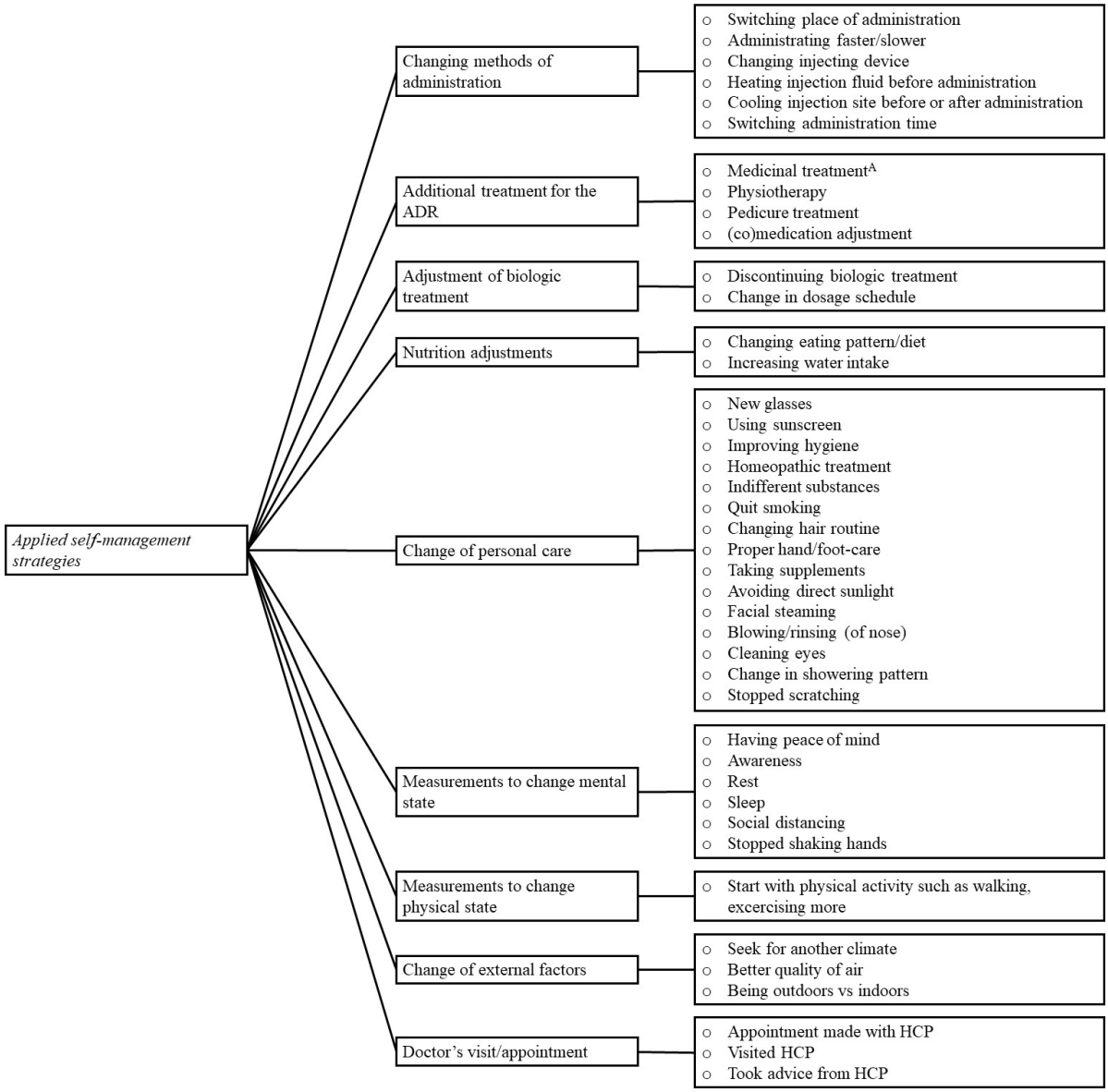


**Figure 9.** Inductively identified (sub)themes of the applied self-management strategies.

[A]A treatment is a medicinal treatment when the formulation contains an active substance, is registered as a drug by the medicines evaluation board (MEB), or is prescribed by an HCP (26).

*Note: ADR= adverse drug reaction, HCP= healthcare professional.*

#### 3.2.3.3 Injection site reactions

Forty-two patients who applied self-management strategies were included and reported 85 ADRs concerning injection site reactions. Some patients described multiple self-management strategies in one report, so a total of 88 self-management strategies were given in the open-ended text fields. Most strategies included subdomain 1 'changing methods of administration' (56.8%), of which most reports indicated that the patient cooled the injection site before or after administration (48%) or switched the administration place (26%) (e.g. from leg to stomach). Also, subdomain 5 'change of personal care' was

frequently (23.8%) mentioned as patients indicated they put indifferent substances on the place of administration, such as creams, plasters or ointments. Furthermore, five reports (5.7%) indicated they treated the injection site with lidocaine cream or took paracetamol to reduce the pain. Other self-management strategies that were less frequently applied were: administrating faster/slower, changing injecting device, switching administration time, discontinuing biologic treatment, having peace of mind, rest, being indoors, and taking advice from HCP (table 10).

#### 3.2.3.4 Infections

A total of 88 patients reporting infections were eligible for inclusion. These patients reported 231 ADRs, including 272 self-management strategies. 'additional treatment for the ADR' was the most frequently mentioned theme (34.9%), with 'medicinal treatment' being the mainly applied subtheme (30.8%), including the use of antibiotics. Also, strategies that involved 'change of personal care' were frequently applied (35.7%), with many strategies (21.7%) that included the use of indifferent substances or to take supplements (i.e. cranberry pills or vitamin C) to treat the ADR (7%). Furthermore, nutritional adjustments were made (6.7%), and some patients (4.8%) reported they had to rest because of the infection. Strategies that included the themes 'changing methods of administration', 'adjustment of biologic treatment', 'measurements to change physical state', 'change of external factors', and 'doctor's visit/appointment' were less frequently adopted (table 10).

#### 3.2.3.5 Skin reactions

Patients who reported skin reactions mentioned the highest amount of self-management strategies. A total of 62 patients reported 266 ADRs and applied 289 self-management strategies. Most strategies involved the theme 'change of personal care' (60.2%), which mostly included the use of indifferent substances over the affected area (46.4%). These substances could include creams and ointments. The second frequently mentioned theme involved 'additional treatment for the ADR' (30.4%), including medicinal treatment (28.7%). Patients reported they used prescribed creams (e.g. corticosteroid cream) or took antibiotics, for example. Furthermore, patients suffering from alopecia also reported that changes in hair routine (e.g. changes in combing/washing hair or using different shampoos) were applied (3.5%). Other self-management strategies that were applied less often involved the themes 'changing methods of administration', 'nutrition adjustments', 'measurements to change mental state', and 'doctor's visit/appointment' (table 10).

**Table 10**. Self-management strategies categorised per adverse drug reaction (ADR).

| Self-management strategy | Quote | ADR | | |
|---|---|---|---|---|
| | | *ISR* | *INF* | *SR* |
| Theme: not specified[a] | | | | |
| Not specified | ''Did everything possible,'' ''Followed previous tips,'' ''ADR did not resolve.'' | 4 | 7 | 9 |
| Theme: changing methods of administration | | | | |
| Switching place of administration | ''Inject in the belly,'' ''Injecting via rotation scheme.'' | 13 | 1 | |
| Administrating faster/slower | ''Inject very slowly.'' | 3 | | |
| Changing injecting device | ''Other syringe, manually now.'' | 1 | | |
| Heating injection fluid before administration | ''Bring the syringe to room temperature,'' ''Keep syringe longer out of the fridge.'' | 8 | | |
| Cooling injection site before or after administration | ''Cooling with an ice pack,'' ''Cool before and after injection.'' | 24 | | 2 |
| Switching administration time | ''Administer at night.'' | 1 | | |
| Theme: additional treatment for the ADR | | | | |
| Medicinal treatment[a] | ''Take paracetamol,'' ''Apply lidocaine cream before injection,'' ''Took antibiotics,'' ''Used prescribed cream.'' | 5 | 84 | 83 |
| Physiotherapy | ''Visited physiotherapist.'' | | | 1 |
| Pedicure treatment | ''Medical pedicure every six weeks.'' | | 10 | 1 |
| (Co)medication adjustment | ''Took other medication,'' ''Fluticasone dose reduced.'' | | 1 | 3 |
| Theme: adjustment of biologic treatment | | | | |
| Discontinuing biologic treatment | ''Stopped,'' ''Tried to taper the biologic,'' ''Stopped temporarily.'' | 2 | 3 | |
| Change in dosage schedule | ''Inject every two weeks,'' ''Used less Enbrel,'' ''Postponed injection,'' ''Skipped injection.'' | | 9 | |
| Theme: nutrition adjustments | | | | |
| Changing eating pattern/diet | ''Improved eating pattern,'' ''Good nutrition.'' | | 11 | |
| Increasing water intake | ''Drink much water.'' | | 7 | 2 |
| Theme: change of personal care | | | | |
| New glasses | ''Glasses with tinted lenses.'' | | 1 | |
| Using sunscreen | ''SPF 50 on lips,'' ''Use special sunscreen'' | | 3 | 5 |
| Improving hygiene | ''Hygiene better respected,'' ''Keep the affected area as clean as possible.'' | | 2 | 8 |
| Homeopathic treatment | ''More homeopathic substances were taken.'' | | 1 | |
| Indifferent substances | ''Put cream on injection site,'' ''Plaster applied on the injection site,'' ''Used nasal spray,'' ''Nasal douche with saltwater,'' ''Lubricant brand changed,'' ''Keep greasy,'' ''Stopped using paracetamol.'' | 21 | 59 | 134 |
| Quit smoking | ''Quit smoking.'' | | | 1 |
| Changing hair routine | ''Do not wash hair,'' ''Dry first, then comb,'' ''Washing hair less often,'' ''Use special shampoo.'' | | 1 | 10 |
| Proper hand/foot-care | ''Nail removed,'' ''Trimmed nails,'' ''Footbath with soda,'' ''Use gel nail polish,'' ''Wear gloves and socks'' | | 4 | 3 |
| Taking supplements | ''Cranberry pills,'' ''More vitamin C.'' | | 19 | 1 |
| Avoiding direct sunlight | ''No sunbathing.'' | | 1 | 3 |
| Blowing/rinsing (of the nose) | ''Rinsing,'' ''Flushed sinuses.'' | | 2 | |
| Facial steaming | ''Steaming.'' | | 2 | |
| Cleaning eyes | ''With boiled water,'' ''With water and a sterile cloth.'' | | 2 | |

| | | | | |
|---|---|---|---|---|
| Change in showering pattern | ''Shower less often,'' ''Installed water softener,'' ''pH neutral lotion,'' ''More showering,'' ''Not using shower gel.'' | | | 5 |
| Stopped scratching | ''Trying not to scratch.'' | | | 4 |
| Theme: measurements to change mental state | | | | |
| Having peace of mind | ''Staying calm is the best remedy,'' ''Push through.'' | 3 | | |
| Awareness | ''Take good care after me,'' ''Living as healthy as possible,'' ''Be more careful.'' | | 2 | 1 |
| Rest | ''Stayed sick at home,'' ''Rested,'' ''Worked less.'' | 1 | 13 | 4 |
| Sleep | ''Sleep a lot,'' ''Try to get enough sleep.'' | | 3 | |
| Social distancing | ''COVID-19 measures applied.'' | | 3 | |
| Stopped shaking hands | ''Not give a hug/hand,'' ''Be careful when shaking hands.'' | | 2 | |
| Theme: measurements to change physical state | | | | |
| Start with physical activity, such as walking, exercising more | ''Exercise a lot,'' ''More working out.'' | | 6 | |
| Theme: change of external factors | | | | |
| Seek for another climate | ''Stayed two weeks in Spain.'' | | 1 | |
| Better quality of air | ''External air.'' | | 1 | |
| Being outdoors vs indoors | ''Stayed inside a lot.'' | 1 | | |
| Theme: doctor's visit/appointment | | | | |
| Appointment made with HCP | ''Made an appointment with the GP.'' | | 3 | |
| Visited HCP | ''Visited GP,'' ''Visited specialists.'' | | 6 | 8 |
| Took advice from HCP | ''Consulted with a doctor,'' ''Followed GP's advice.'' | 1 | 2 | 1 |
| Total | | 88 | 272 | 289 |

[a] An included report was marked as 'not specified' if the open-ended text field did not describe the applied self-management strategy.

[b] A treatment is a medicinal treatment when the formulation contains an active substance, is registered as a drug by the medicines evaluation board (MEB), or is prescribed by an HCP (26).

*Note: ISR= injection site reactions, INF= infections, SR= skin reactions, GP= general practitioner, HCP= healthcare professional, SPF= sun protection factor, COVID-19= coronavirus disease 2019.*

# 4. Discussion

This section will discuss the main results, limitations of this study, generalisability, and recommendations for future research.

## 6.1 Main results

This study is the first to assess whether data sources of a pharmacovigilance centre contain information about ADRs that is in line with patient preferences regarding ADR information. The results of the first objective were as expected as they showed that most of the current ADR information provision sources in the Netherlands did not provide the information that patients prefer. Therefore, examining whether two different pharmacovigilance data sources can provide this information was necessary, and the main results will be discussed in the following sections.

### 6.1.1 Duration

The uncommon duration of more than three days of injection site reactions is the first interesting finding in 39% of the reports concerning injection site reactions. Literature shows that these reactions mostly last three days or less, supported by 61% of the reports (17,31,32). Nevertheless, the relatively long duration of the remaining reports might be due to misunderstanding what was meant by the start or recovery date of the ADR. As a result, patients with recurrent injection site reactions may have reported the total amount of time the ADR was recurrent instead of the exact recovery date of one injection site reaction. However, experiencing discomfort due to injection site reactions is a common cause of treatment discontinuation (33). Therefore, knowing that injection site reactions can last longer than three days in some biologic users is important.

Other remarkable results considered the duration of some infections. However, comparing the results of infections was challenging as, to our best knowledge, no studies are available that describe the duration of biologic-induced infections. Therefore, the duration of infections is compared to the general, non-biologic user population. The first noticeable result considering infections included the finding that nasopharyngitis was most frequently reported and had the most prolonged median duration of 60.8 days of all reported infections. In the general population, nasopharyngitis usually lasts around 8-10 days, which is much shorter than what this study's findings suggest (34). The same observation was made for cystitis infections with a median duration of 10.2 days, which generally last 2-3.5 days either with or without antibiotic treatment (35–37). This study showed that out of the total of fourteen cystitis reports, five patients (35.7%) indicated the ADR lasted 34 days or longer, of whom two had to receive two antibiotic treatments to resolve this condition. Besides, one report indicated that the ADR resolved after antibiotic treatment of three months, and two patients suffered from multiple cystitis infections a year. In addition, the reports of pneumonia included some striking findings as two out of sixteen patients

(13.3%) reported a duration longer than a hundred days, of which one person was still using antibiotics after the infection. Considering pneumonia infections mostly resolve within two to three weeks, this is a remarkable finding (38,39). Nevertheless, most biologic users who suffered from pneumonia (86.7%) had the same duration as non-biologic users, but in some cases, the infection could have lasted longer. Concluding, the findings of the most frequently reported infections suggest that the duration of biologic-induced infections might be longer compared to the general, non-biologic user population. This is a logical observation as biologic users have an increased infection susceptibility during treatment and are more likely to have recurrent infections or infections that take more time to resolve (40–42).

Furthermore, the results of skin reactions included another irregular finding concerning the median duration of a pruritic rash of 196.0 days. One reason for this relatively long duration found in this study might be that pruritic rash only had five reports, of which one report had a duration of 1219 days. Another reason might be that the ADR was recurrent. This ADR can occur in mild to severe cases. However, the exact duration of biologic-induced pruritic rash is not described before in current literature, so a comparison could not be made. Therefore, the results of this study can provide insight into the median duration of skin reactions in biologic users. Nevertheless, future optimised studies are necessary to describe more accurate durations of skin reactions, as the sample size in this study was small.

Overall, information about the duration of biologic-induced infections and skin reactions is not described in current literature, so comparing these results with similar patient populations could not occur. Nevertheless, the results of this study show that information on duration of the included ADRs can be obtained from the cohort event monitoring data source. However, future studies with greater sample sizes are needed before presenting this information on ADR information tools such as the Bijwerkingwijzer.

### 6.1.2 Time to onset

The second domain analysed in this study was ‘time to onset’, with injection site reactions being the first analysed ADR. Injection site reactions mainly occur within one or two months after starting the treatment (31,32). The median onset of injection site reactions in this study was 1.5 months, which supports this finding. A total of 54 reports (67.5%) indicated that the ADR occurred within the first two months of use, of which 49 reports (90.7%) within the first month.

In addition, according to the review of Lortholary et al., most biologic-induced infections occur within the first year of use (43). In this study, a median time to onset of 10.2 months was found. Out of the total 129 reports, 71 infections (55%) occurred within the first year of biologic use.

Furthermore, the median onset of skin reactions was 2.0 months. Several studies indicated that skin reactions occur within one to three years of biologic use (44,45). This study showed that skin reactions could occur much faster after starting treatment than described in current literature. It is relevant to be aware of this finding, as it may contribute to the treatment's burden, and previous studies

described that the occurrence of skin reactions such as psoriasis or alopecia, for example, might potentially cause early discontinuation of treatment (46,47).

Overall, the results of injection site reactions and infections show that RWD supports what is described in current literature. Nevertheless, the calculated time to onset of skin reactions suggests that these infections can occur faster after starting the treatment than described in current literature.

### 6.1.3 Self-management strategies

The results of the domain 'self-management strategies' were logical and as expected. First, the most frequently applied self-management strategy (56.8%) of injection site reactions involved the subtheme 'changing methods of administration', which makes sense as the advice to cool the injection site before or after administration is often given online or by HCPs (48–50). Both HCPs and patients need to know what strategies can be applied to reduce the discomfort of this ADR because injection site reactions are a reason for treatment discontinuation, as stated in section 6.1.1 of the Discussion chapter.

Furthermore, 'additional treatment of the ADR' was mainly (31%) applied for infections. The management of infections depends on the type of infection. For example, bacterial infections need to be treated with antibiotics, whereas the management of viral infections is based on prevention with vaccines (51–53). Both strategies include using a medicinal treatment, which is supported by the results of this study.

Finally, 'change of personal care' was the most frequently mentioned theme for skin reactions, with the subtheme 'indifferent substances' as mainly applied self-management strategy (46.4%). Considering skin reactions are often treated with the use of creams or ointments, either containing an active substance or not, this is a foreseeable finding. Nevertheless, a remarkable finding is that skin reactions were the least reported ADR but did provide the most applied self-management strategies. This finding may indicate that the burden of skin reactions is high and/or that the duration of skin reactions is relatively long. The latter was also seen earlier in this study, with skin reactions having the highest median duration of all included ADRs. Besides, in a former study, patients stated that the burden of ADRs also involved changes in appearance, which could be the case with skin reactions (54).

In conclusion, self-management strategies of these ADRs are not examined before in current literature and provide insights into aspects that are usually outside the vision of HCPs. Besides, these findings are helpful for future patients experiencing the same ADR(s).

## 6.2 Limitations

Some limitations to this study need to be considered. First, it is essential to clarify that the data used in this study was mainly provided by patients, especially data of the cohort event monitoring system (DBM). Unfortunately, some patients participating in the DBM found it challenging to understand the

questions meant by the questionnaires or had difficulties filling in the correct answer, which caused surrealistic or useless answers. For that reason, many patients had to be excluded. As a result, a relatively small number of patients remained eligible for inclusion, which lowered the accuracy of the results.

Second, some patients suffered from the same recurrent ADR over time and thus indicated a recovery date of the total period in which the recurrent ADR was present instead of the recovery date of one episode of that ADR. As seen in the interpretation of results, this could be a reason for the highly lengthy durations of an ADR, giving a distorted image of the median duration of that ADR.

Another limitation of the DBM data had to do with usability. Patients could report the exact ADR multiple times, which is necessary but made it much work to calculate the average duration of some ADRs. In addition, the average duration had to be calculated by hand and was therefore prone to error. So, using this data source with the methodology of this study was burdensome.

Finally, the applied self-management strategies were identified, but it is unknown if they relieved symptoms or cured the ADR. Besides, only one researcher read the open-ended text fields in which the self-management strategies were described and coded them. This way of coding is bias-sensitive because another researcher might place different self-management strategies in different themes.

### 6.3 Generalisability

To determine this study's generalisability, an examination was made of the usability of the results for presentation on the Bijwerkingwijzer or if more research is necessary. Due to the relatively small sample sizes and divergent results of the ADRs, more studies are needed to get more accurate information of the 'duration' domain for the included ADRs to use on the Bijwerkingwijzer. Besides, a look at the duration of individual infections and skin reactions must be given because one infection/skin reaction is not like another.

Nevertheless, the results obtained for the 'time to onset' and 'self-management strategies' domains are helpful for the Bijwerkingwijzer and may be presented on this online tool. However, more questions on the outcomes are needed to clarify if an applied self-management strategy was effective, to improve the usefulness of these strategies for both patients and HCPs.

At last, only data sources of the national pharmacovigilance centre in the Netherlands were used in this study. It is unknown if foreign pharmacovigilance centres possess the same data sources and can extract comparable data. Nevertheless, the results of this study will be used on a national online tool, so only using national data sources was preferred.

## 6.4 Recommendations for future research

First, to enhance the usefulness of patient-provided data, further research should be more clear in (either verbally or in writing) clarifying the questionnaires that are handed to patients, so it is easy for the patient to understand what to fill in and there is no need for unnecessary exclusion of patients in future studies. Also, a question about the effectiveness of self-management strategies should be added to focus on the effectiveness of these actions and subsequent dissemination or implementation of these strategies if deemed effective. Besides, a look at the usability of the cohort event monitoring data source must be given to improve efficiency in future research.

Furthermore, the seven domains composed by Kusch et al. considering patient preferences regarding ADR information, as mentioned in the Introduction chapter, are formulated through a systematic review but are not yet tested in patients to see if they find these domains truly important. This result should be verified in future studies. Lareb will be holding focus groups in future studies to test these domains, for example.

Finally, as mentioned before, further studies should have a greater sample size to obtain more accurate results of the ‘duration’ domain. Also, calculating the duration of the ADRs ‘infections’ and ‘skin reactions’ should be done for individual PTs instead of generalising this duration for all reported infections and skin reactions.

## 5. Conclusion

Considering that patients have different preferences regarding ADR information provision than HCPs, a look at the current ADR information sources in the Netherlands was given. This study showed that the primary ADR information provision sources in the Netherlands consisting of the PIL, Kijksluiter.nl, FK, Lareb, and Apotheek.nl did not meet patient preferences regarding ADR information. Moreover, information on the domains 'duration', 'time to onset', and 'self-management strategies' was not or partially available and had a low score. Nevertheless, information on these domains could successfully be extracted from pharmacovigilance centre data sources for patients with injection site reactions, infections, and skin reactions using adalimumab or etanercept. Thus, this study's findings showed that pharmacovigilance centre data could provide information about ADR topics that are not readily available and are preferred by patients. Furthermore, as ADRs are one of the main reasons for poor patient adherence, mapping out these domains can contribute to making better-informed treatment decisions and reduce fear or anxiety towards a medicinal treatment. Thus, it can increase treatment adherence.

Furthermore, most results of the 'duration' and 'time to onset' domains supported current literature, but new insights were also generated. The results of self-management strategies were mainly new because this was not been studied before and usually is outside the vision of HCPs. Furthermore, future optimised studies with larger sample sizes are needed to provide more accurate results of the duration of ADRs before this information can be shared with patients and HCPs by presenting them on ADR information tools, such as the Bijwerkingwijzer.

In conclusion, conducting an observational study on ADR information preferred by patients has led to interesting insights. This study has shown that the current ADR information provision in the Netherlands does not comply with the patient preferences and needs regarding ADR information but that data of pharmacovigilance centres can provide in this.

## 6. Reference list


1. Drug and Therapeutics Committee Training Course Session 4. Assessing and Managing Medicine Safety Participants' Guide. [cited 2022 January 12]; Available from: www.msh.org/rpmplus
2. Palleria C, Leporini C, Chimirri S, Marrazzo G, Sacchetta S, Bruno L, et al. Limitations and obstacles of the spontaneous adverse drugs reactions reporting: Two "challenging" case reports. Journal of pharmacology & pharmacotherapeutics [Internet]. 2013 Dec [cited 2022 January 12];4(Suppl 1). Available from: https://pubmed.ncbi.nlm.nih.gov/24347986/
3. Sultana J, Cutroneo P, Trifirò G. Clinical and economic burden of adverse drug reactions. Journal of pharmacology & pharmacotherapeutics [Internet]. 2013 Dec [cited 2022 January 12];4(Suppl 1). Available from: https://pubmed.ncbi.nlm.nih.gov/24347988/
4. Informatiebehoeften van patiënten over geneesmiddelen. | Nivel [Internet]. [cited 2022 Jan 12]. Available from: https://www.nivel.nl/nl/publicatie/informatiebehoeften-van-patienten-over-geneesmiddelen
5. Kusch MKP, Zien A, Hachenberg C, Haefeli WE, Seidling HM. Information on adverse drug reactions—Proof of principle for a structured database that allows customisation of drug information. International Journal of Medical Informatics. 2020 January 1;133:103970.
6. What patients want to know about their medications. Focus group study of patient and clinician perspectives - PubMed [Internet]. [cited 2022 Feb 3]. Available from: https://pubmed.ncbi.nlm.nih.gov/11852597/
7. Leporini C, de Sarro G, Russo E. Adherence to therapy and adverse drug reactions: is there a link? Expert opinion on drug safety [Internet]. 2014 [cited 2022 January 12];13 Suppl 1(SUPPL. 1). Available from: https://pubmed.ncbi.nlm.nih.gov/25171158/
8. Cutler RL, Fernandez-Llimos F, Frommer M, Benrimoj C, Garcia-Cardenas V. Economic impact of medication non-adherence by disease groups: a systematic review. BMJ Open [Internet]. 2018 Jan 1 [cited 2022 Jan 12];8(1). Available from: https://pubmed.ncbi.nlm.nih.gov/29358417/
9. Kusch MKP, Haefeli WE, Seidling HM. How to meet patients' individual needs for drug information - a scoping review. Patient preference and adherence [Internet]. 2018 [cited 2022 Jan 12];12:2339–55. Available from: https://pubmed.ncbi.nlm.nih.gov/30464421/
10. Herber OR, Gies V, Schwappach D, Thürmann P, Wilm S. Patient information leaflets: informing or frightening? A focus group study exploring patients' emotional reactions and subsequent behavior towards package leaflets of commonly prescribed medications in family practices. BMC family practice [Internet]. 2014 Oct 2 [cited 2022 Jan 12];15(1). Available from: https://pubmed.ncbi.nlm.nih.gov/25277783/
11. de Geest S, Sabaté E. Adherence to long-term therapies: evidence for action. European Journal of cardiovascular nursing : Journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology [Internet]. 2003 Dec [cited 2022 Jan 12];2(4):323. Available from: https://pubmed.ncbi.nlm.nih.gov/14667488/
12. Kusch MKP, Haefeli WE, Seidling HM. How to meet patients' individual needs for drug information - a scoping review. Patient preference and adherence [Internet]. 2018 [cited 2022 Jan 12];12:2339–55. Available from: https://pubmed.ncbi.nlm.nih.gov/30464421/
13. Thomas PWA, Römkens TEH, West RL, Russel MGVM, Jansen JM, van Lint JA, et al. Discrepancy between patient- and healthcare provider-reported adverse drug reactions in inflammatory bowel disease patients on biological therapy. UEG Journal [Internet]. 2021 Oct 1

[cited 2022 Jan 12];9(8):919–28. Available from: https://onlinelibrary-wiley-com.proxy.library.uu.nl/doi/full/10.1002/ueg2.12107
14. Kosse LJ, Weits G, Vonkeman HE, Spuls PI, van den Bemt BJF, Tas SW, et al. Immune-mediated inflammatory disease patients' preferences in adverse drug reaction information regarding biologics. Expert Opinion on Drug Safety [Internet]. 2020 [cited 2022 January 12];1049–54. Available from: https://www.tandfonline.com/action/journalInformation?journalCode=ieds20
15. What Is Patient-Centered Care? [Internet]. [cited 2022 January 12]. Available from: https://catalyst.nejm.org/doi/full/10.1056/CAT.17.0559
16. Ruim 10% groei verwacht van gebruikers biologicals — PW | Pharmaceutisch Weekblad [Internet]. [cited 2022 Jan 12]. Available from: https://www.pw.nl/vaste-rubrieken/sfk/2020/ruim-10-groei-verwacht-van-gebruikers-biologicals
17. Pasadyn SR, Knabel D, Fernandez AP, Warren CB. Cutaneous adverse effects of biologic medications. Cleveland Clinic journal of medicine [Internet]. 2020 May 1 [cited 2022 Jan 12];87(5):288–99. Available from: https://pubmed.ncbi.nlm.nih.gov/32357984/
18. Home [Internet]. [cited 2022 Jan 12]. Available from: https://www.mijnbiologischmedicijn.nl/
19. van Lint JA, Jessurun NT, Hebing RCF, Hoentjen F, Tas SW, Vonkeman HE, et al. Patient-Reported Burden of Adverse Drug Reactions Attributed to Biologics Used for Immune-Mediated Inflammatory Diseases. Drug safety [Internet]. 2020 Sep 1 [cited 2022 Jan 12];43(9):917–25. Available from: https://pubmed.ncbi.nlm.nih.gov/32451974/
20. Meldformulier [Internet]. [cited 2022 Jan 12]. Available from: https://meldformulier.lareb.nl/Forms/reportform?id=5fb1a16c-32f8-4496-83c1-53255a4c7fe2
21. COVID-19 | MedDRA [Internet]. [cited 2022 Jan 12]. Available from: https://www.meddra.org/
22. English | MedDRA [Internet]. [cited 2022 Jan 12]. Available from: https://www.meddra.org/how-to-use/support-documentation/english
23. Anatomical Therapeutic Chemical (ATC) Classification [Internet]. [cited 2022 January 12]. Available from: https://www.who.int/tools/atc-ddd-toolkit/atc-classification
24. Commonly Confused Words: A Couple, A Few, Some, Several, or Many? – Marquette University Law School [Internet]. [cited 2022 January 12]. Available from: https://law.marquette.edu/facultyblog/2014/07/commonly-confused-words-a-couple-a-few-some-several-or-many/comment-page-1/
25. Welkom bij Bijwerkingencentrum Lareb [Internet]. [cited 2022 Jan 13]. Available from: https://www.lareb.nl/
26. Home | Geneesmiddeleninformatiebank | College ter Beoordeling van Geneesmiddelen [Internet]. [cited 2022 Jan 13]. Available from: https://www.geneesmiddeleninformatiebank.nl/ords/f?p=111:1:0::NO:RP,1:P0_DOMAIN,P0_LANG:H,NL
27. Apotheek.nl [Internet]. [cited 2022 Jan 13]. Available from: https://www.apotheek.nl/
28. Farmacotherapeutisch Kompas [Internet]. [cited 2022 January 13]. Available from: https://www.farmacotherapeutischkompas.nl/
29. Kijksluiter [Internet]. [cited 2022 Jan 13]. Available from: https://www.kijksluiter.nl/#!
30. Medical Dictionary for Regulatory Activities Terminology (MedDRA) - Injection site reaction - Classes | NCBO BioPortal [Internet]. [cited 2022 Jan 13]. Available from: https://bioportal.bioontology.org/ontologies/MEDDRA?p=classes&conceptid=10022095

31. Clinical, histological, and immunophenotypic characteristics of injection site reactions associated with etanercept: a recombinant tumor necrosis factor-alpha receptor: Fc fusion protein - PubMed [Internet]. [cited 2022 January 13]. Available from: https://pubmed.ncbi.nlm.nih.gov/11453808/
32. Scheinfeld N. A comprehensive review and evaluation of the side effects of the tumor necrosis factor-alpha blockers etanercept, infliximab and adalimumab. The Journal of dermatological treatment [Internet]. 2004 Sep [cited 2022 Jan 13];15(5):280–94. Available from: https://pubmed.ncbi.nlm.nih.gov/15370396/
33. Bolge SC, Goren A, Tandon N. Reasons for discontinuation of subcutaneous biologic therapy in the treatment of rheumatoid arthritis: a patient perspective. Patient preference and adherence [Internet]. 2015 Jan 20 [cited 2022 Feb 3];9:121. Available from: /pmc/articles/PMC4309782/
34. Nasopharyngitis: Symptoms, Treatment, and More [Internet]. [cited 2022 Jan 14]. Available from: https://www.healthline.com/health/cold-flu/nasopharyngitis
35. Heytens S, de Sutter A, de Backer D, Verschraegen G, Christiaens T. Cystitis: symptomatology in women with suspected uncomplicated urinary tract infection. Journal of women's health (2002) [Internet]. 2011 July 1 [cited 2022 January 31];20(7):1117–21. Available from: https://pubmed.ncbi.nlm.nih.gov/21671766/
36. Little P, Merriman R, Turner S, Rumsby K, Warner G, Lowes JA, et al. Presentation, pattern, and natural course of severe symptoms, and role of antibiotics and antibiotic resistance among patients presenting with suspected uncomplicated urinary tract infection in primary care: observational study. BMJ (Clinical research ed) [Internet]. 2010 Feb 20 [cited 2022 Jan 31];340(7743):408. Available from: https://pubmed.ncbi.nlm.nih.gov/20139213/
37. Little P, Moore M v., Turner S, Rumsby K, Warner G, Lowes JA, et al. Effectiveness of five different approaches in management of urinary tract infection: randomised controlled trial. BMJ (Clinical research ed) [Internet]. 2010 Feb 20 [cited 2022 Jan 31];340(7743):405. Available from: https://pubmed.ncbi.nlm.nih.gov/20139214/
38. Treatment of community-acquired pneumonia in adults who require hospitalization - UpToDate [Internet]. [cited 2022 Jan 13]. Available from: https://www.uptodate.com/contents/treatment-of-community-acquired-pneumonia-in-adults-who-require-hospitalization
39. Pneumonia Treatment and Recovery | American Lung Association [Internet]. [cited 2022 January 13]. Available from: https://www.lung.org/lung-health-diseases/lung-disease-lookup/pneumonia/treatment-and-recovery
40. Fernández-Ruiz M, Aguado JM. Risk of infection associated with anti-TNF-α therapy. https://doi.org/101080/1478721020181544490 [Internet]. 2018 Dec 2 [cited 2022 Jan 31];16(12):939–56. Available from: https://www.tandfonline.com/doi/abs/10.1080/14787210.2018.1544490
41. Downey C. Serious infection during etanercept, infliximab and adalimumab therapy for rheumatoid arthritis: A literature review. International Journal of Rheumatic Diseases [Internet]. 2016 June 1 [cited 2022 January 31];19(6):536–50. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/1756-185X.12659
42. Galloway JB, Register on behalf of the BS for RB, Hyrich KL, Register on behalf of the BS for RB, Mercer LK, Register on behalf of the BS for RB, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology [Internet]. 2011

Jan 1 [cited 2022 Jan 31];50(1):124–31. Available from: https://academic.oup.com/rheumatology/article/50/1/124/1789740

43. Lortholary O, Fernandez-Ruiz M, Baddley JW, Manuel O, Mariette X, Winthrop KL. Infectious complications of rheumatoid arthritis and psoriatic arthritis during targeted and biological therapies: a viewpoint in 2020. Annals of the rheumatic diseases [Internet]. 2020 Dec 1 [cited 2022 Jan 13];79(12):1532–43. Available from: https://pubmed.ncbi.nlm.nih.gov/32963049/
44. Garcovich S, de Simone C, Genovese G, Berti E, Cugno M, Marzano AV. Paradoxical skin reactions to biologics in patients with rheumatologic disorders. Frontiers in Pharmacology. 2019;10(MAR):282.
45. Fréling E, Baumann C, Cuny JF, Bigard MA, Schmutz JL, Barbaud A, et al. Cumulative incidence of, risk factors for, and outcome of dermatological complications of anti-TNF therapy in inflammatory bowel disease: a 14-year experience. The American Journal of gastroenterology [Internet]. 2015 August 13 [cited 2022 January 14];110(8):1186–96. Available from: https://pubmed.ncbi.nlm.nih.gov/26195181/
46. Brown G, Wang E, Leon A, Huynh M, Wehner M, Matro R, et al. Tumor necrosis factor-α inhibitor-induced psoriasis: Systematic review of clinical features, histopathological findings, and management experience. Journal of the American Academy of Dermatology [Internet]. 2017 Feb 1 [cited 2022 Feb 3];76(2):334–41. Available from: https://pubmed.ncbi.nlm.nih.gov/27720274/
47. Garcovich S, de Simone C, Genovese G, Berti E, Cugno M, Marzano AV. Paradoxical Skin Reactions to Biologics in Patients With Rheumatologic Disorders. Frontiers in Pharmacology [Internet]. 2019 [cited 2022 Feb 3];10(MAR). Available from: /pmc/articles/PMC6443901/
48. Halper J, Centonze D, Newsome SD, Huang DR, Robertson C, You X, et al. Management Strategies for Flu-Like Symptoms and Injection-Site Reactions Associated with Peginterferon Beta-1a: Obtaining Recommendations Using the Delphi Technique. International Journal of MS Care [Internet]. 2016 July 1 [cited 2022 January 14];18(4):211. Available from: /pmc/articles/PMC4984793/
49. Bijwerkingen van biologicals - ReumaMagazine [Internet]. [cited 2022 Jan 14]. Available from: https://reumamagazine.nl/farmacie/bijwerkingen-van-biologicals/
50. St Clair-Jones A, Prignano F, Goncalves J, Paul M, Sewerin P. Understanding and Minimising Injection-Site Pain Following Subcutaneous Administration of Biologics: A Narrative Review. Rheumatology and Therapy [Internet]. 2020 Dec 1 [cited 2022 Jan 14];7(4):741. Available from: /pmc/articles/PMC7672413/
51. McConachie SM, Wilhelm SM, Bhargava A, Kale-Pradhan PB. Biologic-Induced Infections in Inflammatory Bowel Disease: The TNF-α Antagonists. Annals of Pharmacotherapy [Internet]. 2018 June 1 [cited 2022 January 14];52(6):571–9. Available from: https://journals-sagepub-com.proxy.library.uu.nl/doi/10.1177/1060028018754896
52. Farraye FA, Melmed GY, Lichtenstein GR, Kane S v. ACG Clinical Guideline: Preventive Care in Inflammatory Bowel Disease. American Journal of Gastroenterology [Internet]. 2017 Feb 1 [cited 2022 Jan 14];112(2):241–58. Available from: https://journals.lww.com/ajg/Fulltext/2017/02000/ACG_Clinical_Guideline__Preventive_Care_in.15.aspx
53. Rahier JF, Ben-Horin S, Chowers Y, Conlon C, de Munter P, D'Haens G, et al. European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. Journal of Crohn's and Colitis [Internet]. 2009 June 1

[cited 2022 January 14];3(2):47–91. Available from: https://academic-oup-com.proxy.library.uu.nl/ecco-jcc/article/3/2/47/507952

54. Patient's and Rheumatologist's Perspectives on the Burden of Adverse Drug Reactions Attributed to Biologics: A Qualitative Study - ACR Meeting Abstracts [Internet]. [cited 2022 January 31]. Available from: https://acrabstracts.org/abstract/patients-and-rheumatologists-perspectives-on-the-burden-of-adverse-drug-reactions-attributed-to-biologics-a-qualitative-study/