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Published in:
Drug Safety

DOI:
[10.1007/s40264-020-00946-z](https://doi.org/10.1007/s40264-020-00946-z)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

van Lint, J. A., Jessurun, N. T., Hebing, R. C. F., Hoentjen, F., Tas, S. W., Vonkeman, H. E., van Doom, M. B. A., Sobels, A., Spuls, P., van Puijenbroek, E. P., Nurmohamed, M. T., & van den Bemt, B. J. F. (2020). Patient-Reported Burden of Adverse Drug Reactions Attributed to Biologics Used for Immune-Mediated Inflammatory Diseases. *Drug Safety*, 43(9), 917-925. <https://doi.org/10.1007/s40264-020-00946-z>

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Patient-Reported Burden of Adverse Drug Reactions Attributed to Biologics Used for Immune-Mediated Inflammatory Diseases

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Published online: 25 May 2020
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Abstract

Introduction Although the burden of adverse drug reactions (ADRs) has a significant impact on patients' quality of life, thorough knowledge about patients' perspectives on the burden of ADRs attributed to biologics is lacking.

Objectives This study was conducted to gain insight into the patient burden of ADRs experienced with biologic use.

Methods The Dutch Biologic Monitor is a prospective, multicentre, event monitoring cohort system including information collected by web-based questionnaires from patients using biologics, mainly for immune-mediated inflammatory diseases (IMIDs). Patients were asked to complete bimonthly questionnaires on biologics used, indication for the biologic, experienced ADRs, consequences of ADRs and burden on a five-point Likert-type scale, ranging from 1 (no burden) to 5 (very high burden). We assessed potential factors associated with patient-reported burden of ADRs.

Results A total of 1355 patients completed 6293 questionnaires between 1 January 2017 and 1 May 2019. Almost half of the patients (665 patients, 49%), 69% with rheumatic diseases and 31% with other diseases, collectively reported 1720 unique ADRs. Infections and musculoskeletal complaints were the most burdensome ADRs and injection-site reactions were the least burdensome. ADRs leading to healthcare professional contact were more burdensome than ADRs without healthcare professional contact. Smoking, respiratory and psychiatric comorbidities were associated with higher burden of ADRs. Crohn's disease, use of adalimumab and use of sulfasalazine as combination therapy were associated with lower burden of ADRs.

Conclusions The patient perspective gives important insights into the burden of ADRs experienced with biologics. This information could be used by healthcare professionals to optimise treatment with biologics.

Key Points

Patients experienced infections and musculoskeletal complaints as the most burdensome adverse drug reactions of biologics in the Dutch Biologic Monitor.

A better understanding of patient perceptions of ADRs and the burden these ADRs impose can help healthcare professionals in proposing more personalised treatment options, which may lead to improved clinical outcomes.

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s40264-020-00946-z>) contains supplementary material, which is available to authorized users.

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1 Introduction

Biological therapies have proven to be effective and safe, expanding the therapeutic armamentarium for a range of immune-mediated inflammatory diseases (IMIDs), including inflammatory rheumatic diseases, inflammatory skin diseases and inflammatory bowel diseases. There is extensive knowledge on common adverse drug reactions (ADRs) of biologics, such as infections and injection-site reactions. Most of this information is gathered from the perspective of the healthcare professional [1, 2]. The healthcare professional's attention to biologic-induced ADRs is mainly focused on ADRs that require discontinuation of therapy or hospitalisation, such as respiratory and herpes zoster infections [3, 4]. However, the patient perspective on ADRs is more likely focused on burden and quality of life [5]. It is important to realise this as ADRs may affect adherence [6]. Currently, there is a lack of knowledge about the patients'

perspective on the burden of ADRs attributed to biologics and the consequences these ADRs impose.

The Dutch National Pharmacovigilance Centre Lareb developed the Dutch Biologic Monitor, a system to collect and monitor patient-reported ADRs attributed to biologic treatment over time. It is a multicentre, web-based cohort event monitoring system that follows patients using biologics mainly for IMIDs. Participating patients complete questionnaires about ADRs they attribute to the biologic treatment, including consequences and experienced burden [7].

The primary aim of this study was to gain insight into the patient-experienced burden of ADRs that patients attributed to biologics, mainly prescribed for various IMIDs, in a multicentre longitudinal cohort. The secondary aim was to gain insight into demographic and clinical factors that are associated with the experienced burden of ADRs attributed to biologics. To our knowledge, this kind of study has not been conducted to date.

2 Methods

2.1 The Dutch Biologic Monitor

The Dutch Biologic Monitor is a prospective cohort event monitoring model for patient-reported ADRs attributed to biologics [7]. Nine Dutch hospitals participated in the Dutch Biologic Monitor between January 1, 2017 and May 1, 2019. Patients using one of the monitored biologics, mainly for an IMID, were selected and invited to participate by healthcare professionals of the respective hospitals using consecutive sampling. Patients were eligible from 18 years of age.

Recruitment strategies varied per hospital. Patients were either recruited via letters, during appointments with nurses and specialists, at the outpatient pharmacy or during infusion therapy at the ambulatory care unit. Participating patients were asked to complete a comprehensive web-based baseline questionnaire covering demographic information (gender, date of birth, weight, height, smoking), biologic used, start date, indication for biologic therapy, combination therapy, comorbidities at baseline and ADRs attributed to the biologic. Available options for biologics were the originator or, when available, a biosimilar of abatacept, adalimumab, anakinra, brodalumab, canakinumab, certolizumab pegol, dupilumab, etanercept, golimumab, guselkumab, infliximab, ixekizumab, natalizumab, rituximab, sarilumab, secukinumab, tocilizumab, ustekinumab and vedolizumab. Rheumatoid arthritis (RA), psoriatic arthritis (PsA), psoriasis, axial spondyloarthritis (SpA), ulcerative colitis (UC), Crohn's disease (CD) or other indications were the optional indications for biologic therapy in the questionnaires. Methotrexate, predniso(lo)ne, hydrocortisone, methylprednisolone, hydroxychloroquine, azathioprine, leflunomide,

tioguanine, mercaptopurine, mesalazine, sulfasalazine, olsalazine, chloroquine or no combination therapy were the options for combination therapies. Respiratory disorder, cardiovascular disorder, hypercholesterolaemia, psychiatric disorder, cancer, nervous system disorder, other comorbidities or no comorbidities were the options for comorbidities in the questionnaires. Multiple options could be selected for each of these variables. Patients were asked to report information about ADRs they attributed to the used biologic. This included the type of ADR, start and stop date, course, burden using a five-point Likert-type scale ranging from 1 (no burden) to 5 (very high burden), contact with a healthcare professional, the type of healthcare professional, treatment or other actions taken by the healthcare professional and own action taken by the patient following the ADR. Patients could elaborate on the experienced burden in an open text field. Subsequent questionnaires during follow-up after baseline focused exclusively on drug use and ADRs and included identical questions on these topics. The baseline and subsequent questionnaire translated into English are presented in the electronic supplementary material. Questionnaires were sent out bimonthly and patients received a reminder if they had not completed the questionnaire within 7 days and 14 days. No more questionnaires were sent if the previous questionnaire had expired (after 21 days) or if the patient withdrew from the study. Patients could withdraw from the study at any time.

2.2 Data Collection

Pharmacovigilance centre Lareb collected ADR reports as solicited reports from all questionnaires that were completed between January 1, 2017 and May 1, 2019. Reported ADRs were coded according to Medical Dictionary for Regulatory Activities (MedDRA®) terminology (version 21.0) [8] by qualified pharmacovigilance assessors. We included all reported ADRs in this study and assessed burden at the first time the patient reported the ADR. Long-term or recurring ADRs with the same MedDRA® Preferred Term that were repeated by one patient in subsequent questionnaires were counted once. Multiple ADRs with different MedDRA® Preferred Terms reported by one patient were counted separately. ADRs regarding infections, skin reactions, musculoskeletal and gastrointestinal complaints were clustered as subtypes for separate analysis according to the corresponding MedDRA® default System Organ Class. Additionally, injection-site reactions were clustered according to the MedDRA® Higher Level Group Term 'Administration site reactions'. We considered mean burden and use of care due to the clustered ADRs as indicators for the experienced burden. Use of care was specified as hospitalisation, healthcare professional contact and actions following the ADR.

2.3 Data Analysis

Descriptive statistics were provided using equally weighted mean ($\pm$ SD) values of the reported burden. We assessed differences in mean burden between variables with independent *t* tests. Differences in ADR proportions were tested with Pearson Chi-Square tests. A *p* value < 0.05 was considered statistically significant. As our primary outcome measure, burden, was normally distributed (confirmed with a histogram of standardised residuals), multiple linear regression analysis was performed to assess potential variables associated with higher or lower burden. The variables gender, age, body mass index (BMI), smoking, biologic, duration of use, indication for biologic therapy, combination therapy, comorbidities at baseline and ADR subtype were included in the model following the enter method, in which all variables are entered simultaneously. A sensitivity analysis was conducted to account for missing data in case $> 5\%$ of a variable was missing. Statistics were performed in IBM SPSS Statistics (version 22).

3 Results

A total of 1355 patients completed 6293 questionnaires between January 1, 2017 and May 1, 2019 in the Dutch Biologic Monitor. Most patients (962 patients, 71%) used a biologic for an inflammatory rheumatic disease; 573 for RA (42%), 220 for PsA (16%), 137 for SpA (10%), 20 for PsA and SpA combined (1.5%) and 12 for RA and SpA combined (0.9%); and 29% used a biologic for other indications. Almost one third of the patients (31%) stopped participating in the Dutch Biologic Monitor after completing the first questionnaire. More than half of the patients (54%) were still participating after completing four questionnaires (6 months of participation). After seven questionnaires (1 year of participation) 36% of the patients were still participating. The participants covered 798 patient years in total with a mean of 7.1 months. Almost half of the patients (665 patients, 49%) reported an ADR. Most of these patients had inflammatory rheumatic diseases (461 patients, 69%) and 31% used a biologic for an inflammatory skin disease, an inflammatory bowel disease or another indication. The patients with an ADR collectively reported 1720 unique ADRs during their participation. These patients covered 424 patient years (53%) in the Dutch Biologic Monitor, with a mean of 7.6 months. In total, 55% of all reported ADRs were reported in the first questionnaire and 75% of all reported ADRs were reported in the first three questionnaires. See Table 1 for demographics of the patients with ADRs.

Table 1 Demographics of patients in the Dutch Biologic Monitor who reported at least one adverse drug reaction

Characteristics (<i>N</i> =665)	<i>N</i> (%)
Gender (male)	222 (33)
Age (years) (mean $\pm$ SD)	53 $\pm$ 13
Smoking	119 (18)
BMI (kg/m ²) (mean $\pm$ SD)	25.9 $\pm$ 4.9
Biologic	
Adalimumab	235 (35)
Etanercept	185 (28)
Infliximab	66 (10)
Tocilizumab	34 (5)
Secukinumab	27 (4)
Rituximab	25 (4)
Ustekinumab	25 (4)
Other biologics ^a	101 (15)
Duration of biologic use at inclusion (months) (mean $\pm$ SD)	36.8 $\pm$ 45.5
Indication ^b	
Rheumatoid arthritis	291 (44)
Psoriatic arthritis	100 (15)
Crohn's disease	97 (15)
Axial spondyloarthritis	86 (13)
Ulcerative colitis	32 (5)
Psoriasis	31 (5)
Other indications ^c	64 (10)
Patients with reported combination therapy at any time during participation	387 (58)
Methotrexate	186 (28)
Corticosteroids ^d	120 (18)
Leflunomide	39 (6)
Hydroxychloroquine	38 (6)
Sulfasalazine	33 (5)
Other combination therapy ^e	75 (11)
Patients with reported comorbidities	374 (56)
Cardiovascular disorder	168 (25)
Hypercholesterolaemia	101 (15)
Respiratory disorder	83 (12)
Psychiatric disorder	58 (9)
Nervous system disorder	20 (3)
Cancer	13 (2)
Other comorbidity	146 (22)

BMI body mass index, *SD* standard deviation

^aOther biologics include certolizumab pegol (*n*=22), golimumab (*n*=20), vedolizumab (*n*=18), abatacept (*n*=16), anakinra (*n*=10), dupilumab (*n*=6), canakinumab (*n*=6), sarilumab (*n*=1), natalizumab (*n*=1), guselkumab (*n*=1)

^bPatients could report more than one indication

^cOther indications include uveitis (*n*=9), atopic eczema (*n*=6), vasculitis (*n*=4), hidradenitis (*n*=4), Tumour Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) (*n*=3), diverse (*n*=39)

^dCorticosteroids include prednisolone (*n*=103), methylprednisolone (*n*=4), hydrocortisone (*n*=16)

^eOther combination therapy includes azathioprine (*n*=27), mesalazine (*n*=23), mercaptopurine (*n*=17), tioguanine (*n*=7). Olsalazine and chloroquine were not reported as combination therapy

3.1 Reported Adverse Drug Reactions (ADRs)

Out of 1720 reported ADRs, 65% (1116 ADRs) were included in the following predefined ADR subtypes: injection-site reactions, infections, skin reactions, gastrointestinal complaints, musculoskeletal complaints and fatigue (Table 2). These ADRs were reported by 83% of the patients with an ADR (547 patients).

Musculoskeletal complaints were reported by 43 RA patients, 11 PsA patients and 8 SpA patients, accounting for 60% of patients with musculoskeletal complaints. Gastrointestinal complaints were reported by 22 patients with an inflammatory bowel disease, accounting for 21% of patients with gastrointestinal complaints. Skin reactions were reported by 9 psoriasis patients and 23 PsA patients, accounting for 20% of patients with skin reactions.

3.2 Burden of ADRs

The burden was reported for 1689 ADRs, with a mean burden of 2.7 ($SD \pm 1.1$) on a five-point Likert-type scale. A healthcare professional was contacted for 932 ADRs (54%) (Table 2). Hospitalisation was reported by 29 patients (4%) following 32 ADRs (2%), including five infections, five cardiovascular reactions, four ADRs regarding benign or malignant tumours, two gastrointestinal complaints and two skin reactions. Patients experienced infections and musculoskeletal complaints as the most burdensome of all clustered ADRs (infections: 3.1 $SD \pm 1.1$; musculoskeletal: 3.2 ± 0.9) and injection-site reactions as the least burdensome (1.8 ± 0.8 , $p < 0.001$ for both comparisons). Patients reported the most healthcare professional contacts for infections (69% of all infections).

The mean burden of ADRs leading to a healthcare professional contact (3.0 ± 1.1) was higher compared with the

mean burden of ADRs without healthcare professional contact (2.4 ± 0.9 , $p < 0.001$) (Table 3). The mean burden of ADRs leading to contact with a general practitioner was higher (3.4 ± 1.1) than the mean burden of ADRs leading to contact with a nurse (2.9 ± 1.2 , $p < 0.001$). Of all actions following an ADR, the mean burden was highest for ADRs leading to drug discontinuation (4.1 ± 0.9) and lowest for ADRs that were mentioned but for which no action was initiated (2.7 ± 1.1 , $p < 0.001$). Patients reported a higher than average burden for ADRs leading to hospitalisation (3.8 ± 1.2).

Patients described various explanations of the experienced burden, including ADRs leading to impaired ability in daily activities, anxiety and sleeping difficulties.

3.3 Factors associated with burden of ADRs

We assessed all demographic and clinical factors that were registered in the Dutch Biologic Monitor for an association with reported burden of ADRs and created a multivariable linear regression model (Table 4). The residuals were normally distributed and the regression model predicted 20.2% of the variance ($F[39,1611] = 10.434$, $p < 0.001$).

A sensitivity analysis was performed since $> 5\%$ of data was missing for combination therapy (6.5%) and comorbidities (11%). The regression analysis was repeated with these variables classified as ‘no combination therapy’ and ‘no comorbidities’. Outcomes shifted statistically significantly for adalimumab and hypercholesterolaemia and did not change for other variables.

A higher burden of ADRs was associated with smoking (β : 0.161 [0.025–0.297]), a respiratory comorbidity (β : 0.248 [0.080–0.416]), psychiatric comorbidity (β : 0.397 [0.207–0.588]), other comorbidity (β : 0.211 [0.058–0.364]) and ADRs regarding infection (β : 0.258 [0.105–0.411])

Table 2 Use of care and mean patient-reported burden following different adverse drug reaction subtypes

	Total	Injection-site reaction	Infection	Skin reaction	Gastro-intestinal complaints	Musculo-skeletal complaints	Fatigue ^a
Patients with ADRs, N (% of total patients with ADRs) ^b	665	172 (26)	187 (28)	157 (24)	105 (16)	103 (15)	97 (15)
ADRs, N (% of total ADRs)	1720	256 (15)	252 (15)	219 (13)	138 (8)	151 (9)	100 (6)
ADRs leading to hospitalisation, N (% of no. of clustered ADR)	32	2 (1)	5 (2)	2 (1)	2 (1)	2 (1)	1 (1)
ADRs with healthcare professional contact, N (% of no. of clustered ADR)	932	89 (35)	175 (69)	133 (61)	70 (51)	76 (50)	63 (63)
Mean reported burden of ADRs $\pm$ SD	2.7 ± 1.1	1.8 ± 0.8	3.1 ± 1.1	2.7 ± 1.1	2.8 ± 1.1	3.2 ± 0.9	2.9 ± 1.0

Burden was measured on a scale from 1 (no burden) to 5 (very high burden)

ADR adverse drug reaction, SD standard deviation

^aFatigue includes MedDRA® Preferred Terms fatigue and asthenia

^bPatients could report more than one adverse drug reaction

Table 3 Mean patient-reported burden following adverse drug reactions leading to different use of care

<i>N</i> = 1689	Mean burden $\pm$ SD
Mean burden for all unique ADRs	2.7 $\pm$ 1.1
Without healthcare professional contact (<i>n</i> = 757)	2.4 $\pm$ 0.9
With healthcare professional contact (<i>n</i> = 932)	3.0 $\pm$ 1.1
Specialist doctor (<i>n</i> = 627)	3.1 $\pm$ 1.2
General practitioner (<i>n</i> = 377)	3.4 $\pm$ 1.1
Pharmacist (<i>n</i> = 39)	3.2 $\pm$ 1.1
Nurse (<i>n</i> = 239)	2.9 $\pm$ 1.2
Other healthcare professional ^a (<i>n</i> = 27)	3.3 $\pm$ 0.8
ADRs with action by healthcare professional (<i>n</i> = 932)	3.0 $\pm$ 1.1
Drug discontinuation (<i>n</i> = 45)	4.2 $\pm$ 0.9
Dose adjustment (<i>n</i> = 82)	3.4 $\pm$ 1.1
Switch to previous drug (<i>n</i> = 8)	3.9 $\pm$ 1.1
ADR treatment (<i>n</i> = 285)	3.2 $\pm$ 1.2
Mentioned but no action initiated (<i>n</i> = 438)	2.7 $\pm$ 1.1
Referral to other healthcare professional ^b (<i>n</i> = 61)	3.4 $\pm$ 1.1
Referral to hospital (<i>n</i> = 42)	3.7 $\pm$ 1.1
Other action ^c (<i>n</i> = 105)	3.4 $\pm$ 1.1
ADRs with hospitalisation (<i>n</i> = 32)	3.8 $\pm$ 1.2
ADRs with action by patient (<i>n</i> = 678)	3.0 $\pm$ 1.0

Use of care could consist of healthcare professional contacts, healthcare professional actions and own actions following ADRs. Patient-reported burden was measured on a scale ranging from 1 (no burden) to 5 (very high burden)

ADR adverse drug reaction, SD standard deviation

^aOther healthcare professionals include dentist (*n* = 16), physiotherapist (*n* = 3), diverse (*n* = 8)

^bReferral to other healthcare professionals include dermatologist (*n* = 12), neurologist (*n* = 6), ophthalmologist (*n* = 4), otolaryngologist (*n* = 3), diverse (*n* = 36)

^cOther actions by healthcare professionals include examination or laboratory test (*n* = 28), diverse (*n* = 77)

and musculoskeletal complaints (β : 0.391 [0.205–0.577]). Infections were reported relatively more often than other ADRs by patients with respiratory comorbidities (25%, 54 ADRs) (Fig. 1). The proportion of respiratory infections in the population with respiratory comorbidities was not higher than the proportion of respiratory infections in the overall population (respiratory comorbidities: 44%; overall: 41%, $p = 0.64$). The mean burden of respiratory infections was not significantly higher in the population with respiratory comorbidities (3.4 ± 1.0) than in the rest of the population (3.0 ± 1.1 , $p = 0.061$). No outstanding proportions of ADR subtypes were seen in ADRs experienced by smokers and patients with a psychiatric or other comorbidity. Relatively more patients with respiratory disorders or psychiatric disorders were smokers (respiratory: 24%, psychiatric: 33%) than in our overall population (18%).

A lower burden of ADRs was associated with Crohn's disease (β : -0.266 [-0.530 to -0.002]), psoriasis (β : -0.359 [-0.703 to -0.014]), hypercholesterolaemia as comorbidity (β : -0.177 [-0.339 to -0.014]), combination therapy with sulfasalazine (β : -0.416 [-0.702 to -0.129]) and ADRs regarding injection-site reactions (β : -0.991 [-1.148 to -0.833]). In the sensitivity analysis, adalimumab use was associated with

a lower burden of ADRs (β : -0.172 [-0.341 to -0.002]) and hypercholesterolaemia was not associated with lower burden anymore (β : -0.153 [-0.321 to 0.015]). Relatively more injection-site reactions than other ADRs were reported by patients with psoriasis and patients who used sulfasalazine as combination therapy (psoriasis: 23%, 15 ADRs; sulfasalazine: 29%, 20 ADRs) (Fig. 2). No outstanding proportions of ADR subtypes were seen in ADRs experienced by patients with CD, hypercholesterolaemia or patients using adalimumab. A total of 46 patients reporting 124 ADRs used adalimumab for CD (20% of adalimumab users; 47% of patients with CD) and 12 patients reporting 21 ADRs used adalimumab for psoriasis (5% of adalimumab users; 39% of patients with psoriasis). A total of 12 patients reporting 16 ADRs used adalimumab and used sulfasalazine as combination therapy (5% of adalimumab users; 36% of sulfasalazine users).

4 Discussion

Patients in the Dutch Biologic Monitor consider infections and musculoskeletal complaints as the most burdensome ADRs and injection-site reactions as the least burdensome

Table 4 Multiple regression model with patient characteristics associated with burden of adverse drug reactions

N= 1689 ADRs	Regression coefficient β [95% CI]
Gender (male) (<i>n</i> =487)	0.072 [−0.045 to 0.189]
Age (years)	0.000 [−0.005 to 0.004]
Smoking (<i>n</i> =320)	0.160 [0.025 to 0.295]
BMI (kg/m ²)	0.007 [−0.003 to 0.018]
Biologic	
Adalimumab (<i>n</i> =547)	−0.168 [−0.338 to 0.001]
Etanercept (<i>n</i> =415)	−0.085 [−0.264 to 0.093]
Infliximab (<i>n</i> =179)	0.154 [−0.078 to 0.387]
Tocilizumab (<i>n</i> =97)	−0.111 [−0.368 to 0.147]
Rituximab (<i>n</i> =77)	−0.018 [−0.289 to 0.254]
Ustekinumab (<i>n</i> =75)	−0.232 [−0.538 to 0.074]
Secukinumab (<i>n</i> =70)	−0.192 [−0.506 to 0.122]
Other biologic ^a (<i>n</i> =232)	Reference
Duration of biologic use (months)	0.001 [−0.001 to 0.002]
Indication	
RA (<i>n</i> =734)	−0.086 [−0.332 to 0.161]
CD (<i>n</i> =271)	−0.271 [−0.535 to −0.007]
PsA (<i>n</i> =240)	−0.158 [−0.404 to 0.087]
SpA (<i>n</i> =233)	0.065 [−0.168 to 0.299]
UC (<i>n</i> =89)	−0.291 [−0.662 to 0.079]
Psoriasis (<i>n</i> =66)	−0.380 [−0.724 to −0.035]
Other indication ^b (<i>n</i> =163)	−0.028 [−0.297 to 0.240]
Combination therapy	
Methotrexate (<i>n</i> =389)	−0.002 [−0.167 to 0.164]
Corticosteroids ^c (<i>n</i> =311)	−0.013 [−0.172 to 0.147]
Hydroxychloroquine (<i>n</i> =102)	0.009 [−0.215 to 0.233]
Leflunomide (<i>n</i> =89)	0.064 [−0.188 to 0.315]
Sulfasalazine (<i>n</i> =70)	−0.354 [−0.629 to −0.080]
Other combination therapy ^d (<i>n</i> =182)	−0.097 [−0.348 to 0.153]
No combination therapy (<i>n</i> =650)	0.064 [−0.106 to 0.234]
Comorbidities	
Cardiovascular disorder (<i>n</i> =420)	0.057 [−0.079 to 0.192]
Hypercholesterolaemia (<i>n</i> =237)	−0.177 [−0.339 to −0.014]
Respiratory disorder (<i>n</i> =218)	0.217 [0.055 to 0.379]
Psychiatric disorder (<i>n</i> =157)	0.368 [0.185 to 0.550]
Nervous system disorder (<i>n</i> =40)	0.063 [−0.269 to 0.394]
Cancer (<i>n</i> =36)	−0.003 [−0.361 to 0.355]
Other comorbidity (<i>n</i> =409)	0.178 [0.046 to 0.310]
No comorbidity (<i>n</i> =547)	−0.064 [−0.204 to 0.077]
Type of ADR	
Injection-site reaction (<i>n</i> =252)	−0.994 [−1.152 to −0.837]
Infection (<i>n</i> =249)	0.261 [0.108 to 0.414]
Skin reaction (<i>n</i> =216)	−0.076 [−0.234 to 0.082]
Musculoskeletal complaint (<i>n</i> =146)	0.396 [0.209 to 0.582]

Table 4 (continued)

N= 1689 ADRs	Regression coefficient β [95% CI]
Gastrointestinal complaint (<i>n</i> =134)	−0.013 [−0.202 to 0.176]
Other ADR (<i>n</i> =692)	Reference

Results in bold indicate statistically significant outcomes

ADR adverse drug reaction, BMI body mass index, RA rheumatoid arthritis, CD Crohn's disease, PsA psoriatic arthritis, SpA axial spondyloarthritis, UC ulcerative colitis

^aOther biologics include certolizumab pegol (*n*=54), golimumab (*n*=51), vedolizumab (*n*=40), abatacept (*n*=35), anakinra (*n*=22), canakinumab (*n*=12), dupilumab (*n*=14), sarilumab (*n*=2), natalizumab (*n*=2), guselkumab (*n*=4)

^bOther indications include uveitis (*n*=21), vasculitis (*n*=24), hidradenitis (*n*=10), Tumour Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) (*n*=9), atopic eczema (*n*=14), diverse (*n*=89)

^cCorticosteroids include predniso(lo)ne (*n*=276), methylprednisolone (*n*=7), hydrocortisone (*n*=36)

^dOther combination therapy includes azathioprine (*n*=62), mesalazine (*n*=80), mercaptopurine (*n*=42), tioguanine (*n*=15)

ADRs. Furthermore, patients rated ADRs leading to drug discontinuation and hospitalisation with the highest burden score, which is in line with the perceived healthcare professional's focus on ADRs [3, 4]. This study provides insight in the experienced burden of ADRs, including ADRs with consequences other than drug discontinuation and hospitalisation. ADRs leading to healthcare professional contact were regarded as more burdensome than ADRs that did not lead to healthcare professional contact. Presumably, a healthcare professional is contacted when the patient is worried about the ADR or believes that action needs to be taken. Infections often need treatment and patients are instructed to contact a healthcare professional when having signs and symptoms of infection, such as fever, explaining the high number of healthcare professional contacts for infections [9]. Although it is not surprising that ADRs leading to drug discontinuation, switch to a previously used drug, dose adjustment or hospitalisation are regarded as more burdensome than ADRs without these actions, the patient's perspective has not been systematically studied in a large population of patients before. Unfortunately, we cannot distinguish whether the characteristics of the ADRs or the actions following the ADRs lead to the experienced burden. Both aspects should be considered when adjusting therapy due to experienced ADRs.

Some patient groups, such as patients with respiratory or psychiatric comorbidities, smokers and patients with ADRs regarding infections and musculoskeletal complaints, experienced their ADRs as more burdensome than other patients. A higher burden for patients with respiratory comorbidities could possibly be caused by the higher proportion of infections in this group. A closer look at the experienced infections showed that these were not respiratory tract

Fig. 1 Proportion of adverse drug reaction (ADR) subtypes for each factor that was associated with higher burden. The displayed ADRs account for 55% of the ADRs experienced by smoking patients, 61% of the ADRs experienced by patients with psychiatric comorbidity, 63% of the ADRs experienced by patients with respiratory comorbidity and 64% of the ADRs experienced by patients with other comorbidities

Fig. 2 Proportion of adverse drug reaction (ADR) subtypes for each factor that was associated with lower burden. The displayed ADRs account for 54% of the ADRs experienced by patients with hypercholesterolaemia, 62% of the ADRs experienced by patients with psoriasis, 66% of the ADRs experienced by patients using sulfasalazine as combination therapy, 50% of the ADRs experienced by patients with Crohn's disease and 59% of the ADRs experienced by patients using adalimumab

infections in particular. This is in line with previous findings that asthma and chronic obstructive pulmonary disease are associated with an increased risk of infections in general [10, 11]. Since these patients experience a combination of diseases, genetic predisposition for an increased risk of infections also cannot be ruled out. Negative thoughts are associated with numerous mental disorders and therefore patients with psychiatric problems might have a more negative approach and may experience the impact of ADRs as more challenging [12, 13]. Even though the association between patient-reported burden of ADRs and drug withdrawal has not been investigated, it is remarkable that

factors associated with higher burden in our study did not correspond with factors associated with increased biologic withdrawal in other studies, such as increasing age, female sex, rheumatoid arthritis and infliximab use [3, 4, 14, 15].

We found that patients with Crohn's disease, psoriasis, use of sulfasalazine as combination therapy, injection-site reactions, hypercholesterolaemia and adalimumab use experienced their ADRs as less burdensome than other patients. Patients with sulfasalazine as combination therapy had a higher proportion of injection-site reactions, which are associated with lower burden. However, sulfasalazine was used more often in combination with etanercept than with

adalimumab and was mainly used by RA patients. Since we cannot explain our findings, further research on the lower experienced burden with sulfasalazine as combination therapy may be indicated. To the best of our knowledge, factors associated with burden of ADRs have not been assessed before. Even though etanercept is suggested to be the safer tumour necrosis factor- α blocking agent in some studies assessing ADR occurrence in rheumatoid arthritis, the findings of this study suggest that ADRs attributed to adalimumab are experienced as less burdensome than ADRs attributed to other biologics, including etanercept [3, 16].

A limitation of this study is that selection bias cannot be ruled out when asking patients to report information on ADRs. Patients that experience higher burden of ADRs may be more willing to participate. Furthermore, the causal relationship of patient-reported ADRs was not verified with the patient's practitioners. More than half of the patients reporting musculoskeletal complaints used a biologic for an inflammatory rheumatic disease. Some of these complaints could possibly be related to the disease rather than the biologic drug. Even though the clinical confirmation of the reported ADRs is lacking, we consider patient reports as a strength since this is the patients' perspective on their drug use and unfiltered patient-reported ADR data is usually not systematically questioned or structurally available.

5 Conclusion

This is the first study addressing patient perspectives on the burden of ADRs that patients experienced with biologic use. This information may advance healthcare professionals' understanding of patients' perceptions of ADRs and the impact these ADRs impose. This may lead to more personalised treatment options, better adherence and finally, better clinical outcomes.

Future research in different aspects of ADR burden, such as the time course of burden, can contribute to a better understanding of patients' ADR experiences.

Acknowledgements We would like to thank all patients for participating in the *Dutch Biologic Monitor* and all centres for inviting patients to participate: Academic Medical Center, Amsterdam; Sint Maartenskliniek, Nijmegen; Radboud University Medical Centre, Nijmegen; Reade Rheumatology, Amsterdam; Jeroen Bosch Hospital, 's-Hertogenbosch; Medisch Spectrum Twente, Enschede; Ziekenhuisgroep Twente, Almelo/Hengelo; Franciscus Gasthuis & Vlietland, Rotterdam; Haga Hospital, Den Haag.

Compliance with Ethical Standards

Funding The *Dutch Biologic Monitor* work was supported by the Netherlands Organisation for Health Research and Development (ZonMw) [grant number 848050005]. No funding was received for this study.

Conflicts of interest JA van Lint, NT Jessurun, RCF Hebing, SW Tas, HE Vonkeman, A Sobels, EP van Puijenbroek, MT Nurmohamed and BJF van den Bemt declare that they have no conflicts of interest. PI Spuls reports unpaid consultancies for Sanofi and Abbvie in the past, a departmental independent research grant for the TREAT NL registry from Leopharma, financial compensation from pharmaceutical industries to her department/hospital for involvement in performing clinical trials and she is chief investigator in the Netherlands national systemic and phototherapy atopic eczema registry (TREAT NL). MBA van Doorn reports grants from Novartis; consulting fees or honorarium from Leopharma, Novartis, Abbvie, BMS, Celgene, Janssen-Cilag, Lilly, MSD, Pfizer and Sanofi-Genzyme; support for travel, manuscript preparation or other purposes from Sanofi-Genzyme, Novartis and Pfizer; payment for lectures from Leopharma, Novartis, Janssen-Cilag and Pfizer, all outside the submitted work. F Hoentjen reports received grants, consulting fees or honorarium and payment for lectures, all outside the submitted work.

Ethics approval Ethical approval was waived for the Dutch Medical Research Involving Human Subjects Act (WMO) by the Medical Research Ethical Committee of Brabant, the Netherlands (file number: NW2016-66). The *Dutch Biologic Monitor* was approved by the medical ethics committees of the participating hospitals. All participants received information about the *Dutch Biologic Monitor* prior to participation and signed a digital informed consent form.

Data availability The dataset analysed during the current study is available from the corresponding author on reasonable request.

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