Burden of Disease Modifying Anti-Rheumatic Drugs Related Adverse Drug Reactions in Patients with Rheumatoid Arthritis

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Abstract

Background: The burden of ADRs related to treatments of various diseases are lesser known or not thoroughly defined. Rheumatoid arthritis is a complex disease with many different therapeutic options used to slow down disease progression and improve the quality of life for the people dealing with this disease. The aim of this article is to assess and compare the burden of the ADRs of DMARDs in patients with rheumatoid arthritis.

Methods: This was a cross-sectional study of data collected in the Dutch ADR Monitor, with patients being sent bimonthly questionnaires. A section of these questionnaires contained follow up questions specifically focused on the burden of any reported ADRs caused by one or multiple DMARDs used for treatment of the RA patients. The burden of these ADRs could be reported for the following seven domains: appearance, medical treatment, daily activities, fatigue, mental health, physical and course. The burden scores per drug group were displayed using a likert type scale. Data was analyzed using Kruskal Wallis and Dunn tests, and presented using a ten point likert type scale.

Results: A total of 48 rheumatoid arthritis patients were included (*71.4% female*) and reported 78 ADRs. In the mental health domain a significant difference (*p=0.044*) was found between bDMARDs and csDMARDs. As a whole csDMARDs don't have a higher or lower burden than other DMARDs or corticosteroids.

Conclusion: These results provide a first look into what burden data could add to current and future treatment considerations. The currently available data shows bDMARDs being more burdensome than csDMARDs in the mental health domain. A larger sample size or database will allow for other and more observations to be made in the future.

Keywords: Burden; ADRs; Rheumatoid Arthritis; bDMARDs; csDMARDs; tsDMARDs; corticosteroids; Burden domains;

Introduction

Rheumatoid arthritis is a thoroughly researched chronic disease in which research has resulted in a multitude of therapies and an overall better understanding of the disease itself. While the pathophysiology isn't completely known and there is still a lot to learn in this field, enough has been understood for integration of this knowledge in different therapeutic options that work through different mechanisms of targeting the immune system. Most drugs that make it through clinical trials and are granted market approval have a well-established overview of the type of ADRs expected for each specific drug. Additional post market surveillance through phase IV monitoring of ADRs adds extra insight into the prevalence of these ADRs while also adding information surrounding unexpected ADRs found in a larger population.
Medical professionals can use this data, including the ADR profiles of these drugs, to make patient-specific choices when it comes to choosing the right therapy for these diseases.

Most of the ADRs will occur in the first weeks or months of a therapy. The daily burden that these treatments are often accompanied by are lesser known and often not well defined. Research into the burden of therapies on the daily lives of patients is unique, for the simple reason there hasn't been a lot of research in this specific area of patient tolerance and overall experience with these therapies.

So far there have been no other studies looking at the burden of ADRs in rheumatoid arthritis patients. Pharmacovigilance center Lareb has set up an ADR Monitor (bijwerkingmonitor) with the goal of collecting burden data for many chronic diseases [1]. At this time there have been less than a handful of studies surrounding the daily or overall burden of adverse drug reactions. Burden, as a term, is most often used when it comes to financial costs of treatments. An article from de Boer et al. looked at the burden over time of skin reactions, infections and injection site reactions [2]. These adverse drug reactions were displayed on a likert type scale ranging from one through five. This is one of the first published researches incorporating burden of ADRs. However this study followed the burden of these various ADRs over time, allowing for longitudinal data to be interpreted and burden changes over time to be established. Additionally only ADRs of TNF-alpha inhibitors were followed in this study.
Using cross-sectional data from the ADR monitor, the burden of ADRs caused by DMARDs used in the treatment of rheumatoid patients could be defined on various predetermined domains of burden [3].

The objective of this article is to assess and compare the burden of the ADRs of DMARDs in patients with rheumatoid arthritis. The primary aim was to assess the burden of these DMARD related ADRs. The secondary aim was to compare the domains of burden between the various available DMARDs.

Methods

Patient selection

The ADR Monitor is a Dutch prospective cohort event monitoring system, which collects ADR data of patients with various chronic diseases living in the Netherlands. For this study all patients with rheumatoid arthritis aged 16 years or older were eligible. All relevant patient data was assembled between November 1st 2022 and June 1st 2023 and was extracted from the ADR Monitor (Bijwerkingmonitor).

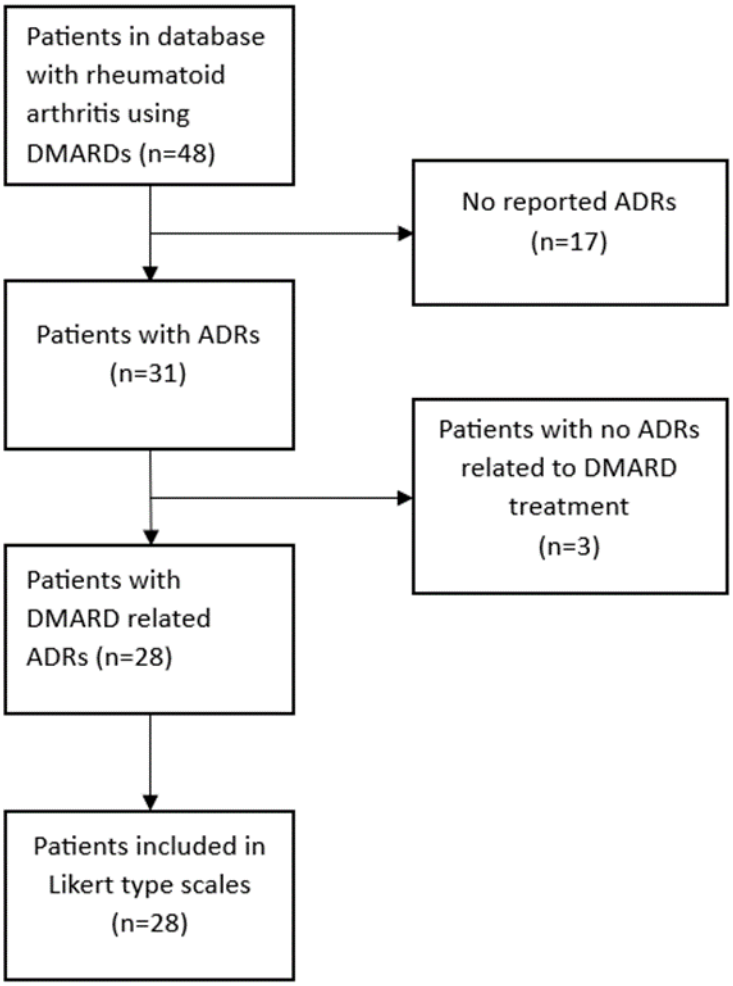

Figure 1: flowchart of patient selection (for the burden domains)

Questionnaires

Upon filling in basic patient information, being eligible to participate and consenting to the use of their data, a first questionnaire was sent. This questionnaire contained a very wide range of questions, including follow up questions specifically catered to the burden of any reported ADR caused by one or multiple drugs used by rheumatoid arthritis patients. Subsection 12 of the questionnaire, which contains all questions related to the burden, is available in Table S6. Questionnaires were sent out every other month for up to a year. After receiving the questionnaires they were coded by qualified pharmacovigilance assessors at the Netherlands Pharmacovigilance Center Lareb [1]. All the ADRs in these questionnaires were coded according to Medical Dictionary for Regulatory Activities (MedDRA®) terminology (version 26.0).

Included ADRs

Due to a shorter timeframe only the first available questionnaire with burden information for every unique ADR was used for data analysis. If a patient reported the same ADR caused by the same DMARD in multiple questionnaires, these ADRs would only add up to one report of this specific ADR.

Burden scaling

The burden of ADRs attributed to DMARDs was scored within the following seven burden domains: appearance, medical treatment, daily activities, fatigue, mental health, physical and course.
These burden scores were reported on a 10-point scale. Participants could assign a burden for each ADR, ranging from 0 [no burden] up to 10 [extremely high burden]. There was no limit to the amount of domains that could be impacted by a single ADR.

Statistical analysis

Patient demographics were presented as mean ± SD, or frequencies with percentages as appropriate. Differences in the burden scores between treatment groups were analyzed per domain using Kruskal Wallis. Using Kruskal-Wallis for analysis overrides the necessity to have normally distributed groups and/or equal sample sizes [4-6].
To assess which groups were different from each other, a post hoc analysis was performed using a Dunn test, allowing for comparison between two groups, instead of multiple groups as is the case with only a Kruskal Wallis test [5-7]. Comparisons of burden scores between two groups were performed using a Mann Whitney Wilcoxon test [8].
Drugs were compared in groups based on their mechanisms of action and origins (Figure 2).

Comparisons between DMARDs and the seven domains of burden were visualized through likert type scales. All of the statistical analyses mentioned above were scripted and ran in R (version 4.2.2).

bDMARDs	Adalimumab
	Abatacept
	Certolizumab pegol
	Etanercept
	Infliximab
	Tocilizumab
	Ustekinumab
Corticosteroids	Prednisone
	Prednisolone
	Triamcinolonacetonide
csDMARDs	Methothrexate
	Hydroxychloroquine
	Leflunomide
	Sulfasalazine
tsDMARDs	Bariticinib
	Filgotinib
	Tofacitinib
	Upadacitinib

Figure 2: breakdown of drug groups for statistical analysis

Results

A total of 48 patients were eligible to participate based on the previously set inclusion criteria. All 48 patients shared the indication of rheumatoid arthritis as well as being treated with at least one DMARD during the time the questionnaires were filled in. The average age of the patients included was 63.4 and the majority (71.4%) of all patients were female (Table 1). Out of all patients, 12 patients had additional chronic diseases that were being followed in the ADR Monitor. A total of 78 DMARD related ADRs were found among the 48 patients. Of these 48 included patients, 31 patients reported at least one ADR in a questionnaire. Of these 31 patients with ADRs, 28 experienced ADRs that were attributed to one or multiple DMARDs (Table 1). The longest follow up time was six months long, which equals to three questionnaires being answered (Table S1).

	n (%)	**SD**
Patients	48 (100)	
Mean age	63.39	12.07
Gender		
Female	34 (71.4)	
Indication(s)		
Rheumatoid arthritis	48 (100)	
Other chronic diseases		
Arthritis Psoriatica*	4 (8.3)	
Psoriasis*	4 (8.3)	
LUTS	2 (4.2)	
Atopic Eczema	1 (2.1)	
Colitis Ulcerosa	1 (2.1)	
Spondyloarthritis	1 (2.1)	
Crohn's disease	1 (2.1)	
DMARDs		
Methotrexate	28 (35.9)	
Hydroxychloroquine	12 (15.4)	
Prednisolone**	7 (9.0)	
Adalimumab	5 (6.4)	
Sulfasalazine	4 (5.1)	
Other***	22 (28.2)	
ADR reported		
Yes	31 (64.6)	
No	17 (35.4)	
DMARD related ADRs		
Yes	28 (90.6)	
No	3 (9.4)	
Total ADRs per patient		
Mean	2.4	1.9

**Two patients had both artritis psoriatica and psoriasis*

***Including one methylprednisolone treatment*

****Lesser used DMARDs [total]*

Etanercept [3], Prednison [3], Filgotinib [2], Leflunomide [2]

Tocilizumab [2], Abatacept [1], Azathioprine [1], Baricitinib [1]

Certolizumab Pegol [1], Infliximab [1], Rituximab [1], Sarilumab [1]

Tofacitinib [1], Triamcinolone acetonide [1], Upadacitinib [1]

Table 1: overview of available patient characteristics and ADR breakdown

Daily activities

More than 90% of all patients that experienced at least one ADR with impact on the domain for daily activities, experienced burden at a minimum of five on this ten point burden scale (figure 3). There were no significant differences between drug groups (*p=0.27*). None of the patients experienced an ADR with very little to no additional burden on their daily activities. None of the patients using corticosteroids and tsDMARDs experienced a burden of less than five when an ADR occurred. Etanercept (bDMARD) and leflunomide (csDMARD) score the lowest average burden within this domain (Figure S5). On average methotrexate scored worst of all DMARDs. Seventeen out of twenty one patients using methotrexate scale the burden of methotrexate as an eight or above, with only one of the other four patients scaling the burden at a four. Hydroxychloroquine had the widest distribution of burden, ranging between three and ten.

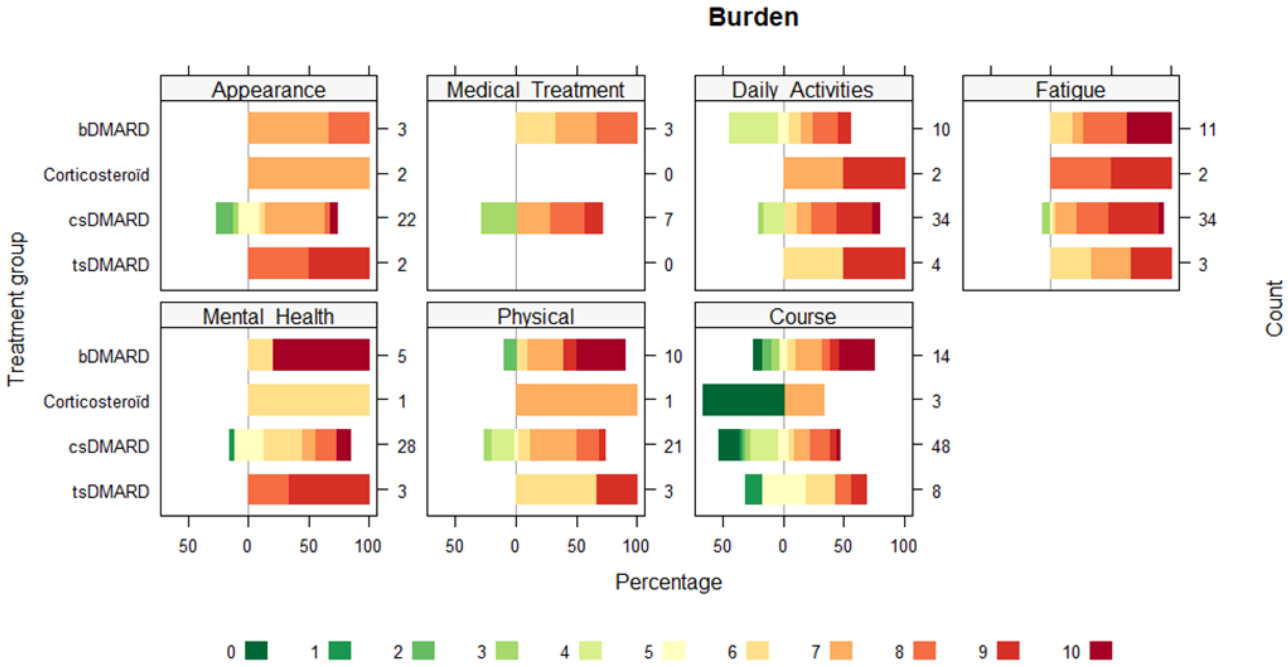

Figure 3: Burden per domain for each drug group. Every DMARD related ADR is tallied on the right (Count).

Appearance

There were some differences between drug groups in the appearance domain. The tsDMARDs had the highest average burden, with the csDMARDs having the widest range of outcomes scoring between 2 and 10. However none of the groups within the appearance domain were significantly different (*p=0.06*).

Mental health domain

The burden of bDMARDs, in the mental health domain, is significantly worse than the burden of csDMARDs (*adj.p= 0.04423*) (Figure S5). The burden for patients using bDMARDs is scaled at a ten for 80% of all ADRs. In comparison, the majority of all csDMARDs score between a five and seven. Although not significant leflunomide seemingly scores lower than hydroxychloroquine and methotrexate. Etanercept has the highest average mental health burden of all bDMARDs (Figure S5).

Fatigue domain

All four drug groups seem to have higher burden averages for fatigue (*p=0.73*). The bDMARDs have more scores of ten than the other drug groups, but also have more variety in their other scores. Only three ADRs in all of the fatigue domain have a burden score of less than five, all three coming from two csDMARDs.

Physical domain

In the physical domain the bDMARDs had more scores of nine and ten than all three other drug groups combined, yet the bDMARDs weren't significantly more burdensome than the other drug groups (*p=0.30*).

Medical treatment domain

Medical treatment got the least response out of all seven domains. Only two drug groups had burden scores for this domain, resulting in a different method of analysis en post hoc testing needing to be used. There were no significant differences between these two groups either (*p=1.00*). Methotrexate and leflunomide made up most of the burden scores in the medical treatment domain.

Course domain

In the course domain, bDMARDs showed a tendency for higher burden compared to the csDMARDs, with noticeable separation in medians (*p=0.10*). The tsDMARDs are somewhere in between the bDMARDs and csDMARDs in terms of burden. When looking at (Figure S5) the corticosteroids that have a zero score for course are prednisone and prednisolone, with the triamcinolone acetonide injection making up the only higher score of seven. Etanercept is responsible for all of the highest burden scores of the bDMARDs, with four scores of ten.

Discussion

In this study we assessed and compared the burden of ADRs of DMARDs, used as the main treatment of rheumatoid arthritis, on the seven predefined domains of burden. All seven domains were of interest for this study. The burden on appearance, daily activities, fatigue, mental health, medical treatment, physical (discomfort) and course could all be used as a comparison for the burden of drug groups and individual drugs, with course giving some insight into the frequency of burden and changes in burden intensity over a certain time period.

Appearance, daily activities

Appearance and daily activities had no significant differences between drug groups. This finding isn't that surprising, as most currently available literature points to tsDMARDs and bDMARDs having very similar ADR profiles [9-10]. There is no indication that one drug group would be better than the other or have worse ADRs, although the current guidelines do have bDMARDs ranked above the tsDMARDs [11]. This mostly being the case since these JAK-inhibitors (tsDMARDs) are newer entities suffering from having less long-term data and active patents barring the release of generic tsDMARDs, leading to inflated prices. Overall there isn't a lot of difference between the tsDMARDs, bDMARDs, csDMARDs and corticosteroids.

One potential observation that could be made is leflunomide having a lesser burden scores than the other (cs)DMARDs in these two domains. Literature is more vague when it comes to this observation. Research of leflunomide has been more quiet in the last 20 years, often comparing combination treatments using leflunomide and methotrexate combination therapies vs other drugs or methotrexate monotherapy. Added on to that, most of these more recent papers are mostly focused on efficacy and/or non-inferiority. However a recent, 2019, systematic review and meta-analysis did note some differences in safety profiles of leflunomide and the golden standard, methotrexate. Based off four other trials leflunomide seems to cause less GI-tract issues, but is responsible for more frequent reports of liver enzyme elevation, when compared to methotrexate [12]. A 2003 systematic review, comparing placebo or methotrexate with leflunomide, found that patients using leflunomide had more GI-tract issues and allergic reactions [13]. These findings partially oppose the observation that in a larger sample size leflunomide could be less burdensome. One would expect there to be less allergic reactions caused by leflunomide than other DMARDs, like methotrexate. Conflicting information surrounding GI-tract problems also doesn't give conclusive insight into what could potentially explain the seemingly lower leflunomide burden scores. A potential explanation for these results could be found in the treatments the leflunomide patients received within our database. Only two patients received leflunomide, with neither of them using leflunomide as monotherapy. The patients were also using hydroxychloroquine or rituximab and combining them with leflunomide. The leflunomide doses for both patients were between 10-20mg, indicating longer leflunomide usage. This would then explain the lower burden scores, as ADRs tend to lessen over time (see course domain) and people learn to live with certain ADRs that aren't as burdensome. In addition the leflunomide patients scored the course of their ADRs as pretty moderate, with only two out of seven ADRs being scored a seven, and the rest being a 5 or below. Lastly an overlooked part could be the age and/or overall perspective of the patients. There is a possibility that these leflunomide patients care less about their appearance and might have less daily activities that are impacted by the ADRs they experienced. Overall it would be a good idea see if this trend and observation holds up in larger sample sizes.

Fatigue, mental health, physical burden

Fatigue, mental health and physical burden domains had somewhat similar results showing bDMARDs as having most of the highest burden scores across these three domains. Within the bDMARDs there was one constant cause for these high burden scores, as etanercept was responsible for nearly all of the highest bDMARD related burden scores within these domains. These domains also could be characterized as having very high average burden scores for nearly all ADRs classed as fatigue, mental health and/or physical burden. Almost all burden scores reported in these three domains were

graded as a five or higher. Significant differences between drug groups were only found in the mental health domain.
This combination of domains being impacted similarly (albeit mostly not significant) shouldn't very surprising. Mental health, fatigue and physical inconveniences all play a part in a vicious cycle, in which they can add to the issues caused when ADRs are impacting these burden domains [14]. Although a decrease in fatigue and any form of physical inconvenience are more commonly reported for anti-TNF-alpha drugs and bDMARDs as a whole, more recent literature also points to varying decreases in fatigue, as well as there being cases of patients in which the treatment is effective but fatigue lingers or even increases [15]. All in all most patients do experience remission of their overall fatigue, but many, including the patient in question, can still experience an extreme amount of burden due to the fatigue caused by some combination of the disease state, progression of the disease, the treatment chosen and other factors including burden of ADRs spread across multiple domains.

There is no literature that can back up claims that bDMARDs would influence mental health more negatively than the csDMARDs. There is an inverse relationship as rheumatoid arthritis is associated with a significantly higher prevalence of major depressive disorder and other mental health disorders [16]. In addition there are some articles, including a 2018 systematic review and network meta-analysis, that show some betterment of the overall mental health due to treatment with DMARDs, mostly stemming from the treatment of rheumatoid arthritis being under (better) control [17].
A potential reason for the bDMARDs burdening the mental health more than the csDMARDs could be the simple fact that bDMARDs are a further step down the treatment pyramid than the csDMARDs. The group using bDMARDs will more than likely have unsuccessfully tried other DMARDs and/or have a worse disease state than the group using csDMARDs at the time of filling in. In addition the likelihood of monotherapy is higher in patients using csDMARDs, and methotrexate in particular, than when at least one bDMARD is being used. This all could negatively affect the mental state of patients, creating a more negative and doubtful attitude towards any future treatment.
For fatigue and physical burden, there could also be some explanation through their mechanism of action, as biological drugs are exclusively administered by injection, whereas the csDMARDs can be administered orally or by injection. Frequency of administration does tend to even things out between the csDMARDs and bDMARDs, as csDMARDs are administered more frequently than most bDMARDs (*e.g. methotrexate weekly, infliximab every eight weeks*). The frequency or lack thereof could also explain how the overall administration of the injectables could still be experienced as more burdensome, even with a lower frequency of drug administration. Injections are generally considered less patient friendly, as they are experienced as being more intense and can cause injection site inflammation and swelling after every hospital visit. Isolation of these few days after treatment, being that the results of the questionnaire remain subjective and there is no objective way of measuring burden, the frequency of treatment could most definitely have some impact on the results in these domains with the bDMARDs coming forward as the most burdensome drug group within the DMARDs. ADRs that are more common in the physical domain are skin conditions (rashes, dry skin), GIT-issues (abdominal discomfort or distension) and injection site issues (pain, swelling, redness) [1]. So at the very least some of the overall burden experienced is split depending on the administration method. Oral administration has larger odds for causing GI-tract issues, with injections having exclusivity for the injection site issues. The intensity of injection site issues tend to diminish to a lesser extent than GI-tract issues. These GI-tract issues are often symptoms of more recently started oral treatments, with many of these ADRs lessening over time. Administration methods can be a cause of burden in all three of these domains, mostly in the physical domain. As mentioned previously these domains are very connected and burden in one of these domains could be a cause of burden in these other domains.
Lastly there could also just be more patients with mental health issues within the bDMARD group than the csDMARD group, resulting in potentially skewed results within the mental health domain.

Medical treatment

Not many results were available for the medical treatment domain, which is a good thing. Only the bDMARDs and csDMARDs were represented in this domain. This makes sense as these most commonly are the first and second choice DMARDs within the treatment pyramid in the Netherlands and internationally. Of all burden scores most of the burden scores stemmed from either methotrexate or leflunomide, meaning most of the results stemmed from the csDMARDs, further indicating that the treatment guidelines were very influential on what could be found within this patient group, while also reflecting the obvious majority does indeed use csDMARDs or bDMARDs currently. There was absolutely no difference in burden between the drug groups in this domain, csDMARDs and bDMARDs ($p=1.00$). Being that there were only ten qualifying ADRs resulting in changes in the treatment plan, this isn't surprising at all. Burden in this domain could be down to outright stopping and changing medication or having to visit a hospital or GP more regularly. Finding any significant differences between drug groups within this single domain would be the hardest out of all domains. As the longest follow up time is one year if all six questionnaires are answered, there is a good chance most patients won't change within this timeframe. However the fact that ten out of a total of seventy eight ADRs did end up finding themselves in this domain, having only filled in a maximum of three questionnaires, might be the most surprising result out of all results in the medical treatment domain.

The course

The course seems to show an overall decrease in burden across all drug groups. This is to be expected, being that the burden not decreasing over time would result in an unsustainable treatment plan. The burden of some DMARDs however did not decrease over time, which also falls in line with the observation that a significant amount of people (temporarily) discontinued usage of DMARDs due to the severity or continuity one or multiple of these ADRs. While the setup of this study was cross sectional and therefore not temporal, these results did indeed give some insight into the course of these DMARD-related ADRs and the burden accompanying them. The oral corticosteroid treatments scored scores of zero, with the only higher score, a seven, coming from a onetime triamcinolone acetonide injection. This could partially show the influence of an administration method on the short term course of the burden.

The corticosteroids, csDMARDs, bDMARDs and tsDMARDs weren't significantly more or less burdensome within this domain. However to a certain extent the course domain reflects the other domains, giving a good overview of what could be expected in the other domains. Some of this may be pure coincidental, however there is also a very probable reason for the course to show an overview of the other six domains. From a more general viewpoint the course of an ADR is heavily influenced and therefore dependent on the initial severity of the ADR and the following trajectory of the severity of this ADR. Along with this change in severity the repetition or frequency of one or multiple ADRs also will influence the course and how this course in experienced. All in all the course is not completely separate from the other domains and the results in these other domains somewhat reflect the overall takeaways from the course domains. This directly shows when looking at the likert type scale of this domain, as outside of the corticosteroids, the tsDMARDs, bDMARDs and csDMARDs all show very similar ranges of outcomes for their overall course. Them not being significantly different also further reflects this similarity between these groups.

The csDMARDs' overall course was mostly dependent on methotrexate. With methotrexate setting the range in which the other csDMARDs fell, as it was responsible for both range extremes within this group. Contrary to most other domains the csDMARDs were represented by all four csDMARDs, as sulfalazine also showed up in this domain. Sulfalazine was also the least burdensome out of all csDMARDs. With there only being one burden score, this obviously can't tell us a lot. Out of the more represented csDMARDs, hydroxychloroquine might have the least burdensome course, followed by leflunomide and methotrexate. This finding is backed up by literature as general consensus at this moment is that hydroxychloroquine has the best safety profile [18]. This mostly being down to its

original development goal of being an anti-malaria drug. This mostly coming down to it not having, what is a pitfall for most DMARDs, any negative influence on the susceptibility to infections. With that one of the main adverse side effects commonly found in DMARDs isn't shared by hydroxychloroquine. The differences between these csDMARDs aren't significant which is also backed up by earlier findings [18].
Most of the higher burden scores in the course domain were the result of repetitive ADRs. These scores didn't reflect the initial severity of an ADR but more often reflected their helplessness in the constantly returning ADRs of their respective DMARDs. Of all patients, six scored the course of one of their ADRs a nine or higher, with a total of ten ADRs being scored a nine or higher. Of these ten ADRS only two were found in the domain of medical treatment. Not all of these ADRs resulted in permanent changes to the DMARD used and/or dosage of this DMARD. This also shows that the decision to change a drug is very patient dependent, as on one side one may experience an ADR as very burdensome and extremely burdensome when compared to other scores and patients, but on the other side they will still continue to use this treatment as for them the efficacy and/or overall upside still outweigh one or multiple ADRs. For this same reason the course also wasn't a good indicator for continuing current treatment, as more of the patients that stopped or changed treatment made this decision based on the domain they felt was most important or most burdensome.

Strengths
There has been no previous research looking at the burden of drug related ADRs in various chronic diseases, like rheumatoid arthritis. This research is unique as drug burden of DMARDs has never been analyzed within these seven domains, until now.
Within the research field five or even seven point scales are most often used to summarize and visualize questionnaire based data. While using smaller point scales come with benefits of there being enough descriptive words to distinguish the various scores from each other, this also is the main downside of using smaller point scales. Smaller point scales, like the five point scale, are more susceptible to oversimplifying the complexity and variety of answers possible. Using a ten point scale gives more options than a five or seven point scale, allowing for more nuance and accuracy in answers. Over time the likert type scales could also be used as a way of informing patients of the burden of the treatments they are using.

Limitations
The biggest limitation of this article is the sample size accrued within the timeframe of the study. This sample size limited not only the significance of the results, but also made it more difficult to differentiate between drug groups or individual drugs, resulting in less overall observations as to these differences. In addition to this, some liberties were taken to increase the overall data available. As the first available questionnaire with burden information for every unique ADR was used as data for analysis, this meant data from questionnaire two and three was also incorporated into the results. This initially wasn't the plan, but was decided on based on the data available at that time. Even with this change in approach the data remained cross-sectional, but this also increased the influence a single patient's experience could have on the eventual burden results of their respective DMARDs. This was already one of the weaker points of this set-up, as multiple ADRs also meant having a larger percentage of share in one or multiple burden scores. Not taking all of these ADRs into account would be even worse, so this is just one of the inherent limitations one will run into with this kind of data.

Due to the smaller sample size drugs had to be put in drug groups in order to even be able to analyze the significance of differences, leading to less focus on the DMARDs by themselves. Using a Dunn test as a post hoc test also further limited the chance of any significance being found, as this specific test is very conservative albeit this showing up more with larger sample sizes. However even with all that being said, the data that was available did give some insight into what kind of results could potentially be expected from future results and provided a good starting point for further research.

Disease burden is not established within the scope of this article. The drug burden will also be influenced by the disease state, and vice versa. The overall disease state and the place of the current treatment in someone's treatment journey at the time of filling in the questionnaire, could also influence these results. The previously used DMARDs and overall sensitivity to drugs are unknown. This balances out a little more as more patients participate in the ADR Monitor.
Discontinuation of DMARD use was not mentioned during this process and could explain some of the loss of questionnaire follow up for questionnaires two and three. For the purpose of this study this also wasn't a priority, as there was an overload in information within this article and its supplementary files.

Being that the burden data was mostly found at the end of questionnaires there also always is a chance that there might be (more of) a lack of focus when filling in burden scores and giving additional context along with these scores. Unfortunately this is just one of the downsides of trying to get as much data as possible without accessing patient data through databases, as is often done in retrospective research setups. The subjective data as a whole is very useful, but does remain subjective in nature. Fallacies of this data type become more apparent with a lower amount of participants/sample size. Subjective patient data in the pharmacological field is often lacking, with this lack of data often having very good reasons.
That being said, patient experience along with effectiveness of a treatment will end up deciding whether a treatment is worth it and therefor sustainable. Innovation in the data being collected and how it's presented can only help educating patients, resulting in shared decision-making in the treatment of for example chronic diseases.

Future direction/considerations
A longitudinal setup can follow the various burden domains over a longer period of time, allowing for more middle ground within the reported burden scores. This would limit the potential of burden scores being in- or deflated due to the timing of filling in questionnaires. A larger timeframe of following up on these burden domains also opens the door for additional insight into the timeframe one can expect for certain more prevalent ADRs. A lot of ADRs can lessen in intensity over time or straight up disappear after a while. For a lot of these ADRs having the ability to quantify timelines for these ADRs could help pharmacists and medical doctors give more detailed advice as well as potentially bettering treatment adherence by patients though these timelines as there is additional information to back this up.

Leaving out NSAIDs but including corticosteroids was a decision that came down to their inability at slowing down the disease progression of rheumatoid arthritis in the long term, being that they are mostly used to treat flare-ups. However in future studies adding NSAIDs as a separate drug group would give a good overview of all drugs used in the overall treatment of rheumatoid arthritis and would give a more complete overview of the total burden picture.

There should be a way to incorporate all the patients that aren't burdened by a single ADR over a one year span. Within, at most, a six month span only 31 out of 48 patients reported an ADR, with 28 being deemed DMARD related. A total of twenty people do use at least one of these DMARDs but end up not reporting a single ADR. While making an eighth burden domain wouldn't be realistic, adding disease activity and overall satisfaction with the current treatment could add some context to all, in this case, 48 patients, as well as be able to give more information about every DMARD or drug used to treat a disease. Effectively you can use some of that information to quantify those 20 people that were a NULL up to that point. It allows for additional information on how each treatment is experienced across all patients. Puzzling all these pieces together would be difficult and also never end up being an exact science, but could potentially give insight into the total experience/burden of a treatment through its potential ADR-related burden contrasting with the overall treatment effectiveness.

Conclusion

These results provide a first look into what burden data could add to current and future treatment considerations and provide a good start point for future articles with larger databases of rheumatoid arthritis or other chronic disease patients using DMARDs or other treatments with various drug groups to choose from.

While larger sample sizes are needed in order to establish a more based burden profile per domain, some considerations could be made, based on the current results presented, when choosing a therapy option for patients with specific priorities aligning with the mental health domain.

The csDMARDs aren't significantly more or less burdensome than other DMARDs and therefor remain the first choice when treating rheumatoid arthritis. Methotrexate shows the largest range in burden scores and should remain to be monitored closely. However if methotrexate treatment is too burdensome or has other contra-indications, leflunomide monotherapy might have a similarly moderate burden profile. The bDMARDs and tsDMARDs both have domains in which they might be more burdensome that each other, as they do show some non-significant difference in score. If a patient has a history of bad mental health trying a first or second csDMARD over starting a bDMARD could be considered and preferred based on the available data in the mental health domain.

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Supplementary files

Questionnaires filled in	n	Percentage	People with an ADR	Percentage of patients with ADR	Patients with first ADR
Questionnaire 1	48	100%	28	58%	28
Questionnaire 2	38	80%	6	16%	1
Questionnaire 3	28	57%	4	14%	2

Table S1: overview of questionnaires filled in and newly reported ADRs per questionnaire

GenericDrugName	Reported ADRs	Percentage	Most common ADRs
METHOTREXATE	30	38.46%	Fatigue (6), Nausea (3), Tinnitis, Headache (2)
HYDROXYCHLOROQUINE	14	17.95%	Tinnitis (2), Pigmentation disorder (1)
LEFLUNOMIDE	7	8.97%	Abdominal discomfort (1), Dizziness (1)
BARICITINIB	5	6.41%	Blood blister (1), Palpitations (1), Hot flush (1)
ETANERCEPT	5	6.41%	Malaise (1), Hot flush (1), Rash (1)
FILGOTINIB	3	3.85%	Diarrhoea (2), Increased blood cholesterol (1)
ABATACEPT	2	2.56%	Bronchitis (1), Cough (1)
ADALIMUMAB	2	2.56%	Dry skin (1), Fatigue (1)
INFLIXIMAB	2	2.56%	Fatigue (1), Headache (1)
TOCILIZUMAB	2	2.56%	Inj. site erythema (1), Pharyngeal swelling (1)
CERTOLIZUMAB PEGOL	1	1.28%	Cystitis-like symptom (1)
PREDNISOLONE	1	1.28%	Therapeutic response unexpected (1)
PREDNISONE	1	1.28%	Hyperhidrosis (1)
SULFASALAZINE	1	1.28%	Nausea (1)
TRIAMCINOLONACETONI	1	1.28%	Cough (1)
UPADACITINIB	1	1.28%	Hypercholesterolaemia (1)
Totaal	78	100%	

Figure S2: DMARD usage and the most common ADRs reported by participants

GenericDrugName	PTName	n
ABATACEPT	Bronchitis	1
ABATACEPT	Cough	1
ADALIMUMAB	Dry skin	1
ADALIMUMAB	Fatigue	1
BARICITINIB	Blood blister	1
BARICITINIB	Headache	1
BARICITINIB	Hot flush	1
BARICITINIB	Liver injury	1
BARICITINIB	Palpitations	1
CERTOLIZUMAB PEGOL	Cystitis-like symptom	1
ETANERCEPT	Abdominal discomfort	1
ETANERCEPT	Hot flush	1
ETANERCEPT	Injection site pain	1
ETANERCEPT	Malaise	1
ETANERCEPT	Rash	1
FILGOTINIB	Diarrhoea	2
FILGOTINIB	Blood cholesterol increased	1
HYDROXYCHLOROQUINE	Tinnitus	2
HYDROXYCHLOROQUINE	Abdominal discomfort	1
HYDROXYCHLOROQUINE	Abdominal distension	1
HYDROXYCHLOROQUINE	Alopecia	1
HYDROXYCHLOROQUINE	Anxiety	1
HYDROXYCHLOROQUINE	Depressed mood	1
HYDROXYCHLOROQUINE	Fluid retention	1
HYDROXYCHLOROQUINE	Palpitations	1
HYDROXYCHLOROQUINE	Pigmentation disorder	1
HYDROXYCHLOROQUINE	Poor quality sleep	1
HYDROXYCHLOROQUINE	Rash pruritic	1
HYDROXYCHLOROQUINE	Retinal disorder	1
HYDROXYCHLOROQUINE	Vision blurred	1
INFLIXIMAB	Fatigue	1
INFLIXIMAB	Headache	1
LEFLUNOMIDE	Abdominal discomfort	1
LEFLUNOMIDE	Cognitive disorder	1
LEFLUNOMIDE	Dizziness	1
LEFLUNOMIDE	Infection susceptibility increased	1
LEFLUNOMIDE	Nausea	1
LEFLUNOMIDE	Rash pruritic	1
LEFLUNOMIDE	Tinnitus	1
METHOTREXAAT	Fatigue	6
METHOTREXAAT	Nausea	3
METHOTREXAAT	Abdominal discomfort	2
METHOTREXAAT	Headache	2
METHOTREXAAT	Tinnitus	2
METHOTREXAAT	Abdominal pain	1
METHOTREXAAT	Asthenia	1
METHOTREXAAT	Cognitive disorder	1
METHOTREXAAT	Depressed mood	1
METHOTREXAAT	Diarrhoea	1
METHOTREXAAT	Feeling abnormal	1
METHOTREXAAT	Hyperhidrosis	1
METHOTREXAAT	Influenza like illness	1
METHOTREXAAT	Injection site erythema	1
METHOTREXAAT	Injection site pain	1
METHOTREXAAT	Liver injury	1
METHOTREXAAT	Malaise	1
METHOTREXAAT	Memory impairment	1
METHOTREXAAT	Palpitations	1
METHOTREXAAT	Pneumonia	1
PREDNISOLON	Therapeutic response unexpected	1
PREDNISON	Hyperhidrosis	1
SULFASALAZINE	Nausea	1
TOCILIZUMAB	Injection site erythema	1
TOCILIZUMAB	Pharyngeal swelling	1
TRIAMCINOLONACETONIDE	Cough	1
UPADACITINIB	Hypercholesterolaemia	1
Totaal		78

Figure S3: overview of all DMARD related ADRs

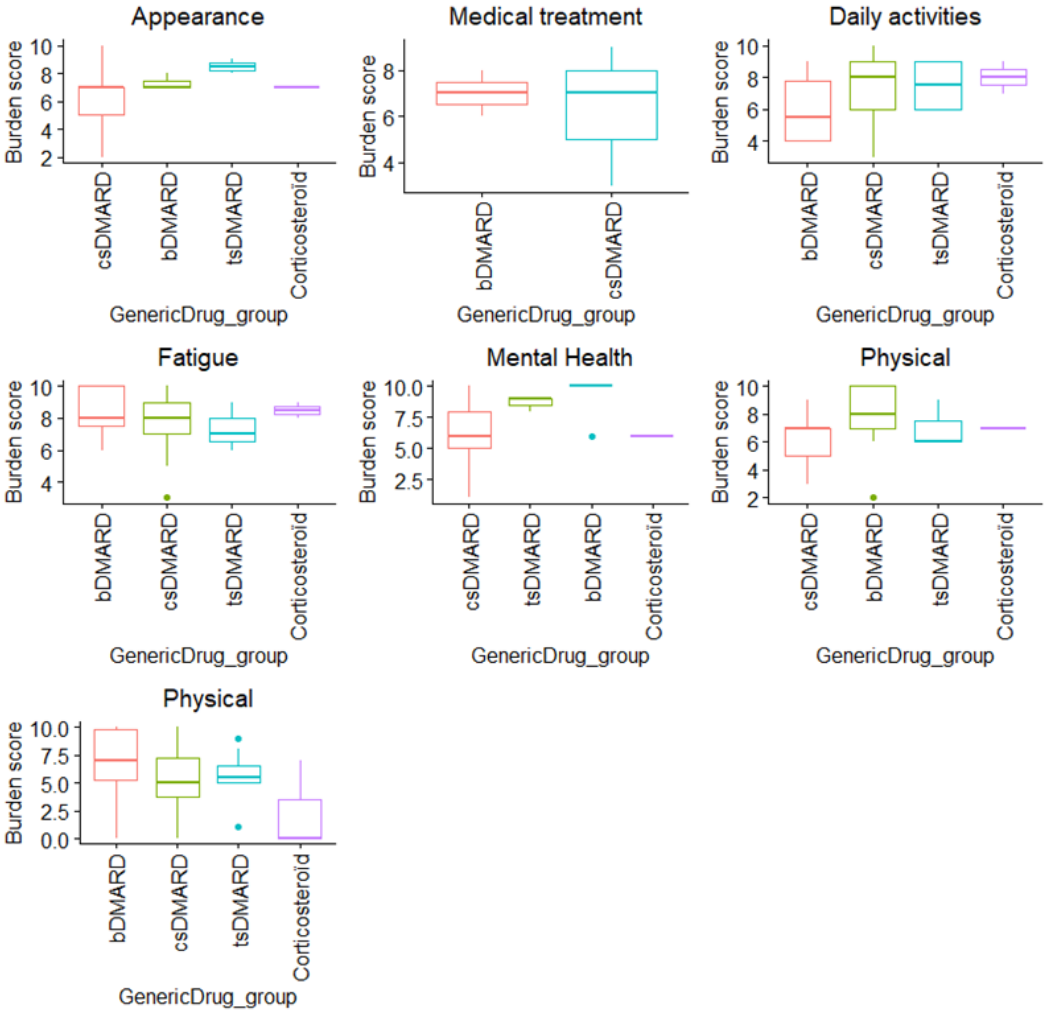

Figure S4: boxplot of each domain for every drug group

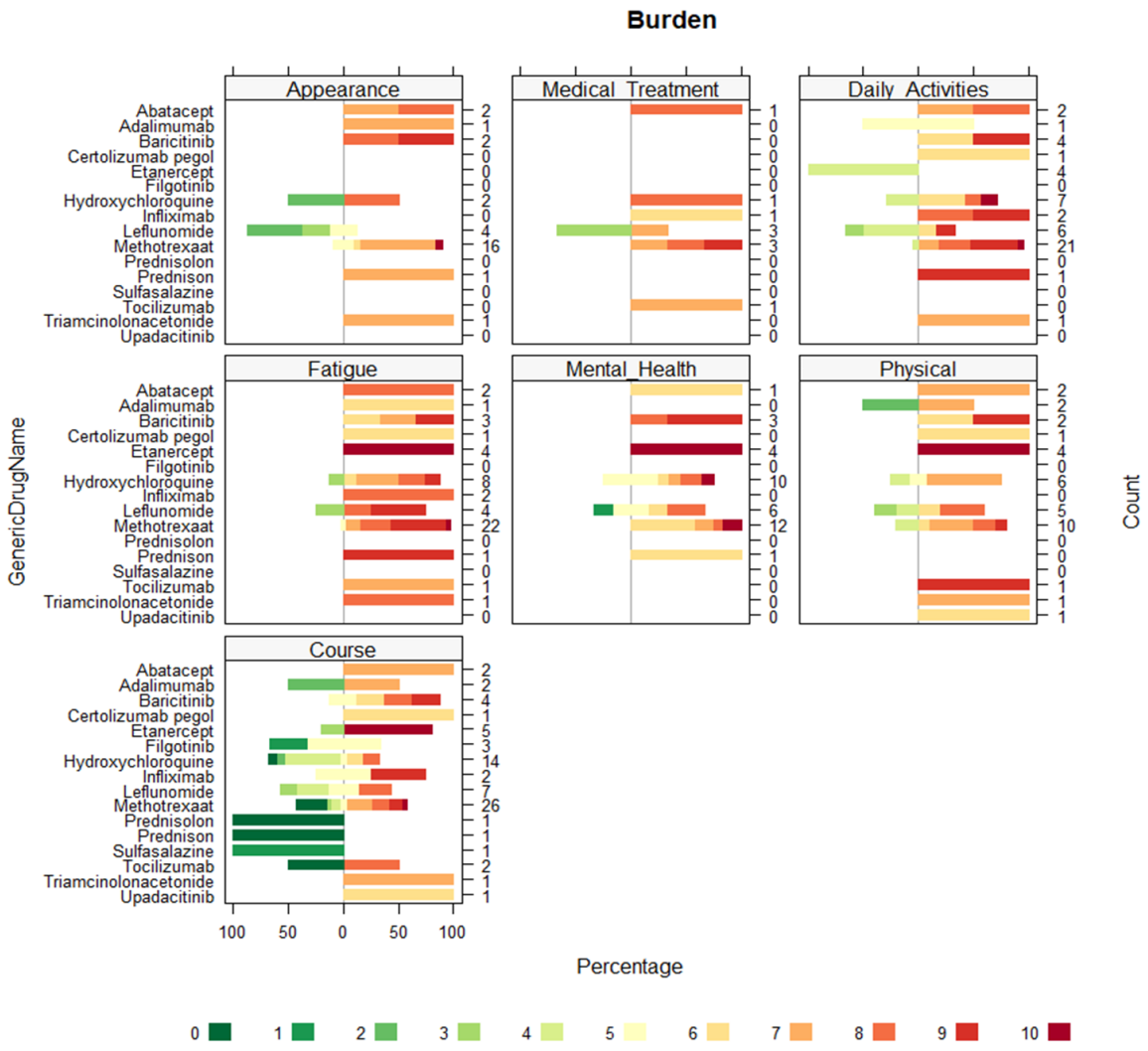

Figure S5: Likert type scale of the burden of all DMARDs for the 7 predetermined domains of burden

Table S6: Full transcript of questionnaire sections pertaining to burden

12.	The following questions are about the burden of the adverse drug reaction?		
	In the last 2 months:		
12.a.1	Did the adverse drug reaction influence what you looked like?	For example your body, hair and/or choice of clothing	Yes
			No
	When answered Yes, expand to question 12.a.2		
12.a.2	How much did this bother you?		Grade 0-10, score of 0: None at all, score of 10: A lot
12.b.1	Did the adverse drug reaction influence your medical treatment?	For example changes to your medication and/or additional visits to your GP or hospital.	Yes
			No
	When answered Yes, expand to question 12.b.2		
12.b.2	How much did this bother you?		Grade 0-10, score of 0: None at all, score of 10: A lot
12.c.1	Did the adverse drug reaction impact your daily activities?	Being able to decide for yourself what activities you will participate in and determining how they happen. For example this could be at home, family, hobbies, social contacts, work and/or education.	Yes
			No
	When answered Yes, expand to question 12.c.2		
12.c.2	How much did this bother you?		Grade 0-10, score of 0: None at all, score of 10: A lot

12.d.1	Were you tired because of the adverse drug reaction?	For example feeling tired, impact on sleep and/or reduced energy during the day.	Yes
			No
	When answered Yes, expand to question 12.d.2		
12.d.2	How much did this bother you?		Grade 0-10, score of 0: None at all, score of 10: A lot
12.e.1	Did the adverse drug reaction cause any changes mentally?	For example anxiety, gloominess, uncertainty or stress.	Yes
			No
	When answered Yes, expand to question 12.e.2		
12.e.2	How much did this bother you?		Grade 0-10, score of 0: None at all, score of 10: A lot
12.f.1	Did the adverse drug reaction have any physical consequences?	For example think of pain due to a bladder infection, itching as a result of a skin rash or shortness of breath due to lung problems.	Yes
			No
	When answered Yes, expand to question 12.f.2		
12.f.2	How much did this bother you?		Grade 0-10, score of 0: None at all, score of 10: A lot
12.g.	How much did the course of the adverse drug reaction bother you?	For example think of an adverse drug reaction returning, getting worse and/or lingering around for a longer time.	Grade 0-10, score of 0: None at all, score of 10: A lot
	Would you like to explain the burden of the side effect? (optional)		[open text field]
13	In the last 2 months, did you have any other adverse drug reactions because of		Yes

	the medication used for the disease(s) you entered? *		
			No