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ORIGINAL RESEARCH

Immune-mediated inflammatory disease patients' preferences in adverse drug reaction information regarding biologics

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ABSTRACT

Objectives: Patient-reported outcomes (PROs) are increasingly used in studies and medical practice to obtain information on patients' perspectives toward their treatment or disease. However, most study outcomes are primarily directed at healthcare professionals. It was aimed to obtain insight in which type of information immune-mediated inflammatory disease (IMID) patients prefer to receive after participating in the Dutch Biologic Monitor (DBM), a PRO-based prospective cohort event monitoring system focused on adverse drug reactions (ADRs).

Methods: A survey was conducted among DBM participants that wanted information about the results. Patients' preferences were identified using twelve statements and rated with five-point Likert-type scales. Subgroup analyses and differences between statements were performed using Mann-Whitney U Tests.

Results: The survey was completed by 591 patients (response rate 67.6%). Most respondents had inflammatory rheumatic diseases (76.8%) and used adalimumab (37.2%) or etanercept (33.2%). Respondents preferred results per IMID over aggregated results ($p = <0.001$). Information on whether patients with similar IMIDs experience ADRs (average 4.5), which biologics are most likely to cause ADRs (4.4) and whether ADRs disappear (4.4) were most interesting.

Conclusion: DBM participants prefer to receive disease-specific information on ADRs that is tailored to their own biologic and IMID, including the outcome of ADRs.

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Adverse drug reactions; biologics; communication; immune-mediated inflammatory diseases; patient preferences; study results

1. Introduction

Patients are increasingly regarded as stakeholders in medicine who, alongside clinicians, are more and more involved in decision-making of health interventions concerning their own health. A growing share of the information on patients' perspectives is collected via questionnaires that register patient-reported outcomes (PROs). PROs provide first-hand information on various aspects of a patient's treatment or disease and measure factors, such as pain and disability. These factors are normally difficult to assess by healthcare providers (HCPs) and researchers [1]. Although this information is mainly collected to share with HCPs, for example to monitor the progress of patients and to timely identify, treat or prevent problems, PRO-based questionnaires are also used to improve communication and to facilitate patient-centered care and shared decision-making [2].

The Netherlands Pharmacovigilance Center Lareb (hereinafter: Lareb) conducts Cohort Event Monitoring (CEM) studies, using web-based questionnaires, to capture patients' perspectives on experienced adverse drug reactions (ADRs). These studies gain information on ADRs as experienced in the 'real world', such as the course of ADRs and the actions taken to treat ADRs, with the purpose to contribute to post-marketing surveillance activities. One of these studies is the 'Dutch Biologic Monitor', which is the first CEM system that focuses on ADRs attributed to biologics reported by patients with immune-mediated inflammatory diseases (IMIDs). Besides the collection and analysis of data for new information on ADRs and the detection of unknown ADRs, data can also be shared on an individual level with HCPs and on an aggregated level among patients. As a result, HCPs will obtain more insight in the perspectives of patients, such as knowledge on the burden

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of the experienced non-serious ADRs. When shared among patients, the data can provide insight in what to expect of their treatment and how other patients experienced the drugs.

Real-world information on ADRs, including the course of ADRs and the accompanying impact on a patient's life, is rarely systematically collected. Even though there is little published evidence, analysis and disclosure of data on ADRs to patients may enhance acceptance and contribute to adherence of the prescribed therapeutic treatment. The preferences of HCPs and IMID patients on ADR information regarding biologics, such as the course and burden of ADRs, and the potential preference for results per IMID over aggregated results, have not yet been studied [3–5]. To capture the preferences of patients on the communication of the reported ADR information and to let them co-decide on the content of the results that are communicated to patients, the participants of the Dutch Biologic Monitor were invited to complete a survey to enquire their preferences toward the content of the communicated results.

2. Methods

2.1. The Dutch Biologic Monitor

This study was performed as a part of the pilot 'Dutch Biologic Monitor'. The Dutch Biologic Monitor is a prospective CEM system for patient-reported ADRs attributed to biologics. Nine Dutch hospitals participated between January 1st, 2017 and May 1st, 2019. Patients who used a biologic, mostly for an IMID, were selected and invited to participate by HCPs of the participating hospitals using consecutive sampling. Patients were eligible in case they were eighteen years or older and proficient in Dutch. All patients received information on the study prior to registration and had to sign a web-based informed consent form. More information on the recruitment strategy and the inclusion criteria is described elsewhere [6].

After enrollment, the participants were invited to complete an extensive web-based baseline questionnaire covering demographic information (gender, birth date, body weight, height, smoking behavior), indication for and start date of biologic therapy, combination therapy and comorbidities at baseline. Patients were further asked to report detailed information about signs and symptoms presumably related to the use of biologics, hereinafter referred to as ADRs. This included the type of ADR, start and stop date, course, experienced burden (five-point Likert-type scale), contact with HCPs, actions taken by HCPs and the patient to treat, prevent or relieve ADRs, and whether they wanted to receive the results of the monitor. Subsequent follow-up questionnaires focused exclusively on drug use and ADRs and included identical questions on these topics.

Questionnaires were sent out bimonthly and patients received reminders after 7 days and 14 days. Participation ended in case the previous questionnaire had expired (after 21 days) or if the patient actively withdrew from the study.

The Dutch Medical Research Involving Human Subjects Act (WMO) does not apply to the Dutch Biologic Monitor, and the research project received a 'non-WMO' declaration by the regional medical ethics committee (METC) Brabant (file number: NW2016-66). Additionally, approval of the local medical ethics committees was obtained from all participating hospitals.

2.2. Survey on patients' preferences for information on ADRs

A survey was developed by Lareb to inquire patients' preferences for the communication of the results of the Dutch Biologic Monitor. The survey consisted of five domains with a total of twelve statements (Supplementary item 1). These domains were:

- The preference for the results per type of IMID over aggregated results;
- The interest in ADRs experienced by patients with similar and other IMIDs;
- The interest in baseline characteristics of all patients participating in the DBM;
- The interest in biologic-specific information;
- The interest in ADR-specific information.

Statements were rated using a five-point Likert-type scale for relevance and importance. The relevance scale consisted of (1) 'not interesting at all' to (5) 'very interesting', whereas the importance scale ranged from (1) 'very unimportant' to (5) 'very important'. An open-ended comment field concluded the survey. The survey was pre-tested by a panel of three patients of which two are member of the patient organization 'Dutch Arthritis Society' (ReumaNederland). In addition, five staff-members of Lareb (including GW, LK, NJ) assessed the survey on functionality, consistency and comprehensibility. The survey was subsequently amended where necessary and was digitalized using an online survey tool (SurveyMonkey, San Mateo, California, USA).

An invitation was sent in May 2018 to those participants of the Dutch Biologic Monitor who indicated that they wanted to be kept informed about the results (70.6% of participants). A reminder was sent after one week and the survey closed two weeks after the invitation. Characteristics of the survey participants (hereinafter: respondents) were derived from the baseline questionnaires of the Dutch Biologic Monitor based on e-mail addresses. ADR reporting of the respondents was derived from the completed Dutch Biologic Monitor questionnaires up to May 2018.

2.3. Statistical analysis

Missing values were omitted per statement, as the amount of missing values did not exceed 5%. Averages (avg) were used to reveal the mean interest or relevance per statement. Data was tested for normality using the Shapiro-Wilk Test. Despite the ordinal nature of the data, nonparametric Mann-Whitney U Tests were used to test preferences for aggregated or separate results per IMID, and discrepancies in preferences per statement between 1) inflammatory rheumatic disease (IRD) patients versus the entire respondent population, 2) inflammatory bowel disease (IBD) patients versus the entire respondent population, 3) IBD patients versus IRD patients 4) males versus females and 5) patients that had reported one or more ADRs in the DBM versus patients that had not reported an ADR [7]. Descriptive statistics,

Shapiro-Wilk Tests and Mann-Whitney U Tests were performed in IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA). *p*-values below 0.05 were considered statistically significant.

3. Results

3.1. Respondent characteristics

An invitation for the survey was sent to 874 patients. A total number of 591 patients (67.6%) responded to the survey. Median age was 59.0 years and 59.7% were female. Almost half (256 patients, 43.3%) had reported one or more ADRs in the Dutch Biologic Monitor. The majority (82.9%) used a TNF-α inhibitor, as adalimumab and etanercept were used by respectively 220 (37.2%) and 196 (33.2%) respondents. Most respondents (454 patients, 76.8%) used a biologic indicated for an IRD. Almost half (277 patients, 46.9%) used a biologic indicated for rheumatoid arthritis, followed by psoriatic arthritis (111 patients, 18.8%) and a disease variant of axial spondyloarthritis (83 patients, 14.0%). Inflammatory bowel diseases, i.e. Crohn's disease and ulcerative colitis, were less frequent (11.0% and 2.5%). Combination therapy with methotrexate was reported by 195 respondents (33.0%), whereas 231 respondents (39.1%) reported biologic monotherapy. Comorbidities were registered by 356 respondents (60.2%), of which cardiovascular disorders were the most frequent (170 patients, 34.6%). More detailed information on the respondent characteristics is provided in Table 1.

Table 1. Respondent characteristics.

	All		Inflammatory rheumatic disease patients	
Characteristics	***n* = 591**	**%**	***n* = 454**	**%**
Female gender	353	59.7	287	63.2
Age, median IQR, years	59.0	51.0–67.0	60.0	53.0–68.0
Adverse drug reactions reported	256	43.3	191	32.3
TNF α-inhibitors	490	82.9	391	86.3
Adalimumab	220	37.2	164	36.1
Etanercept	196	33.2	190	41.9
Infliximab	43	7.3	8	1.8
Golimumab	19	3.2	18	4.0
Certolizumab pegol	12	2.0	12	2.6
Interleukin inhibitors	74	12.5	41	9.0
Tocilizumab	21	3.6	17	3.7
Ustekinumab	21	3.6	7	1.5
Secukinumab	19	3.2	17	3.7
Anakinra	6	1.0	0	0.0
Canakinumab	6	1.0	0	0.0
Dupilumab	1	0.2	0	0.0
Antilymphocyte agents	21	3.6	21	4.6
Abatacept	14	2.4	14	3.1
Rituximab	7	1.2	7	1.5
Integrin antagonist	6	1.0	0	0.0
Vedolizumab	6	1.0	0	0.0
Combination therapy[a]	*n*	%	*n*	%
Methotrexate	195	33.0	183	40.3
Corticosteroids[b]	65	11.0	51	11.2
Thiopurines[c]	41	6.9	10	2.2
Aminosalicylates[d]	37	6.3	28	6.2
Hydroxychloroquine	25	4.2	25	5.5
Leflunomide	24	4.1	24	5.3
No combination therapy	231	39.1	157	34.6
Unknown	37	6.3	30	6.6
Indications for biologic therapy[a]	*n*	%	*n*	%
Rheumatoid arthritis	277	46.9	277	61.0
Psoriatic arthritis	111	18.8	111	24.4
Ankylosing spondylitis/axSpA	83	14.0	83	18.3
Crohn's disease	65	11.0	6	1.3
Psoriasis	38	6.4	2	0.4
Ulcerative colitis	15	2.5	1	0.2
Other	41	6.9	10	2.2
Comorbidities[a]	*n*	%	*n*	%
Cardiovascular disorder	170	34.6	155	34.1
Hypercholesterolemia	116	23.6	101	22.2
Cancer	89	18.1	71	15.6
Nervous system disorder	43	8.8	30	6.6
Respiratory tract disorder	26	5.3	20	4.4
Psychiatric disorder	14	2.9	12	2.6
Other	129	26.3	95	20.9
No comorbidity	170	34.6	122	26.9
Unknown	65	13.2	44	9.7

IQR: interquartile range; axSpA: axial spondyloarthritis.
[a]The percent of total adds up to more than 100% since patients can have a combination therapy consisting of more than one drug, more than one indication for biologic therapy or more than one comorbidities.
[b]Corticosteroids include predniso(lo)ne (n = 60) and hydrocortisone (n = 5).
[c]Thiopurines include azathioprine (n = 27), mercaptopurine (n = 12) and thioguanine (n = 2).
[d]Aminosalicyclates include sulfasalazine (n = 26) and mesalamine (n = 11).

3.2. Patients' preferences in ADR information

The preferences of patients on the communication of the reported ADR information resulting from the Dutch Biologic Monitor were assessed for the entire respondent population and various subgroups (IRD patients, IBD patients, males, females, respondents that reported ADRs and respondents that had not reported ADRs). No discrepancies were found during subgroup analysis. For this reason, only the preferences of the total respondent population are shown (Figure 1).

3.2.1. The preference for presentation per IMID over aggregated results

The respondents were requested to mark the importance of the presentation of the results per IMID and for all indications together using a five-point scale, as shown in Figure 1A. A presentation per IMID was statistically significantly preferred over aggregated results ($p = <0.001$), as 90.4% of the respondents rated a separate presentation as (very) important (avg 4.3), whereas an aggregated presentation was scored as (very) important by 68.9% of the respondents (avg 3.8).

3.2.2. Interest in ADR information

Next, we assessed which information on ADRs was regarded to be the most interesting using a five-point scale of interest. Figure 1B reveals that the three most interesting aspects were whether patients with the same IMID also experience ADRs (avg 4.5), which biologics are most likely to cause ADRs (avg 4.4) and whether ADRs resolve (avg 4.4). Respectively 92.2%, 90.3% and 92.5% of the respondents rated these statements as (very) interesting.

Information on patients with other IMIDs (avg 3.5), patient characteristics (avg 3.7) and injection site reactions (avg 3.8) were regarded as least interesting and were labeled as (very) interesting by merely 50.5%, 59.6% and 65.4% of the respondents.

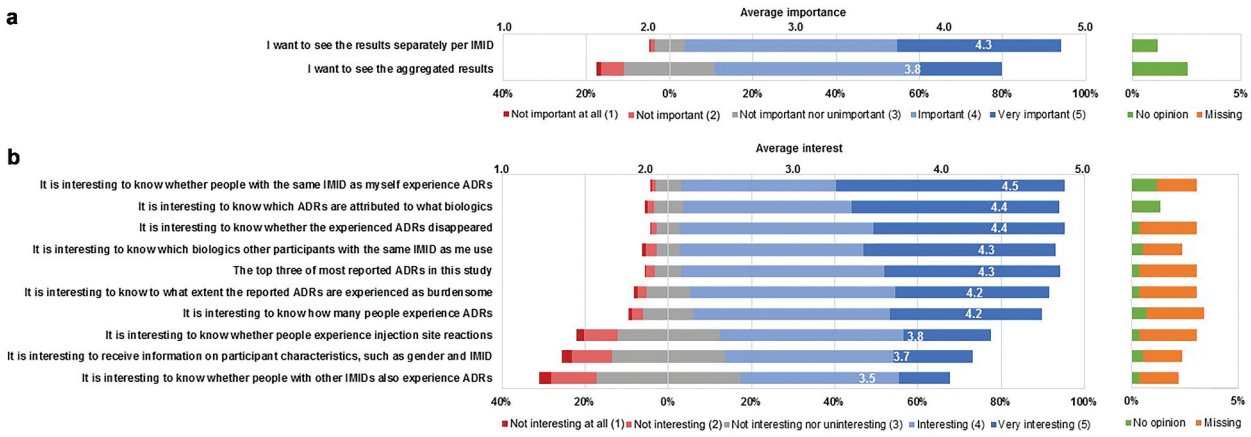

Figure 1. Patients' preferences on the preferred information resulting from the Dutch Biologic Monitor. a: Perceived importance of the presentation of the results per IMID or altogether. b: Patient preferences towards the degree of interest in the results of the Dutch Biologic Monitor. The upper x-axis represents the average importance or interest on a five-point scale from 1.0 to 5.0. The lower x-axis reflects the distribution of the perceived importance and interest per statement in percentage of patients. ADRs: Adverse drug reactions; IMIDs: Immune-mediated inflammatory diseases.

4. Discussion

This is the first study on patients' preferences regarding the preferred information on ADRs attributed to biologics used in the treatment of IMIDs. Considering that patients were the source in this PRO-based drug surveillance study, we highly value their preferences on patient-reported ADR information and try to meet them as much as possible in the communication of the results.

The outcomes of this survey show that patients are mostly interested in which biologics lead to what kind of ADRs, whether patients with the same IMID experience the same ADRs and whether ADR(s) disappear(s) or not. Respondents regard information concerning their own disease as more important than information on other diseases or all IMIDs together. This is illustrated by the relatively low scores for the statements on general information and information on other IMIDs than their own. This is in line with previous studies among patients on the preferred content of the feedback after the reporting of ADRs to Lareb via the spontaneous reporting system, as it was found that patients preferred information on the prevalence of ADRs and again, whether ADRs resolve or not [4]. Lastly, we found no discrepancies between the preferences of the entire respondent population versus IRD patients, the entire respondent population versus IBD patients, IRD patients versus IBD patients, males versus females and patients that reported one or more ADRs versus patients that had not reported ADRs. This implies that the preferences of IMID patients can be regarded as similar, despite the type of IMID, gender or occurrence of ADRs.

Although we captured the voice of many biologic users with various IMIDs, the conducted survey has some limitations. We have no information on ethnicity or education level of our population. Furthermore, proficiency in Dutch and web-access are required for participation in both the Dutch Biologic Monitor and the survey, which limits the generalizability of the results. In addition, although the statements are pretested and the panel contributed to the kind of statements, the conducted study is more or less an inventory of patients' wishes and not a formal patient preference study as such [8,9]. Another limitation is that the survey was only sent to those participants of the Dutch Biologic Monitor that wanted to be informed about the results (70.6%). Therefore, a form of selection bias cannot be excluded for the patients who completed the survey. However, considering that almost 70% of the invited participants of the Dutch Biologic Monitor completed the survey, we assume that the effects are limited.

4.1. Implications for clinical practice

To meet patients' preferences on drug information, HCPs can include the wishes of patients in the drug information that they provide when describing and/or prescribing therapeutic options. Others, such as researchers, information officers of patient associations and pharmaceutical companies, can also take the preferences of patients into account to provide tailored information to patients depending on demographics, disease and therapy. Based on the results of this survey we thus advocate to generate tailored, if possible disease-specific, information on ADRs for patients with IMIDs.

4.2. Conclusion

Participants of the Dutch Biologic Monitor prefer to receive ADR information that is tailored to their own biologic and IMID. Furthermore, patients want to receive information on the expected outcome of the ADR(s) that they experience.

Author contributions

All authors were involved in the conception and design of the study. LJ Kosse, G Weits and NT Jessurun collected, researched, analyzed and interpreted the data. LJ Kosse, G Weits, NT Jessurun and EP van Puijenbroek were involved in the drafting of this manuscript. All authors critically reviewed, revised the paper for intellectual content, provided detailed feedback, read and approved the final manuscript and agreed to be accountable for all aspects of the work.

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Declaration of interest

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Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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