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Exploring the perspective of patients with immune-mediated inflammatory diseases and care providers on the use of immunomodulatory drugs in infections: an interview study

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Abstract

Objectives: Immunomodulatory agents are safe and effective as treatment for various immune-mediated inflammatory diseases (IMIDs), but are associated with a slightly increased infection risk. It is uncertain whether, in the event of an infection, continuation or temporary interruption of immunomodulatory agents leads to better outcomes. Owing to this uncertainty, it is of importance to explore the perspectives of health-care providers (HCPs) and patients on this topic. In this study, we set out to identify and provide an overview of reasons for both treatment strategies.

Methods: Semi-structured interviews were conducted with HCPs involved in the pharmacological treatment of IMIDs and with IMID patients using one or more immunomodulatory agent. Purposive sampling was used to enrich data variation. Interviews were conducted until data saturation was reached and subsequently analysed using qualitative content analysis.

Results: In total, 13 HCPs and 19 IMID patients were interviewed. A wide range of reasons for both treatment strategies were identified, categorized into 10 overarching themes, including IMID characteristics, infection characteristics and the patient–HCP relationship.

Conclusion: In this interview study, we identified various reasons for continuation or temporary interruption of immunomodulatory agents during infections for both IMID patients and HCPs. We found overlapping themes, such as IMID characteristics; however, the content and interpretation of these themes might differ between HCPs and patients. Both HCPs and patients mentioned that the decision for a treatment strategy is often about weighing benefits against risks (e.g. infection severity *vs* disease flare).

Lay Summary

What does this mean for patients?
People with an immune-mediated inflammatory disease, such as rheumatoid arthritis, often use medication that affects their immune system (immunomodulatory medication). The immune system is involved in these diseases but is also needed to control infections (such as influenza or urinary tract infections). Consequently, immunomodulatory medication can also affect the way in which the immune system responds to such infections. When an infection occurs, it can be difficult to decide whether this medication should be continued or temporarily interrupted. We wanted to study what patients and health-care providers think about this and why they would decide either to continue or temporarily to interrupt the immunomodulatory medication during an infection. We interviewed patients and health-care providers about the factors that contribute to this decision. These interviews resulted in 10 themes that play a role in the decision-making process. Examples of these themes are disease (including disease activity) and infection characteristics (including the severity of the infection). We conclude that the decision for a treatment strategy is often about weighing benefits against risks (e.g. infection severity *vs* disease flare). In clinical practice, health-care providers could use these themes as a tool when deciding, together with a patient, what to do during an infection.

Keywords: RA, PsA, SpA, infections, immunomodulatory agents, qualitative research

Key messages

- It is uncertain whether it is best temporarily to interrupt or continue immunomodulatory agents during infections.
- Reasons for health-care providers and patients to choose a treatment strategy can be categorized in 10 themes.
- Among others, infection and disease characteristics are weighed.

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Introduction

Immune-mediated inflammatory diseases (IMIDs) are often treated with immunomodulatory agents [1–3]. Despite their proven efficacy and safety, the use of some immunomodulatory agents is associated with a slightly increased infection risk [4, 5]. Once an infection occurs, it remains uncertain whether it is best to continue or temporarily to interrupt immunomodulatory agents [6]. Most guidelines and summaries of product characteristics advise the temporary interruption of immunomodulatory agents in the event of a (severe) intercurrent infection [7–9]. On the contrary, perhaps counterintuitively, indirect but high-level evidence suggests that the continuation of immunomodulatory agents could have a beneficial effect on infection outcome.

First, activation of the IMID after interruption of immunomodulatory agents could lead to a higher risk of a more severe infection outcome itself [10, 11]. Second, many immunomodulatory agents interfere in the cytokine pathways involved in inflammation and can be used to treat hyperinflammation occurring in severe infections [12–14]. Moreover, there are practical issues, such as long half-lives and administration intervals, that can hamper interruption of the immunomodulatory agents once an infection occurs. Given the little evidence available on the use of immunomodulatory agents during infections, possible beneficial effects of immunomodulatory agents on infections and struggles in clinical practice, a large pragmatic exploratory trial is being executed by the Sint Maartenskliniek to provide evidence on whether continuation or temporary interruption of immunomodulatory agents in IMID patients results in a better outcome of an intercurrent infection (COVIDI^2 trial) [15]. The results of this trial can improve daily clinical practice by providing guidance to patients and health-care providers (HCPs) in the decision process of continuation or interruption of immunomodulatory agents in the event of an infection.

When evidence is low or inconclusive, the decision for either continuation or temporary interruption of immunomodulatory agents might be driven by the beliefs and preferences of patients and HCPs. In this case, shared decision-making is of importance, because it can enable patients to assess the various reasons for either treatment strategy and provide HCPs with insight on what is important to patients. Combining these factors can contribute to making a decision together [16]. However, little is known about the beliefs of patients and HCPs on the use of immunomodulatory agents during infections. A study among different medical specialists showed that perceived infection risks owing to immunomodulatory agents differ between specialists. Family medicine physicians and internal medicine physicians rated the infection risk for TNF-inhibitors higher (85 and 79, respectively, on a scale from 0 to 100), compared with dermatologists (52 of 100) [17]. Beliefs about infection risk can also vary between HCPs and IMID patients. A study among patients with Crohn's disease and gastroenterologists showed that gastroenterologists accepted a higher infection risk in exchange for improvement from severe to moderate disease than patients [18]. In very severe plaque psoriasis, patients were more willing to accept a risk of serious adverse events compared with dermatologists [19]. A study among patients with RA and JIA who had undergone an arthroplasty showed that avoiding an infection was of greater importance than avoiding a disease flare in the perioperative period [20]. Finally, it is known that patients with RA and Crohn's disease are willing to accept a potential small additional risk of (severe) infections if treatment with immunomodulatory agents causes a significant reduction of complaints [21–24].

In conclusion, perceived infection risks might differ between HCPs and patients. They might also have different points of view regarding acceptable infection risk, possibly dependent on IMID disease severity. Nevertheless, to our knowledge, no research has been performed on the perspective of IMID patients and HCPs regarding the use of immunomodulatory agents in the event of an infection. We therefore set out to identify and provide an overview of reasons either to continue or temporarily to interrupt immunomodulatory agents in the event of an infection for both IMID patients and HCPs using semi-structured interviews.

Methods

Participants

The patients were recruited by their treating physician from the rheumatology department at the Sint Maartenskliniek and dermatology and gastroenterology departments at the Radboudumc. From each department, patients were recruited by at least two different physicians, because patients' beliefs might be influenced by their physician's opinion or advice about immunomodulatory agent use during infections. Purposive sampling was used to enrich data variation (and obtain a diverse and complete set of reasons either to continue or to interrupt immunomodulatory agents). We aimed to include a broad variety of patients with regard to age, sex, diagnosis, type of immunomodulatory agent used, combinations of immunomodulatory agents used and experience with (severe) infection [25, 26]. Patients could be included if they were $\geq$16 years, able to understand (read, listen) and communicate in Dutch, mentally competent and had a clinical diagnosis of at least one IMID (RA, SpA, PsA, psoriasis, ulcerative colitis and/or Crohn's disease), for which they used one or more immunomodulatory agents.

The HCPs were recruited from various rheumatology, dermatology and gastroenterology departments at seven different hospitals (specialized, academic and peripheral). HCPs were approached directly by the research team (via e-mail, face to face or by telephone). Purposive sampling was used, and we aimed to include a broad variety of HCPs with regard to age, sex, specialization, work experience, PhD degree and type of hospital. HCPs could be included if they were able to understand (read, listen) and communicate in Dutch and were involved in the pharmaceutical treatment of IMID patients as either a medical doctor or physician assistant (in training). We mainly included medical specialists because they are (in Dutch health care) the ones responsible for treatment decisions such as the continuation or interruption of immunomodulatory agents in the event of an infection.

Data collection

Semi-structured interviews were used and are suitable to obtain information about experiences, thoughts and beliefs in health care [26]. Two interview guides were developed by M.A.A.O. (medical doctor and PhD candidate) and L.M.V. (postdoctoral researcher with experience in conducting qualitative research). The interview guides were reviewed by J.E.V. (psychologist with experience in qualitative research) and

Table 1. Topics with one example key question addressed in the interview guides

Patients
Experiences with infections during use of immunomodulatory agents
Q: Have you ever had an infection while using immunomodulatory agents?
Experiences with continuation or interruption of immunomodulatory agents in the event of an infection
Q: What did you do with your immunomodulatory agents during a past infection?
Patient preference for treatment strategy in the event of an infection and instructions from their physician
Q: What would you do if you were to experience an infection at this moment?
Barriers and facilitators for continuation of immunomodulatory agents during an infection
Q: What could be reasons for you to continue your immunomodulatory agents during an infection?
Barriers and facilitators for temporary interruption of immunomodulatory agents during an infection
Q: What could be reasons for you temporarily to interrupt your immunomodulatory agents during an infection?
Health-care providers
What they would do if a patient has an infection
Q: If a patient were to call because they have an infection, what would you do?
Perceived patient preferences for treatment strategy in case of an infection
Q: How do you think patients feel about immunomodulatory agent use during infections?
Agreements/protocols within their own work field
Q: Are there agreements on immunomodulatory agent use and infection in your department? If yes, which?
Barriers and facilitators for continuation of immunomodulatory agents during an infection
Q: What determines your decision on continuation of immunomodulatory agents during an infection?
Barriers and facilitators for temporary interruption of immunomodulatory agents during an infection
Q: Do you think there are benefits of temporary interruption of immunomodulatory agents during an infection?

Q: question.

A.A.d.B. (rheumatologist–epidemiologist). The topics addressed and examples of questions asked in the interview guides are shown in Table 1. M.A.A.O. conducted the interviews either by telephone or face to face, because face-to-face contact was not desirable owing to the coronavirus disease 2019 (COVID-19) pandemic. Evidence shows that telephone interviews, compared with face-to-face interviews, do not lead to inferior results [27]. Before the study, there was no relationship between M.A.A.O. and the interviewed patients. With some HCPs, M.A.A.O. had no previous connection, whereas some HCPs were colleagues of M.A.A.O. Information that patients or HCPs shared during the interview was not shared with other HCPs or colleagues. All interviews were recorded and transcribed verbatim by a commercial third party (Tekstuitschrijven). A summary written by the interviewer was sent to the interviewee after each interview as a check to assure data validity. None of the participants indicated that they did not agree with this summary.

Data analysis

Transcribed interviews were analysed by qualitative content analysis using Atlas.ti [28]. Initially, all interviews were read, reread and coded (familiarization with and condensation of the data). The first three interviews with both the HCPs and the patients were coded independently by two researchers (L.M.V. and M.A.A.O.). These codes were discussed until consensus about the codes was reached, and codes were reformulated or adapted if needed. An example of the reformulation of questions is the adaption of the question, 'Have you experienced the occurrence of an infection while taking immunomodulatory drugs?' into 'Have you ever had an infection while using this medication?'. After this, the interviews were coded by M.A.A.O. alone, checked by L.M.V., then discussed. If necessary, codes were reformulated, adapted or merged (abstraction). During the process, the results of the interviews were discussed by the two researchers, and the interview guide was adapted if necessary. This did not lead to new questions being added to the interview guide but did lead to rephrasing of questions. Content analysis led to identification of reasons to choose and reasons not to choose for each of the treatment strategies. These reasons were divided into four categories: reasons to interrupt immunomodulatory agents temporarily, reasons not to interrupt immunomodulatory agents temporarily, reasons to continue immunomodulatory agents and reasons not to continue immunomodulatory agents in the event of an intercurrent infection. Some codes derived from the interviews did not form a reason for one or both treatment strategies and were coded as 'neutral' (contextual codes). Subsequently, these reasons were categorized into themes and subthemes. Themes could be grouped into one or multiple categories. Data collection and data analysis were alternated continually in a cyclic process. Interviews were conducted and analysed until data saturation was reached. Data saturation was defined as no new subthemes emerging from the last three interviews. After all transcripts were coded and initial themes formed, M.A.A.O. and L.M.V. discussed the categories and (sub)themes with L.M.V. and A.A.d.B. This was first done for the patient and HCP interviews separately; ultimately, the themes that were identified from all interviews were merged into the final themes.

Ethics

This study was performed in compliance with the Declaration of Helsinki. The Medical Research Ethics Committee (MREC) region Arnhem–Nijmegen exempted the study from ethical approval according to the Dutch Medical Research Involving Humans Acts (file numbers 2020-6593 and 2020-7207). Participants were included after they had given informed consent given either in writing or orally (in accordance with Dutch legislation).

Results

Participant characteristics

Between June 2020 and November 2020, 39 patients agreed to be approached by the research team, and eventually 19

Table 2. Participant characteristics

Patients ($n = 19$)		Health-care providers ($n = 13$)	
Female, *n* (%)	11 (58)	**Female, *n* (%)**	9 (69)
Age, mean (SD), years	50 (17), range 20–80	**Age, mean (SD), years**	49 (8), range 34–66
Disease duration, mean (SD), years	17 (14), range 1–49		
Diagnosis, *n* (%)		**Specialized in, *n* (%)**	
RA	4 (21)	**Rheumatology**	6 (46)
PsA/axial SpA	5 (26)	**Gastroenterology**	3 (23)
Psoriasis	4 (21)	**Dermatology**	4 (31)
IBD (ulcerative colitis/Crohn's disease)	6 (32)		
Immunomodulatory agent used[a], *n* (%)		**Profession, *n* (%)**	
MTX	3 (16)	**Medical specialist**	10 (77)
Thioguanine	1 (5)	**Physician assistant**	2 (15)
HCQ	1 (5)	**Resident (in training)**	1 (8)
Rituximab	1 (5)		
TNF inhibitors	8 (42)	**Type of hospital, *n* (%)**	
JAK inhibitors	2 (11)	**Academic**	2 (15)
Anti-IL-12/23	1 (5)	**Peripheral**	8 (62)
Anti-IL-23	1 (5)	**Specialized**	3 (23)
Anti-IL-17	3 (16)		
Phosphodiesterase 4 inhibitor	1 (5)		
Experience with infection during immunomodulatory agent use, *n* (%)	Yes: 9 (47) No: 10 (53)		
Experience with severe infection during immunomodulatory agent use[b], *n* (%)	Yes: 4 (21) No: 15 (79)		

[a] Use of more than one agent is possible (three patients were on combination therapy).
[b] Severe infection defined as requiring hospitalization.

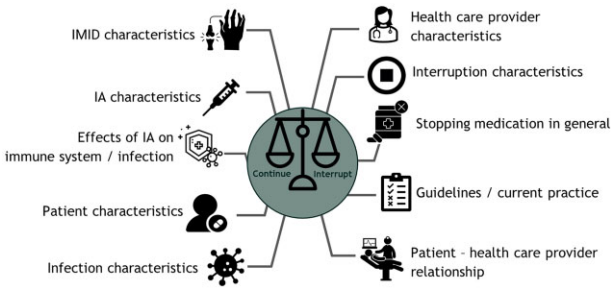

Figure 1. Identified themes

IMID patients were interviewed. Not all patients provided a reason for not participating. With regard to the HCPs, 23 HCPs were approached by the research team, and 13 HCPs were interviewed between March 2021 and November 2021. In Table 2, the characteristics of patients and HCPs are displayed. The mean duration of the interviews was 23 min (S.D. 5.3 min, range 14–41 min) for the patients and 28 min (S.D. 5 min, range 18–36 min) for the HCPs.

Main results

Qualitative content analysis led to the identification of 936 codes (483 in the HCP interviews and 453 in the patient interviews) and 108 subthemes (60 from the HCP interviews and 48 from the patient interviews). In total, 10 themes were extracted from the reasons (not) to choose one of the treatment strategies (portrayed in Fig. 1). Most themes were identified from both the patient and HCP interviews, except for 'Health-care provider characteristics' and 'Guidelines/current practice', which were mentioned only by HCPs. In Table 3, quotations from patients and HCPs are displayed for each theme. Contextual codes are not included in these themes; however, they might affect the process of decision-making by patients and/or HCPs. For example, participants stressed the importance of shared decision-making, and HCPs mentioned that they struggle with the limited evidence available on the topic.

Theme 1: IMID characteristics

The IMID characteristics, including the disease activity, was mentioned by both HCPs and patients as a reason (not) to continue or to interrupt immunomodulatory agents in the event of an infection. (Risk of) high disease activity or high impact of a flare (with risk of permanent damage or increased infection risks) was mentioned as a reason to continue immunomodulatory agents. In contrast, mild or stable disease was identified as a reason to interrupt immunomodulatory agents. Enhanced disease activity can have an impact on daily life on different levels; patients stated that it might affect their mobility, independence and ability to work or participate in social events. One patient said that interruption of her medication would not be a topic for discussion.

Theme 2: characteristics of immunomodulatory agents

Patients and HCPs addressed the characteristics of immunomodulatory agents during the interviews. HCPs mentioned, for example, that long half-times would be a reason not to interrupt the immunomodulatory agents, because they did not expect any effect from the interruption on a current infection. They also noted that there might be differences between immunomodulatory agents and their degree of immunosuppression, and that this influences their choice of a treatment strategy. For example, HCPs said that they would be more likely to continue a classical immunomodulatory agent, such as MTX, compared with TNF inhibitors. Both HCPs and patients talked about possible interactions with other medication, such as antibiotics. This could be a reason to interrupt the immunomodulatory agents during an infection.

Table 3. Themes and quotations

Theme		Quotation
1. IMID characteristics	HCP	. . .but more so, I could imagine with IBD you can really undergo damage, a fistula or something, that could be a disadvantage to stop or a reason to continue.
	Patient	With me it is just, if they stop it, then I know for certain that I will get a flare, so I really just don't dare to stop . . . if I really have a flare, I can't even walk. I'll be lying in bed all day and that's it.
2. Characteristics of immunomodulatory agents	HCP	. . .you are working towards a [blood level] and the medication only starts to work after 8 or 10 weeks and some only after 12 weeks. So skipping [the medication] for 1 week is not very useful in my opinion. . . . Since your immune system has been suppressed for the long term. So then it is not so useful to skip the medication once.
	HCP	Q: [Are there] disadvantages or undesired consequences of continued use of medication during an infection? A: The interaction with antibiotics, but with MTX that only concerns cotrimoxazole.
3. Effects of immunomodulatory agents on immune system/ infection	HCP	Well, with those severe infections as we now also see with COVID-19, then you have a real inflammatory response and I think that that occurs more often. But then you do talk about serious infections with hospital admission and perhaps even the ICU. . . . Then I could imagine that the inflammation due to the infectious disease, that [immunomodulatory medication] could have an additional effect. Yes.
	Patient	Q: What do you think could be the reasons or advantages of temporarily interrupting [medication]? A: For example, that your immune system would get somewhat stronger in the meantime and that it [the immune system] would be able to stop the infection or at least improve the course of the infection.
4. Patient characteristics	HCP	It also depends a bit on the prior medical history and the underlying disease. If people have COPD and it is possible [to skip], for example they [are] about to use the humira, then I will advise them to skip [the medication] once.
	Patient	And to be honest I have not thought about stopping, because I have had erysipelas three times and I have just kept [the medication] at every 8 weeks. Q: Yes, you just continued using [the medication] and you did not consider that . . . A: No, no.
5. Infection characteristics	HCP	Yes, if people are really sick then I typically say just stop [the medication], even if it wouldn't make a big difference. When people are close to a hospital admission and stay in the hospital longer to recuperate or it [the infection] lasts longer. Yes, then I am glad that I stopped the DMARD on time, but that is more a feeling.
	Patient	Yes, well, you see, there are COVID patients admitted to the ICU and then there's a small cold, there is quite a difference between those two, whether you continue something [the medicine] or not. But as long as it [continue medication] is possible and somewhat justified, yes.
6. Health-care provider characteristics	HCP	Nowadays, medicine is getting more defensive. Meaning that there is also a fear that what if it goes wrong, that you could be held accountable as doctor in the sense of why didn't you stop [the medication]? And you don't stop because of vague reasons, it isn't a sort of solid scientific basis, that allows you to continue and then it goes wrong with the patient and then yes, perhaps it could lead to claims. And being found guilty, like, you should have stopped . . . yes, that applies more nowadays. That they [doctors] don't dare.
7. Interruption characteristics	Patient	It is not like if you don't inject for a week then the medication directly stops working. It continues to work a bit. You can safely mess around with that a bit; it isn't all pinned down to a day or a week.
8. Stopping medication in general	HCP	But the advantage is, you in fact get a free chance to stop.
	Patient	I would like to try in the long term to stop the medication completely, to see if my body can just handle it, but not so soon after it [the disease] has been diagnosed.
9. Guidelines/current practice	HCP	My perspective is a bit from the past. Yes, the biologicals were new and it was all a bit unclear, at least I think it was unknown, and the thought was [these agents are] immunosuppressing, while MTX was, of course, much better known and that was . . . yes, it [the immunosuppressive effect of MTX] was never really emphasized, I believe, in my training as well.
10. Patient–HCP relationship	HCP	We put a pretty big emphasis on it [the infection risk], so I also think that for the patient relationship and credibility towards the patient to say, 'just continue', if they have a pneumonia, even though you previously said it [pneumonia] is a possible side effect of the medication. It sounds a little strange.
	Patient	Q: So for you, what would be reasons or advantages of temporarily stopping or, for example, postponing the medication during an infection? A: As I said, the doctor knows much better than I do. If he says it is better, than that is the case. I cannot judge that myself. I will just assume that.

A: answer; COPD: chronic obstructive pulmonary disease; COVID-19: coronavirus disease 2019; HCP: health-care professional; ICU: intensive care unit; IMID: immune-mediated inflammatory disease; Q: question.

Furthermore, HCPs brought up the financial aspect. Some immunomodulatory agents are expensive, and continuation would therefore lead to higher costs. On the contrary, interruption would lead to lower costs, and this could be taken into account when considering either continuation or interruption of immunomodulatory agents during infections.

Theme 3: effects of immunomodulatory agents on immune system/infection

The observed effect of immunomodulatory agents on the immune system or infections and beliefs about these effects were identified as reasons either to interrupt or to continue immunomodulatory agents in the event of an infection. Some patients mentioned that they believed their immunomodulatory agent had a negative impact on infection risk (which was identified as a reason to interrupt immunomodulatory agents), whereas others believed that their immunomodulatory agent could have a positive effect on the immune system (which was identified as a reason to continue immunomodulatory agents). HCPs also expressed both views, and they specifically mentioned that immunomodulatory agents could have beneficial effects on hyperinflammation, which is the case, for example, in severe COVID-19 and could be a reason to continue immunomodulatory agents during an infection.

Theme 4: patient characteristics

Several patient characteristics were identified as reasons to choose a certain treatment strategy. HCPs, for example, mentioned that they would be more likely to interrupt immunomodulatory agents in patients with previous severe infections or in vulnerable patients with significant co-morbidities. HCPs also mentioned decreased therapy adherence as a reason not to choose temporary interruption. They explained that if patients notice that an immunomodulatory agent is stopped easily or quickly in response to infections, patients might be more likely to stop or skip their immunomodulatory agents at their own convenience. As for the patients, some might not be aware that temporary interruption of immunomodulatory agents is an option in the event of infection, hampering the use of this treatment strategy.

Theme 5: characteristics of infection

More severe, recurrent or long-lasting infections were identified as reasons to interrupt immunomodulatory agents, whereas mild infections were reasons to continue immunomodulatory agents. This applied to both patients and HCPs.

Theme 6: characteristics of HCPs

The HCPs mentioned peer influence as a reason to interrupt immunomodulatory agents in the event of an infection. For example, if a supervisor or infectious disease specialist were to advise them to interrupt the immunomodulatory agents, they would follow this advice. Another topic that came up was the fear of making mistakes or being health liable. HCPs indicated that this could be a reason to interrupt immunomodulatory agents temporarily during an infection.

Theme 7: characteristics of the interruption

As for interruption characteristics, both patients and HCPs expressed that an (expected) short duration of interruption was a reason to interrupt, because the risk of, for example, disease flare is low in this case.

Theme 8: stopping medication in general

The wish or chance to stop immunomodulatory agents generally came up as a reason to interrupt immunomodulatory agents. Patients mentioned their wish to stop or taper immunomodulatory agents in general. HCPs said that the interruption of immunomodulatory agents in the event of an infection could be considered a 'free' opportunity to stop the immunomodulatory agents.

Theme 9: guidelines/current practice

Only HCPs mentioned the guidelines or current protocols as a reason to interrupt immunomodulatory agents. They also stated that there is not a lot of evidence on this topic and that this is a major struggle. HCPs also mentioned that guidelines are not always based on high-level evidence, but more on expert opinion or on previous experience.

Theme 10: patient–HCP relationship

The patient–HCP relationship is of importance for both patients and HCPs. Patients indicated that if an HCP were to tell them or advise them to interrupt their medication, they would follow this advice. In contrast, HCPs mentioned that they value shared decision-making and that they would comply with the wishes and preferences of the patient, if medically justified.

Another topic that came up was being consistent with patients about infection risks. When treatment with immunomodulatory agents is first started, patients are often advised temporarily to interrupt their immunomodulatory agents in the event of an infection. When an infection occurs, and the HCP tells them to continue their immunomodulatory agents, this would be contrary to the previously given advice (regardless of the current evidence available on the topic). HCPs were concerned that this could harm the relationship; therefore, maintaining the patient–HCP relationship was identified as a reason to interrupt immunomodulatory agents.

Discussion

In this interview study, we identified various reasons provided by both IMID patients and HCPs for either continuation or temporary interruption of immunomodulatory agents during infections. We found overlapping themes, such as IMID characteristics, but the content and interpretation of these themes differed. Regarding IMID disease activity, for example, HCPs focused on the risk of permanent damage, whereas patients were concerned about flares and the impact on daily life activities. The focus of HCPs on risk of damage was also seen in a study showing that gastroenterologists, in comparison to patients, are more willing to accept treatment risks in exchange for improvement from severe to moderate symptoms [18]. As for patients, another interview study showed that when tapering immunomodulatory agents, RA patients fear disease flare and impact on daily life [29]. Some of the identified reasons appear contradictory; for example, patients and HCPs noted that they would be more likely to interrupt immunomodulatory agents temporarily if the interruption were to be only short lived. This is because the risk of a flare is relatively small when interrupting immunomodulatory agents for a short period of time. The same argument was used to suggest that there is no point in interrupting the immunomodulatory agents, owing to the long half-times of these agents.

The lack of unambiguous, high-level evidence on this topic is a burden for HCPs and causes them to be unable to make a substantiated decision. Results of the explorative COVIDI[2] trial can provide guidance, but more research might still be needed to provide conclusive evidence on specific immunomodulatory agents (e.g. the extent to which they have immunosuppressive effects, because they all target different components of the immune system) and specific types of infections. In current practice, HCPs sometimes take a 'better safe than sorry' approach and interrupt the immunomodulatory agents to prevent escalation of the infection. Furthermore, clear communication and shared decision-making influence the beliefs and behaviours of patients and HCPs. First, patients mentioned that they would follow their physician's advice on use of immunomodulatory agents during an infection. A previous study shows that at the beginning of the COVID-19 pandemic, patients interrupted their immunomodulatory agents because they believed they were at increased risk for COVID-19 owing to their immunomodulatory agents, and this belief might have been caused by previous instructions to stop immunomodulatory agents in the event of an infection [30]. Second, HCPs place value on shared decision-making and responding to the wishes of the patient. They are also concerned about treatment adherence, their own credibility and the relationship with their patients.

One of the strengths of this study is that, to our knowledge, this is the first study investigating the perspectives of IMID patients and HCPs on this topic. Another strength is that the interviews were conducted by a PhD candidate who did not have a relationship with the interviewed patients before the study, reducing the risk of response bias. Furthermore, purposive sampling and participant recruitment from different departments allowed the inclusion of a wide variety of participants, leading to a thorough overview of all possible reasons that could contribute to the decision to interrupt or continue immunomodulatory agents during infections.

Potential limitations are the timing of the patient interviews, which were conducted between June and November 2020, a few months after the start of the COVID-19 pandemic. Patients mentioned that they were worried or afraid of getting infected with the SARS-Cov-2 virus, which is in line with other studies on this topic [30]. However, patients said that these concerns declined over time. The interviews with HCPs were conducted 1 year later. HCPs mentioned that the COVID-19 pandemic had reassured them, because in general the IMID patients did not appear to be at increased risk for (severe) COVID-19 [31]. It is possible that had these interviews been conducted earlier, the answers to some of the questions would have been different. Nonetheless, especially in light of the COVID-19 pandemic, it is of great value to understand how patients and HCPs feel about infections and the use of immunomodulatory agents. Another limitation is the absence of involvement of a patient research partner.

Regarding generalizability, only patients and HCPs who were able to communicate (read and speak) in Dutch were included in our study, because the interviews were conducted in Dutch. Therefore, the perspective of non-Dutch-speaking patients and/or HCPs, patients with illiteracy or patients and/or HCPs with hearing impairment might be missing from our data. Also, in countries with different health-care systems, other factors could play a role that we were not able to identify in this study.

In conclusion, we identified reasons given by HCPs and IMID patients for both continuation and interruption of immunomodulatory agents in the event of an infection. When making a decision on the use of immunomodulatory agents during an infection, several factors have to be weighed. To improve insight into the importance of the identified reasons and the relationships between them, a quantitative research assessment (e.g. a questionnaire in a larger patient population) is required. The results of the present study can inform strategies to facilitate implementation of either continuation or interruption of immunomodulatory agents during infections, depending on the results of the COVIDI[2] trial. Moreover, the results are of value in clinical practice. Shared decision-making is of great value, and HCPs can use the identified reasons as a tool in communication with IMID patients experiencing an infection.

Data availability

Deidentified data obtained, used and/or analysed during the current study are available from the corresponding author upon reasonable request.

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References

1. Lamb CA, Kennedy NA, Raine T *et al.* British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut 2019;68(Suppl 3): s1–s106.
2. Nast A, Jacobs A, Rosumeck S, Werner RN. Methods Report: European S3-Guidelines on the systemic treatment of psoriasis vulgaris – update 2015 – EDF in cooperation with EADV and IPC. J Eur Acad Dermatol Venereol 2015;29:e1–22.
3. Sepriano A, Kerschbaumer A, Smolen JS *et al.* Safety of synthetic and biological DMARDs: a systematic literature review informing the 2019 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2020;79:760–70.
4. Kalb RE, Fiorentino DF, Lebwohl MG *et al.* Risk of serious infection with biologic and systemic treatment of psoriasis: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). JAMA Dermatol 2015;151:961–9.
5. Singh JA, Cameron C, Noorbaloochi S *et al.* Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. Lancet 2015;386:258–65.

6. Swoger JM, Regueiro M. Stopping Continuing, or restarting immunomodulators and biologics when an infection or malignancy develops. Inflamm Bowel Dis 2014;20:926–35.
7. Biologicals (Infectie als bijwerking van biologicals). https://richtlijnendatabase.nl/richtlijn/biologicals/bijwerkingen_van_biologicals/infectie_als_bijwerking_van_biologicals.html (23 November 2022, date last accessed).
8. (EMA) EMA. Summary of product characteristics. Humira. https://www.ema.europa.eu/en/documents/product-information/humira-epar-product-information_en.pdf (6 December 2022, date last accessed).
9. (EMA) EMA. Summary of product characteristics. Xeljanz. https://www.ema.europa.eu/en/documents/product-information/xeljanz-epar-product-information_en.pdf (6 December 2022, date last accessed).
10. Au K, Reed G, Curtis JR *et al.*; CORRONA Investigators. High disease activity is associated with an increased risk of infection in patients with rheumatoid arthritis. Ann Rheum Dis 2011;70:785–91.
11. Takeshita J, Grewal S, Langan SM *et al.* Psoriasis and comorbid diseases: epidemiology. J Am Acad Dermatol 2017;76:377–90.
12. World Health Organization. Therapeutics and COVID-19: living guideline. 2022. https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.2 (3 March 2022, date last accessed).
13. Lv S, Han M, Yi R *et al.* Anti-TNF-α therapy for patients with sepsis: a systematic meta-analysis. Int J Clin Pract 2014;68:520–8.
14. Qiu P, Cui X, Sun J *et al.* Antitumor necrosis factor therapy is associated with improved survival in clinical sepsis trials: a meta-analysis. Crit Care Med 2013;41:2419–29.
15. COntinuation Versus Interruption of Immunomodulating Drugs in case of an Infectious disease in IMID patients (COVID I2 study), with special attention for COVID 19: a pragmatic, explorative randomized controlled trial. https://www.trialregister.nl/trial/8922 (27 September 2021, date last accessed).
16. Berger Z. Navigating the unknown: shared decision-making in the face of uncertainty. J Gen Intern Med 2015;30:675–8.
17. Sharim R, Thomas P, Mathew L, George M, Rosenbach M. Perceptions of infection risk with immunomodulatory medications. J Clin Rheumatol 2018;24:80–4.
18. Johnson FR, Hauber B, Özdemir S *et al.* Are gastroenterologists less tolerant of treatment risks than patients? Benefit–risk preferences in Crohn's disease management. J Manag Care Pharm 2010;16:616–28.
19. Gonzalez JM, Johnson FR, McAteer H, Posner J, Mughal F. Comparing preferences for outcomes of psoriasis treatments among patients and dermatologists in the U.K.: results from a discrete-choice experiment. Br J Dermatol 2017;176:777–85.
20. Goodman SM, Miller AS, Turgunbaev M *et al.* Clinical practice guidelines: incorporating input from a patient panel. Arthritis Care Res 2017;69:1125–30.
21. Johnson FR, Ozdemir S, Mansfield C *et al.* Crohn's disease patients' risk-benefit preferences: serious adverse event risks versus treatment efficacy. Gastroenterology 2007;133:769–79.
22. Hsiao B, Fraenkel L. Patient preferences for rheumatoid arthritis treatment. Curr Opin Rheumatol 2019;31:256–63.
23. Hazlewood GS, Pokharel G, Deardon R *et al.* Patient preferences for maintenance therapy in Crohn's disease: a discrete-choice experiment. PLoS One 2020;15:e0227635.
24. Hazlewood GS, Bombardier C, Tomlinson G *et al.* Treatment preferences of patients with early rheumatoid arthritis: a discrete-choice experiment. Rheumatology 2016;55:1959–68.
25. Flottorp SA, Oxman AD, Krause J *et al.* A checklist for identifying determinants of practice: A systematic review and synthesis of frameworks and taxonomies of factors that prevent or enable improvements in healthcare professional practice. Implement Sci 2013;8:35.
26. Pope C, van Royen P, Baker R. Qualitative methods in research on healthcare quality. Qual Saf Health Care 2002;11:148–52.
27. Novick G. Is there a bias against telephone interviews in qualitative research? Res Nurs Health 2008;31:391–8.
28. Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. Nurse Educ Today 2004;24:105–12.
29. Verhoef LM, Selten EMH, Vriezekolk JE *et al.* The patient perspective on biologic DMARD dose reduction in rheumatoid arthritis: a mixed methods study. Rheumatology 2018;57:1947–55.
30. Michaud K, Wipfler K, Shaw Y *et al.* Experiences of patients with rheumatic diseases in the United States during early days of the COVID-19 pandemic. ACR Open Rheumatol 2020;2:335–43.
31. Hyrich KL, Machado PM. Rheumatic disease and COVID-19: epidemiology and outcomes. Nat Rev Rheumatol 2021;17:71–2.