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Discrepancy between patient- and healthcare provider-reported adverse drug reactions in inflammatory bowel disease patients on biological therapy

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Abstract

Background: Only limited data is available on the extent and burden of adverse drug reactions (ADRs) to biological therapy in inflammatory bowel disease (IBD) patients in daily practice, especially from a patient's perspective.

Objective: The aim of this study was to systematically assess patient-reported ADRs during biological therapy in IBD patients and compare these with healthcare provider (HCP)-reported ADRs.

Methods: This multicentre, prospective, event monitoring study enrolled IBD patients on biological therapy. Patients completed bimonthly comprehensive web-based questionnaires regarding description of biological induced ADRs, follow-up of previous ADRs and experienced burden of the ADR using a five-point Likert scale. The relationship between patient-reported ADRs and biological therapy was assessed. HCP-reported ADRs were extracted from the electronic healthcare records.

Results: In total, 182 patients (female 51%, mean age 42.2 [standard deviation 14.2] years, Crohn's disease 77%) were included and completed 728 questionnaires. At baseline, 60% of patients used infliximab, 30% adalimumab, 9% vedolizumab and 1% ustekinumab. Fifty percent of participants reported at least one ADR with a total of 239 unique ADRs. Fatigue ($n = 26$) and headache ($n = 20$) resulted in the highest burden and a correlation in time with the administration of the biological was described in 56% and 85% respectively. Out of 239 ADRs, 115 were considered biological-related. HCPs reported 119 ADRs. Agreement between patient-reported ADRs and HCP-reported ADRs was only 13%.

Conclusion: IBD patients often report ADRs during biological therapy. We observed an important significant difference between the type and frequency of patient-

On behalf of IBDREAM.

reported ADRs versus HCP-reported ADRs, leading to an underestimation of more subjective ADRs and patients' ADR-related burden.

KEYWORDS
adalimumab, ADR, adverse drug reactions, biological therapy, healthcare provider-reported, IBD, inflammatory bowel disease, infliximab, patient-reported

Key summary

Summarise the established knowledge on this subject

- Adverse drug reactions (ADRs) are severely underreported by healthcare providers (HCP) and do not capture the full spectrum of biological-related ADRs.
- Patient self-reporting may be used to detect ADRs and offers more insight in the patient's perception and experience of an ADR.
- Data on self-reporting ADRs in inflammatory bowel disease (IBD) patients is limited.

What are the significant and/or new findings of this study?

- IBD patients frequently reported ADRs during biological use (50%) and 48% of these ADRs were considered biological-related.
- Fatigue and headache resulted in the highest patient-reported burden.
- Patients often reported a correlation in time (44%) for the top six patient-reported ADRs.
- There was a significant difference between type and frequency of patient-reported ADRs and HCP-reported ADRs.

INTRODUCTION

Biologicals are increasingly used for the treatment of inflammatory bowel disease (IBD) with an increase from 22% to 42% for Crohn's disease (CD) and from 5% to 16% for ulcerative colitis between 2007 and 2015.[1,2] Despite the effectiveness of biologicals, they are also associated with adverse drug reactions (ADRs) that may potentially harm the patient or lead to discontinuation of therapy.[3]

The drug safety profiles are based on data from registration trials, spontaneous reporting by healthcare providers (HCPs) in clinical practice and post-marketing cohorts. However, registration trials only provide short term data on the safety profiles, which may lead to underreporting of ADRs that require more time to develop. Furthermore, these trials do not include sufficiently large number of patients to detect ADRs that rarely occur. In addition, ADRs are significantly underreported by HCPs for several reasons.[4] First, HCPs do not always recognize ADRs, especially when these reactions are less severe or in absence of a clear causality.[5] Second, ADR reporting is often time-consuming and withholds the HCP from filing the paperwork. Lastly, these reports mainly include the HCP's perception rather than the patient's perception. Therefore, long term data retrieved from clinical practice are pivotal for detecting all ADRs.

Patient self-reporting may be used to timely detect ADRs, timely identify and prevent associated significant burden, and create more awareness of new ADRs. It also offers more insight in the patient's perception and experience of an ADR.[6] Unrecognized ADRs have shown to negatively affect the quality of life, lead to drug non-adherence and may even result in increased disease activity.[7] Moreover, patients are not restrained by the limited time of an outpatient visit to report ADRs. We hypothesized that the use of ADR self-reporting by patients will provide a better understanding of the full spectrum of ADRs and the patient-experienced burden.[8]

This study aimed to assess (a) systematic patient-reported ADRs during biological therapy in IBD patients and (b) the gap and overlap with HCP-reported ADRs, using a web-based tool from the Dutch Pharmacovigilance centre (Lareb).[9]

METHODS

Study design and patients

This prospective multicentre study systematically assessed ADR self-reporting during biological therapy in IBD patients and evaluated the difference and overlap in patient-reported ADRs and HCP-reported ADRs, using the *Dutch Biologic Monitor*.[9] The study was conducted in four medical centres in the Netherlands between 1 January 2017 and 31 December 2018. Patients ≥18 years of age were eligible if they had an established diagnosis of CD or UC, were treated with a biological, including infliximab (IFX), adalimumab (ADA), vedolizumab

(VEDO) or ustekinumab (UST), and sufficient knowledge of the Dutch language. Patients were recruited consecutively during outpatient visits, via letters from the outpatient pharmacy, or during infusion therapy in hospital. All participants signed a web-based informed consent form.

Data collection

Patient-reported data

At baseline, participants of the *Dutch Biologic Monitor* completed a comprehensive web-based questionnaire, which included demographic data, IBD drug use and ADRs. Specific information regarding ADRs included the type of ADR, start and stop date, whether the ADR was discussed with a HCP, experienced burden on a five-point Likert scale,[10] and therapeutic consequences. The two-monthly follow-up questionnaires only focused on IBD drug use and ADRs. Patients did not receive a subsequent questionnaire if they withdrew informed consent or if the previous questionnaire had expired (no response within 21 days of receiving the questionnaire).

HCP-reported data

At baseline, disease-specific information was retrieved from the electronic healthcare records including type of IBD (CD or UC), disease location and disease behaviour according to the Montreal classification, disease activity using the physician global assessment which ranges from remission to severe, previous and concomitant IBD medication use, previous failure of IBD medication due to ADRs, and dose of the used biological. During follow-up changes in drug use were registered. HCP-reported ADRs were retrieved from the electronic healthcare records with a range up to 6 months prior to the baseline questionnaire completion date depending on the start date of ADR according to the participant until the last questionnaire completion date. For each ADR, we recorded the possible relationship between the ADR and used biological, time relationship with infusion or injection and treatment changes.

Coding and selection of adverse drug reactions

Plain text of the HCP-reported ADR was extracted from the electronic healthcare records and was coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 23.0) by trained assessors.[11] The hierarchical structure of MedDRA contains five levels. For the analyses, High Level Groups Terms were used and reports considering infection, musculoskeletal conditions and skin conditions were grouped according to the corresponding System Organ Class. Reports concerning the preferred term 'fatigue' were reported separately.

Patient-reported ADRs and HCP-reported ADRs

Patient-reported ADRs were defined as any side effect that the patient reported attributed to the biological. Long-term or recurring patient-reported ADRs with the same preferred terms that were reported repeatedly by one patient in subsequent questionnaires were counted as one ADR. Multiple ADRs with different preferred terms reported by one patient were counted separately. For all ADRs we described the highest reported burden during the course of the ADR. HCP-reported ADRs were extracted from the electronic healthcare records if the relationship to the biological was specifically described as likely, possible or definite in the electronic healthcare records or deemed by the author (P.T.). The relationship between ADRs and biological was assessed by the author (P.T.) based on the ADR description. In case of doubt whether the ADR was possibly related to the biological, this ADR was discussed with a second assessor (F.H.) in order to reach consensus.

ADRs included for agreement analysis

For the agreement analysis, patient-reported ADRs and HCP-reported ADRs were compared. Only ADRs that were considered biological-related were included for the agreement analysis. Agreement was met if MedDRA grouping terms matched, or the same ADR was described based on the additional description. No agreement was met if a patient described an ADR which the HCP did not, if a HCP described an ADR which the patient did not or if patient and HCP described different ADRs.

Outcomes

The primary outcome of this study was the type and frequency of patient-reported ADRs during biological use. Secondary outcomes included: patient-experienced burden per ADR, time-relationship between ADR and biological administration, patient-reported communication with their HCP per ADR, treatment changes due to the ADR, patient-reported ADRs stratified per biological, the gap and overlap between patient- and HCP-reported ADRs, and predictors for patients reporting ADRs. In this study, we described the outcomes for the patient-reported ADRs with ≥15 cases in further detail.

Statistical analysis

Continuous parametric variables were presented as means with standard deviation (SD) and continuous non-parametric variables as median with interquartile range (IQR). Subsequently, variables were compared using a student's *T*-test or Mann-Whitney *U* test. Categorical variables were presented as percentages and compared using the chi-square or Fisher's exact test. Agreement was analysed as

absolute numbers and percentage of ADRs agreed between patient and HCP. Multivariate analysis was performed on variables with $p < 0.2$ on univariate analysis or with relevant effect based on previous studies, using log-likelihood backstep-wise logistic regression. p-values < 0.05 were considered to be statistically significant. Data analysis was performed with SPSS 25.0 (SPSS Inc.).

Ethical approval

The study protocol was approved by the ethics committee [NW2016-66] (METC Brabant), and by the local ethics committees from the participating hospitals. All participants provided written consent prior to study enrolment.

RESULTS

Study population

In total, 193 IBD patients were enrolled in the study. Eleven patients were excluded from the analysis because they did not provide informed consent ($n = 9$), did not use a biological at the time of the questionnaire ($n = 1$) or were under the age of 18 years ($n = 1$). The first patient was enrolled 17 February 2017 and the last patient 29 May 2018. Enrolled patients completed a total of 728 questionnaires. On average patients completed four questionnaires, 124 (68%) patients completed at least the baseline and one follow-up questionnaire and 92 (50%) patients had a follow-up ≥6 months. Follow-up per patient is provided in Table S1. Overall, biological use at baseline was 108 (60%) IFX, 55 (30%) ADA, 17 (9%) VEDO and 2 (1%) UST. Information on disease activity was available in 173 (95%) patients. Of these patients, 129 were in remission, 33 had mild disease and 11 had moderate disease (Tables 1 and 2).

Patient-reported ADRs

In total, 239 ADRs were reported, 91 (50%) of patients reported at least one ADR, 51 (28%) reported ≥2 ADRs and 34 (19%) reported ≥3 ADRs. Patient-reported ADRs were discussed with a HCP in 59% and in these cases subsequent actions were taken in 35% including 12% adjustment of biological prescription. All patient-reported ADRs are provided in Table S2.

Top-six patient-reported ADRs

The top six patient-reported ADRs with patient-reported burden are shown in Figure 1. In this study, 26 (14%) unique patients reported fatigue, 19 (10%) reported headache, 19 (10%) reported infection, 19 (10%) reported musculoskeletal conditions and 18 (10%) reported skin conditions. Patients described a time-relationship between the infusion or injection and ADRs in 100% ($n = 17$) for administration site reactions, 85% ($n = 17$) for headaches, 56% ($n = 15$) for fatigue, 20% ($n = 5$) for musculoskeletal conditions and 13% ($n = 3$) for skin conditions. Patients most often reported fatigue with 27 reports (11%) in total, and patients reported the highest burden attributed to fatigue (mean burden 3.3 ± 1.0). Patients reported that ADRs were discussed with their HCP in 78% for skin conditions, 74% fatigue, 65% headaches, 63% infections, 56% musculoskeletal conditions, and 35% administration site reactions. Subsequently, patients reported adjustment of biological prescription in 7% and treatment of the ADR in 28%. For the ADRs that were discussed with a HCP, in 65% no treatment alterations or adjustments were made.

Patient-reported ADRs per biological

Patient-reported ADRs per biological are presented in Figure 2. At baseline, patients had used the prescribed biological for a median 32.1 months [IQR 13.8–61.4] for IFX, 56.0 months [IQR 16.6–94.1] for ADA, 6.1 months [IQR 3.2–12.8] for VEDO and 0.23 to 3.3 months for UST. Median follow-up per biological was 3.1 months [IQR 0.0–11.9] for IFX, 7.9 months [IQR 1.0–8.4] for ADA, 6.1 months [IQR 0.0–8.6] for VEDO and 6.8 months [IQR 3.6–9.3] for UST. At least one follow-up questionnaire was completed by 63 (68%) patients on IFX, 46 (67%) on ADA, 13 (68%) on VEDO and 3 (75%) on UST. Overall, ADA and VEDO users most frequently reported ADRs. Headache was most frequently reported during VEDO and UST use, and fatigue during IFX, VEDO and UST use. During the study period, six patients switched to another biological, and six patients discontinued a biological and did not start a subsequent biological. Three of these changes were safety-related. The top six patient-reported ADRs that were biological-related are shown in Tables S3–S6.

Predictors for patients reporting ADRs

Patients who reported at least one ADR had a higher median body mass index, 25.1 versus 23.6 ($p = 0.016$), had used the biological for a shorter period of time with a median of 26.8 months versus 45.3 months ($p = 0.006$), and more often had active disease based on the physician global assessment ($p = 0.001$) at baseline when compared with patients who did not report an ADR. Univariate and multivariate predictors of patients reporting ≥1 ADR are reported in Table S7. Disease activity was not included in these analyses due the variable disease course of IBD with a relapsing and remitting pattern. In the multivariate analysis body mass index per point (odds ratio [OR] 1.069; 95% confidence interval [CI] 1.004–1.139) was associated with a higher risk of reporting ≥1 ADR and longer use of a biological was associated with a lower risk of reporting ≥1 ADR. The use of VEDO showed a trend towards the risk of experiencing and reporting ≥1 ADR (OR 2.890; 95% CI 0.923–7.373), but this effect

TABLE 1 Baseline disease and demographic characteristics

		Study population N = 182	Patients reporting no adverse drug reactions N = 91	Patients reporting ≥1 adverse drug reaction N = 91	p-value
Sex, female	N (%)	92 (50.5)	41 (45.1)	51 (56.0)	0.138
Age in years	Mean ± SD	42.2 ± 14.2	41.7 ± 15.8	42.7 ± 12.4	0.629
BMI	Median (IQR)	24.7 (21.9–26.8)	23.6 (21.3–26.4)	25.1 (22.1–28.7)	0.016*
Smoking					0.570
Active	N (%)	35 (19.3)	15 (16.5)	20 (22.0)	
Previous	N (%)	32 (17.5)	18 (19.8)	14 (15.4)	
Never	N (%)	115 (63.2)	58 (63.7)	57 (62.6)	
Total questionnaires	N	728	345	383	0.661
Follow-up in months	Median (IQR)	5.9 (0.0–12.1)	4.0 (0.0–12.1)	7.9 (0.0–13.8)	0.242
IBD type					0.379
Crohn's disease	N (%)	140 (76.9)	73 (80.2)	67 (73.6)	
Ulcerative colitis	N (%)	42 (23.1)	18 (19.8)	24 (26.4)	
Disease duration, years	Median (IQR)	10.0 (5.1–20.9)	10.8 (5.8–20.1)	9.5 (3.8–23.6)	0.265
Disease location CD					0.337
Ileum	N (%)	37 (26.4)	17 (23.6)	20 (30.3)	
Colon	N (%)	37 (26.4)	23 (31.9)	14 (21.2)	
Ileocolonic	N (%)	64 (45.7)	32 (44.4)	32 (48.5)	
Upper GI tract involvement	N (%)	21 (15.0)	11 (15.1)	10 (14.9)	1.000
Disease behaviour					0.708
Inflammatory	N (%)	54 (38.6)	31 (42.5)	23 (34.3)	
Stricturing	N (%)	56 (40.0)	26 (35.6)	30 (44.8)	
Penetrating	N (%)	48 (34.3)	24 (32.9)	24 (35.8)	
Peri-anal disease	N (%)	37 (26.4)	21 (28.8)	16 (23.9)	0.568
Disease location UC					1.000
Proctitis	N (%)	0 (0)	0 (0)	0 (0.0)	
Left-sided	N (%)	11 (26.2)	5 (27.8)	6 (25.0)	
Pancolitis	N (%)	31 (73.8)	13 (72.2)	18 (75.0)	
Disease activity PGA					0.001
Remission	N (%)	129 (70.9)	76 (83.5)	53 (58.2)	
Mild	N (%)	33 (18.1)	9 (9.9)	24 (26.4)	
Moderate	N (%)	11 (6.0)	2 (2.2)	9 (9.9)	
Severe	N (%)	0 (0)	0 (0)	0 (0)	
Missing	N (%)	9 (4.9)	4 (4.4)	5 (5.5)	

Abbreviations: BMI, body may index; CD, Crohn's disease; GI, gastrointestinal; IBD, inflammatory bowel disease; PGA, physician global assessment; UC, ulcerative colitis.

*A *p*-value <0.05 was considered statistically significant.

TABLE 2 Baseline therapeutic characteristics

		Study population *N* = 182	Patients reporting no adverse drug reactions *N* = 91	Patients reporting ≥1 adverse drug reaction *N* = 91	*p*-value
Biological					0.265
Adalimumab	*N* (%)	55 (30.2)	26 (28.6)	29 (31.9)	
Infliximab	*N* (%)	108 (59.3)	59 (64.8)	49 (53.8)	
Ustekinumab	*N* (%)	2 (1.1)	1 (1.1)	1 (1.1)	
Vedolizumab	*N* (%)	17 (9.3)	5 (5.5)	12 (13.2)	
Duration of biological therapy before baseline, in months	Median (IQR)	32.5 (10.7–65.9)	45.3 (16.7–78.2)	26.8 (8.1–55.7)	0.006*
Combination therapy					0.338
Mesalamine	*N* (%)	19 (10.4)	21 (23.1)	12 (13.2)	
Immunomodulator	*N* (%)	93 (51.1)	47 (51.6)	46 (50.5)	
Corticosteroids	*N* (%)	9 (4.9)	4 (4.4)	5 (5.5)	
Sulfasalazine	*N* (%)	2 (1.1)	0 (0.0)	2 (2.2)	
None	*N* (%)	74 (40.7)	40 (44.0)	34 (37.4)	
Prior biological use					0.498
0	*N* (%)	121 (66.5)	62 (68.1)	59 (64.8)	
1	*N* (%)	53 (29.1)	26 (28.6)	27 (29.7)	
2	*N* (%)	7 (3.8)	2 (2.2)	5 (5.5)	
3	*N* (%)	1 (0.5)	1 (1.1)	0 (0.0)	
Prior IBD treatment failure due to ADR					
None	*N* (%)	107 (58.8)	34 (37.4)	41 (45.1)	0.366
Mesalamine	*N* (%)	7 (3.8)	4 (4.4)	3 (3.3)	-
Thiopurine	*N* (%)	57 (31.3)	26 (28.6)	31 (34.1)	0.523
Methotrexate	*N* (%)	9 (4.9)	4 (4.4)	5 (5.5)	-
Corticosteroids	*N* (%)	1 (0.5)	1 (1.1)	0 (0.0)	-
Biological	*N* (%)	0 (0.0)	0 (0.0)	0 (0.0)	-
Total IBD therapies failed due to ADR					0.615
0	*N* (%)	118 (64.8)	61 (67.0)	57 (62.6)	
1	*N* (%)	55 (30.2)	26 (28.6)	29 (31.9)	
2	*N* (%)	8 (4.4)	3 (3.3)	5 (5.5)	
3	*N* (%)	1 (0.5)	1 (1.1)	0 (0)	

Abbreviations: ADR, adverse drug reactions; IBD, inflammatory bowel disease.
*A *p*-value <0.05 was considered statistically significant.

was less pronounced when evaluated as a multivariable predictor (OR 0.924; 95% CI 0.271–3.153).

Patient-reported ADRs versus HCP-reported ADRs

In total, 115 (48%) of patient-reported ADRs were considered biological-related and 68 (37%) patients reported at least one ADR that was biological-related. Of all patient-reported ADRs, infections and administration site reactions were most often biological-related (100%) followed by headaches (85%) and fatigue (41%). Skin conditions resulted in the highest burden for these ADRs (Figure S1). HCPs reported a total of 119 ADRs in 71 unique patients (39%). These patient-reported ADRs and HCP-reported ADRs are listed in Tables S8 and S9.

Differences between patient reporting and HCP reporting were observed. HCPs more often reported infection-related ADRs when compared with patients (71 vs. 24 cases, resp.). ADRs regarding skin

conditions were similar among HCPs and patients (6 and 7 cases, resp.). However, HCPs rarely reported administration site reactions, headaches and fatigue (1, 1 and 3 cases resp.) whereas patients often reported these ADRs (17, 17 and 11 cases, resp.). When comparing patient-reported ADRs and HCP-reported ADRs, agreement on the type of ADR was met in 13% which means that HCPs and patients did not report the same ADRs in 87%. Agreement percentages for the top six patient-reported ADRs are shown in Figure 3. For these specific ADRs, patients reported that they discussed the ADR with a HCP in 52 out of 82 cases (63%). HCP-reported treatment changes were recorded in 6/71 (8%) infection-related ADRs in which the administration was postponed and in 1/4 (25%) arthralgia-related ADRs in which the dosing interval was reduced without effect on symptoms.

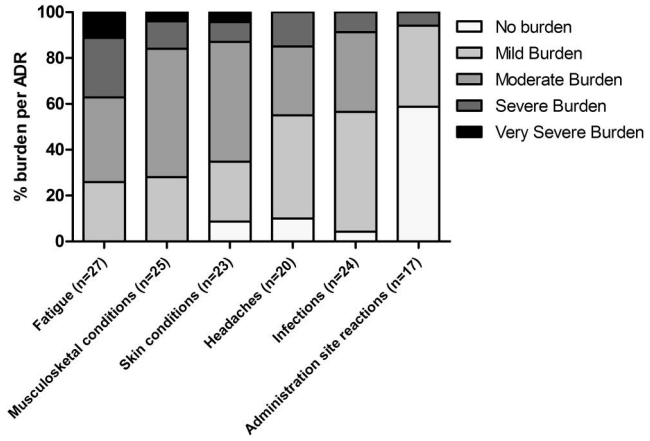

FIGURE 1 Top six patient-reported adverse drug reactions with patient-reported burden

DISCUSSION

In this prospective multicentre study, we systematically assessed patient-reported ADRs during biological therapy in IBD patients and compared patient-reported ADRs and HCP-reported ADRs. Half of the patients reported at least one ADR and 37% of all patients reported at least one ADR that was biological-related. HCPs reported a similar ADR rate (39%) for these patients. However, we observed a significant difference for occurrence and type of ADR between patient reporting and HCP reporting (13% agreement). HCPs predominantly reported infection-related ADRs whereas patients provided a variety of more subjective ADRs including fatigue and headache.

The proportion of patients reporting an ADR (50%) in our study is comparable with a study that showed 69% of IBD patients self-reported ADRs during the use of any IBD medication.[12] Indeed, a recent prospective study in IBD patients confirmed this high rate of ADRs during biological administration. In line with our study, musculoskeletal reactions and fatigue were commonly reported ADRs.[13] In addition, the rate of ADRs during biological use in IBD is similar to rheumatoid arthritis and psoriatic arthritis (43%) with an average of 1.6 ADRs per patient.[14]

One third of the patient-reported ADRs that were discussed with the HCP required therapeutic action. Change in biological dosage or withdrawal of the biological took place in 12% of all patient-reported ADRs and 7% of the top six patient-reported ADRs. This rate of ADRs that needed treatment probably is an underestimation. Some patient-reported ADRs may not have been recognized by the HCP and therefore not treated,[5] and biological-related ADRs may be difficult to treat even when recognized. However, patients may not have always reported treatment of the ADR or the burden of the ADR was too low to justify intervention. Of note, 41% of all patient-reported ADRs were not discussed with a HCP and thus not considered for

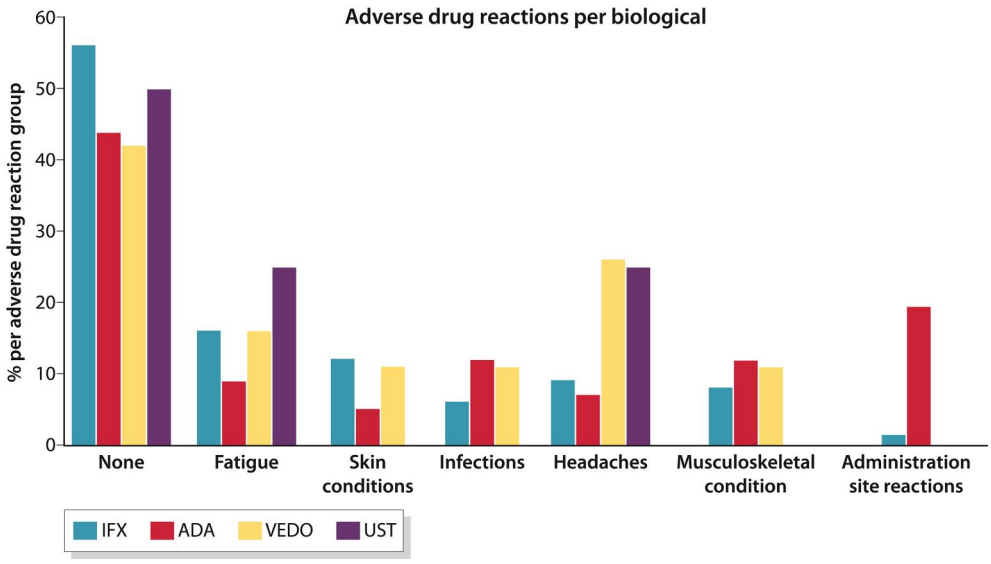

FIGURE 2 Patient-reported adverse drug reactions per biological presented as proportion of patients that reported one of the adverse events displayed on the *x*-axis. IFX = infliximab (n = 108); ADA = adalimumab (n = 57); VEDO = vedolizumab (n = 19); UST = ustekinumab (n = 4)

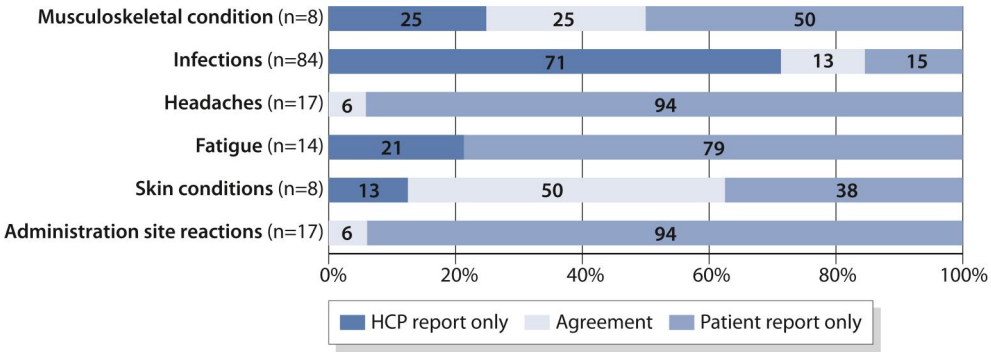

FIGURE 3 Agreement between patient- and healthcare provider-reported adverse drug reactions that were related to the biological. HCP, healthcare provider

adjustment of biological therapy. There may be a certain threshold or limitation to discuss ADRs with the HCP, or these were self-limiting ADRs that the patient did not feel to have to discuss with the HCP.

Of all patient-reported ADRs, 48% were considered biological-related. For these ADRs, skin conditions resulted in the highest patient-reported burden and all of these skin conditions required treatment. The reported rate of skin conditions is in line with previous studies.[15] Headaches were considered biological-related in 85% and were most often reported during vedolizumab and ustekinumab use. The patient-reported rates for these ADRs were slightly higher than the rates in the registration trials that may be the result of the small number of patients using these biologicals in our cohort.[16,17] Fatigue and musculoskeletal conditions were the most common patient-reported ADRs and resulted in the highest burden. Although fatigue and musculoskeletal conditions coincide with IBD in up to 50%,[18,19] patients described a specific time-relationship with the administration of the biological in 56% and 20%, respectively. Overall for the top six patient-reported ADRs a correlation in time was often described (44%). This points towards an ADR rather than disease-related symptoms. However, from a patient's perspective all ADRs are considered biological-related and therefore warrant discussion with their HCP.

Currently, HCP reporting is the main source for ADR recording in the post marketing surveillance on drugs. However, HCPs significantly underreport ADRs in daily practice due to various reasons.[5] Moreover, we observed a significant difference between patient reporting and HCP reporting. Patients frequently reported subjective ADRs whereas HCPs reported infection-related ADRs three times more than patients. Recall bias may have occurred in patients reporting infection-ADRs due to bimonthly reports whereas HCPs immediately registered the ADR. The discrepancy between patient reporting and HCP reporting was in line with the differences observed in rheumatoid arthritis patients.[20] This finding highlights the importance of using patient reporting to determine the full spectrum of ADRs.[21] Moreover, even when ADRs are documented by HCP, these are rarely reported to the pharmacovigilance centres.[4] Consequently, the real-world ADRs are underreported and drug safety profiles are not updated. Patient reporting can therefore contribute to updating drug safety profiles.

We found two variables that were associated with patients reported at least one ADR. First, patients receiving biologics for a longer period showed lower rates of ADRs. This may be explained by the fact that these patients have shown to tolerate the drug well and these patients may be more educated on the drug and have more experience with possible previous ADRs. Consequently, these patients experience less ADRs and may be able to distinguish biological-related ADRs from different ADRs or disease-related symptoms. Secondly, lower BMI scores correlated with lower rates of ADRs. No previous study in IBD patients have reported this association. Obesity is considered a low-grade inflammatory state which may result in different interaction with the drugs. For infliximab specifically, patients with a higher weight receive a higher dose which may result in a higher ADR risk. Indeed, studies in patients on immune checkpoint inhibitors showed an association between higher BMI and immune-related ADRs.[22] Lastly, high BMI may be associated with reduced health status, more comorbidities and co-treatment which may in turn lead to more ADRs.

Our results show that patient reporting provides more insight into the patients' perspective on biological-related ADRs and the experienced burden. The high rate of patient-reported ADRs and low agreement between patient-reported ADRs and HCP-reported ADRs suggests that more awareness is warranted. Considering that patients underreported infection-related ADRs, strategies should aim at improving detection and recognition of these ADRs in this susceptible population. In this study, patients discussed 59% of the ADRs with their HCP at any timepoint during the study. The use of patient reporting may therefore be used to discuss both related and unrelated ADRs in an earlier stage in order to prevent further progression and potential damage of ADRs, as suggested by the considerable number of patient-reported ADRs that required treatment in this study.

Strengths of this multicentre study include the demonstrated feasibility of the system of electronic patient reporting which yielded extensive patient-reported information about the patient's perspective on ADRs. In addition, our findings are representative of IBD patients using biological treatment in daily practice.[23] Limitations of our study include a possible participation bias that may have occurred as patients received an open invitation to report ADRs. This

may have resulted in a slight overestimation of ADRs. However, this bias is inherent to this type of research. Nonetheless, a large proportion of patients reported no ADRs and the rate of patient-reported ADRs was similar to previously published studies (43%–69%).[12,14] Moreover, recall bias may have affected patient-reported ADRs and probably resulted in an underestimation of less significant and non-recurring ADRs.[24] This may partially explain our finding of discrepancy between patient- and HCP-reported infections. Recurring ADRs may have been reported during any of the follow-up questionnaires and may therefore be less affected by recall bias. Selection bias of ADRs may have occurred due to the different purpose of ADR reporting in which patients were requested to report all ADRs whereas HCPs only reported a selection of ADRs. Furthermore, ADR incidences could not be calculated because ADRs were followed-up and not documented during every administration, and patients reported ADRs that may have been present prior to the study participation. Finally, we did not systematically collect data on biological or endoscopic disease activity in addition to disease activity measured to the physician global assessment. Luminal inflammation may result in high patient-reported ADRs, because it may be difficult to distinguish disease-related symptoms from ADRs. Future studies should look into ADRs experienced by patients specifically starting biological treatment, and use patient-reported disease activity and objective disease measures to obtain more understanding of the relationship between patient-reported ADRs during the induction phase and disease activity.

In conclusion, we showed that IBD patients frequently reported ADRs during the use of a biological and often reported a correlation in time for the most frequent patient-reported ADRs. Importantly, there was a significant difference between type and frequency of patient-reported ADRs and HCP-reported ADRs, leading to an underestimation by the HCP of more subjective ADRs and patients' ADR-related burden. More awareness of the patient's perception of ADRs may result in better compliance and safer treatment.

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CONFLICT OF INTERESTS

Tessa E.H. Römkens has participated in advisory boards, or as a speaker or consultant: Janssen, Takeda, Ferring. Rachel L. West has participated in advisory boards, or as a speaker, or consultant for the following companies: Abbvie, Janssen. Jeroen M. Jansen has served on advisory boards, or as speaker, or consultant for Abbvie, Amgen, Ferring, Fresenius, Janssen, MSD, Pfizer, Takeda. Frank Hoentjen has served on advisory boards, or as speaker, or consultant for Abbvie, Celgene, Janssen Cilag, MSD, Takeda, Celltrion, Teva, Sandoz, and Dr Falk, and has received unrestricted grants from Dr Falk, Janssen-Cilag, Abbvie. Pepijn W. A. Thomas, Maurice G.V.M. Russel, Jette A. van Lint, Naomi T. Jessurun report no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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