



Real-World Patient Experience of Switching Biologic Treatment in Inflammatory Arthritis and Ulcerative Colitis – A Systematic Literature Review

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Purpose: To obtain an up-to-date overview of the measurement of patient experience of switching biologic treatment in patients with inflammatory arthritis (IA) or ulcerative colitis (UC). Secondary objectives included summarizing the types of patient-reported outcomes (PROs) used (if any), and related findings; and summarizing medical and non-medical reasons for treatment switch and/or discontinuation.

Methods: A systematic literature review (SLR) was performed, searching Medline and Embase for relevant publications.

Results: In total, 70 relevant publications were identified. While the majority of these reported reasons for switching and/or discontinuing treatment, only four provided information explicitly regarding patient-reported experience of switching biologic treatment. All four utilized ranking tools to assess patient experience of switching biologic treatment. The most common reason for switching and/or discontinuing treatment was loss of efficacy, while the least common reason was patient preference.

Conclusion: Although the number of available treatments in IA and UC have increased, there is a sparsity of information regarding patient-reported experience of switching biologic treatment. Further research regarding patient preference and/or experience would benefit this therapeutic area and help guide treatment choices.

Keywords: arthritis, colitis, ulcerative, biological products, patient reported outcome measures, treatment switch

Introduction

Ulcerative colitis (UC) and inflammatory arthritis (IA; including rheumatoid arthritis [RA] and spondyloarthropathies [SpA], the latter comprising ankylosing spondylitis [AS] and psoriatic arthritis [PsA]) are conditions for which biologics and novel small molecules have revolutionized treatment.¹

The growing treatment armamentarium results in an increase in treatment switches among patients with UC and IA. Previously, patients have transitioned between treatments with different modes of action (MoA) – a phenomenon also known as swapping² – and between different treatments with the same MoA (also known as cycling). With the availability of biosimilars, a new type of treatment transition has been introduced: transitioning between different brands of the same medication. This type of transition is expected to increase the rate of switching further as more biosimilar treatments become available to a larger number of patients. Indeed, a substantial proportion of the estimated cost savings from biosimilar introduction is expected to

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be realized through patients transitioning from more expensive originator products to less expensive biosimilars.^{3,4}

Previous studies have reported that reduced persistence with biologic treatment is associated with increased costs.^{5–7} In addition, treatment persistence may also be considered as a proxy for safety and efficacy with treatment, as well as patient satisfaction.^{8–10} In line with this view, several studies have reported that biologic treatment properties such as administration route and dosing frequency have an impact on patient preference, and by extension, persistence and adherence with treatment.^{11,12} Worsened adherence to treatment, in turn, decreases treatment efficacy and affects clinical outcomes.¹¹

Real-world effectiveness of novel systemics and biologics in UC and IA have been studied extensively and systematic reviews on the subject exist.¹³ However, few studies have described the patient experience of treatment transitions, and to the best of our knowledge, no review of such data has been published. Better understanding of the patient expectations may allow for improved clinical decision-making and better outcomes. To this end, we performed a systematic review of real-world and observational studies

with two objectives: i) To describe the patient experience of transitioning between different biologic treatments for IA or UC and ii) To summarize reported reasons for treatment switching and discontinuation.

Materials and Methods

Literature Search and Study Eligibility Criteria

The literature search was performed on October 25th, 2018 in Medline and Embase via Ovid as well as in relevant conference databases (United European Gastroenterology [UEG] week; European Crohn's and Colitis Organisation [ECCO]; Digestive Disease Week [DDW]; European League Against Rheumatism [EULAR]; American College of Rheumatology [ACR]; and The Professional Society for Health Economics and Outcomes Research [ISPOR]). The full search strings are available in [Supplementary Tables 1–3](#). An overview of eligibility criteria for study inclusion according to the Population, Interventions, Comparators, Outcomes, and Study design (PICOS) approach can be seen in [Table 1](#). Any publication failing to meet either of these eligibility criteria was excluded, with the reason for

Table 1 Study Eligibility Criteria

	Inclusion Criteria	Exclusion Criteria
Population	<ul style="list-style-type: none"> Adult patients (≥18 years) with IA Adult patients (≥18 years) patients with UC 	<ul style="list-style-type: none"> Pediatric patients Studies with fewer than 20 patients
Intervention	Switching from biologic to biologic; from biologic to biosimilar; from biosimilar to biologic	Studies without biologic or biosimilar treatment
Comparators	No restrictions	No restrictions
Outcomes	Studies reporting reasons for switching and/or discontinuing treatment as noted by: <ul style="list-style-type: none"> HCP Patient (PRO) 	No PROs and/or no HCP-reported reasons for switching and/or discontinuing treatment
Study design	All study designs that include real-world data, observational and interventional studies (prospective/retrospective)	<ul style="list-style-type: none"> RCTs Editorials Guidelines Case reports Reviews/meta-analyses
Language	English	All other languages
Time period	<ul style="list-style-type: none"> Publication date from Jan 1st, 2013 to present (October 25th, 2018) Conference abstracts: from 2016 to present* 	<ul style="list-style-type: none"> Publications before 2013 Conference abstracts before 2016
Geographic scope	<ul style="list-style-type: none"> Europe North America 	Continents other than Europe or North America

Note: *Only most recent conference searched.

Abbreviations: HCP, healthcare professional; IA, inflammatory arthritis; PRO, patient-reported outcome; RCT, randomised controlled trial; UC, ulcerative colitis.

exclusion listed (eg, not meeting the criteria for Population, Intervention, Outcomes, etc.) as shown in [Figure 1](#). To restrict the scope to biologics and biosimilars with similar formulation and dosage, the literature search was limited to European and North American studies. The search was restricted to studies published in English.

Study Screening and Data Extraction

Publications identified from the Ovid and conference database searches were entered in an abstract screening sheet following the removal of duplicates using EndNote X8.2. This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹⁴ Where several publications reported results for the same patient population, the publication reporting the most information on patient population and/or outcomes of interest was included.

We developed a data extraction file containing information obtained from the identified publications, including underlying studies, patient populations, treatment switch types, and outcomes of interest. Data on the reported switches were extracted and sorted in terms of first, second,

and (if applicable) third biologic in a given sequence, including data on whether the biologic was a biosimilar or originator product. To describe the patient experience and reasons for switching treatments, we extracted data on three outcomes: (1) Patient-reported data directly describing the experience of a switch; (2) Patient-reported data indirectly describing the experience of a switch (ie, patient-reported outcomes (PROs) reported before and/or after a treatment switch); and (3) Investigator-reported data on the reason for switch/discontinuation. A full list of data extraction variables can be found in [Supplementary Table 4](#).

Risk of Bias Assessment

The risk of bias of the included publications was assessed using the Newcastle–Ottawa scale (NOS) for cohort studies.¹⁵ Typically, risk of bias is not assessed for conference abstracts due to the limited amount of information; however, these were nonetheless included since the majority of publications were only available in abstract format. In addition, minor modifications were made to the assessment template to maintain relevance for the included studies and the primary objective of the current review, as shown in

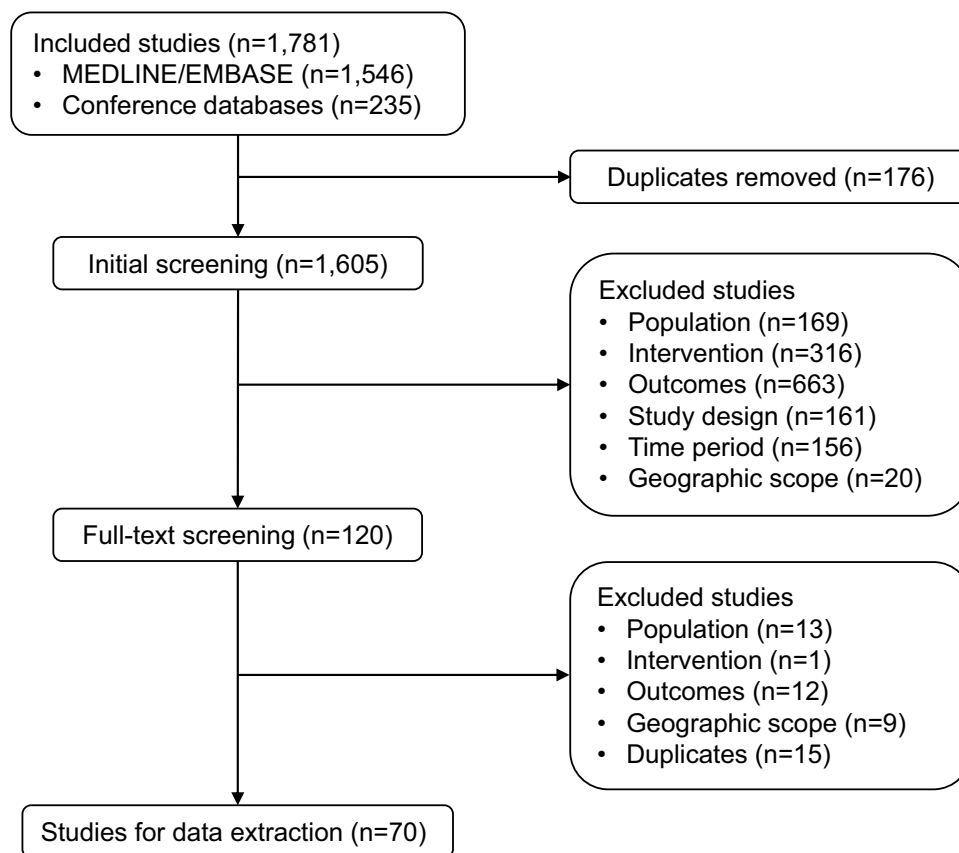


Figure 1 PRISMA study selection flowchart.

[Supplementary Table 5](#). Categories “Selection of the non-exposed cohort”, “Demonstration that outcome of interest was not present at start of study”, and “Was follow-up long enough for outcomes to occur?” were all set as not applicable (NA). Consequently, the minimum score for any publication was 0 (indicating a high risk of bias), while the maximum possible score was 6 (indicating a low risk of bias). It is also worth noting that all studies relevant to the primary objective of the current review were necessarily designed as self-assessment or self-reported studies; hence, all of them received 0 points in the “Assessment of outcome” category. Owing to the large proportion of conference abstracts with insufficient information, as well as to the built-in low score in the NOS for studies utilizing a self-reported approach when measuring outcomes, we decided not to exclude any studies from the current review based on their risk of bias assessment score.

Results

Identified Studies

In total, the Ovid and conference database searches generated 1781 hits. [Figure 1](#) illustrates the selection process through a PRISMA flow chart. Following title/abstract (initial) screening and full-text screening, 70 studies were selected for inclusion.

Study Characteristics

Of the 70 included studies, 19 were full-text articles,^{7,16–33} while 51 were conference abstracts.^{34–84} Study characteristics are described in [Supplementary Table 6](#). 28 studies were performed in patients with IA;^{18,19,26–28,30–36,47,49–51,55–57,59–63,67,79,80,83} 25 in patients with RA,^{7,16,17,23,24,37,39,40,42–45,53,54,58,66,68,70,73–78,84} 5 in patients with AS;^{21,25,46,48,65} 4 in patients with PsA;^{41,64,71,81} 4 in patients with UC;^{22,69,72,82} 2 in patients with IBD (with results reported separately for UC),^{38,52} and one in patients with SpA.²⁹ Most studies were retrospective (n=37), while 28 were prospective and one was cross-sectional. Four studies did not report the study design. A majority of studies were from various countries in Europe (n=61), while nine studies were from North America (including Canada, Mexico, and USA).

Patient Characteristics

In studies investigating IA patient populations, the years of data collection ranged between 2000 and 2018, with a mean number of patients of 494 (range: 27–9139) and an average maximum follow-up time of 31.3 months (range: 6–200). On

average, 70% of patients were female, mean age was 53.5 years (range: 27–68), and mean disease duration was 11.1 years (range: 4.3–19.2).

In the studies including patients with UC, the years of data collection ranged between 2009 and 2016, with a mean of 126 patients (range: 27–321) and an average maximum follow-up time of 21.2 months (range: 12–26). On average, 47% of study participants were female, mean age was 45 years (range: 44–46), and mean disease duration was 10.6 years.

Reported Switches

All studies included in this review reported the flow of patients between biologic treatments. Of the included studies investigating PROs and/or reasons for treatment switching and/or discontinuation among patients with IA, 24 reported relevant outcomes for one treatment only; 23 studies included two treatments in the sequence; and 17 studies included three treatments.

For UC, four studies only included one treatment in the sequence, while two studies reported treatment sequences of two treatments. An overview of the treatment sequences and specific treatment types is shown in [Figure 2](#), in which the types of treatment in each part of the sequence are listed.

The most common treatment transition sequence was from a tumor necrosis factor inhibitor (TNFi) biologic (ie, adalimumab [Humira[®]], certolizumab pegol [Cimzia[®]], etanercept [Enbrel[®]], golimumab [Simponi[®]], or infliximab [Remicade[®]]) to a biosimilar (ie, Benepali/SB4[®] or Inflectra/Remsima/CT-P13[®]). Non-TNFi biologic treatments included abatacept, anakinra, rituximab, tocilizumab, ustekinumab, and vedolizumab, while non-TNFi non-biologic treatments comprised novel small molecule tofacitinib.

Of the 17 studies including three treatments in the sequence, 12 report patients switching back from the second treatment to the first treatment of the sequence (so-called “back-switches”). Among these 12 studies, the “back-switch” proportion ranged from 1% to 26% of patients, where the most common type of switch was from the biosimilar Benepali/SB4[®] to the originator Enbrel[®] (7 of 12 studies).

Directly Reported Patient Experience of Switching

Four studies on patients with IA presented direct, patient-reported data on patient experience of switching treatment.^{27,36,57,77} All four studies deployed a ranking

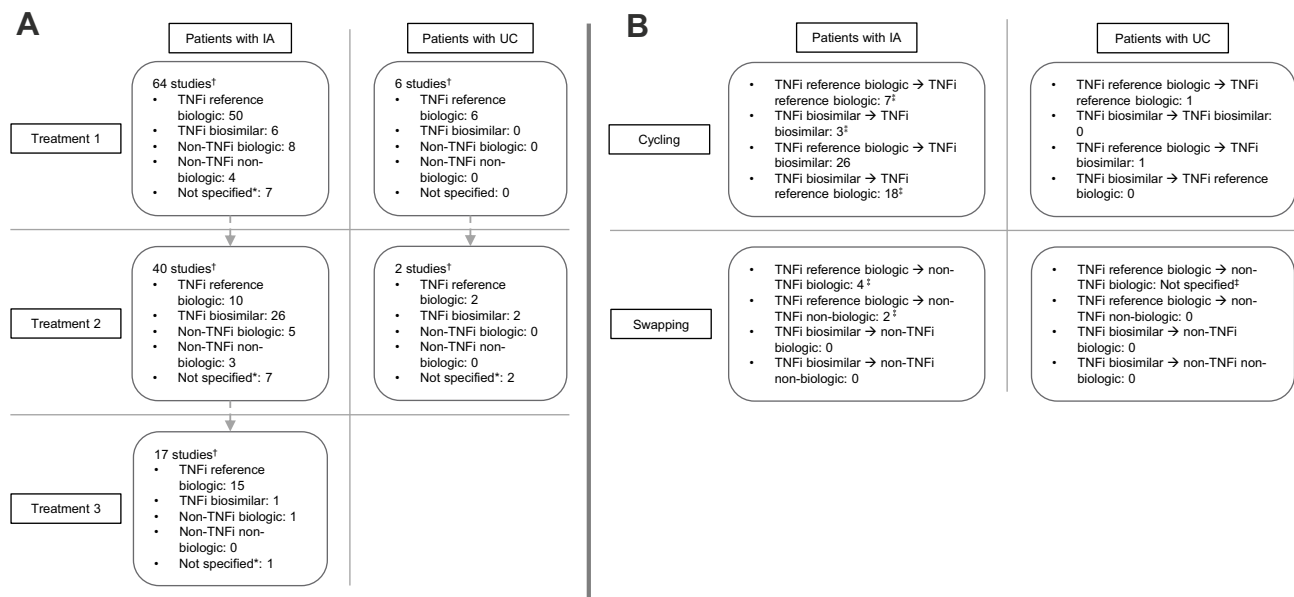


Figure 2 Treatment sequences of included studies. **(A):** Distribution of treatment types by position in treatment sequence in patients with IA and UC, respectively. **(B):** The number of studies reporting treatment transitions in patients with IA and UC, respectively.

Notes: [†]Some studies include more than one treatment type for each part of the sequence; hence, at each part of the sequence, the number of treatment types is greater than the number of studies. ^{*}Includes “Biologic therapy”, “TNFi”, and “bDMARD”. [‡]Includes treatment switching between first and second treatment, and between second and third treatment, in the sequence, respectively. [‡]Second treatment type stated as “biologic therapy” only.

Abbreviations: bDMARD, biological disease-modifying antirheumatic drug; IA, inflammatory arthritis; TNFi, tumor necrosis factor inhibitor; UC, ulcerative colitis.

tool, the results of which are summarized in Table 2. While the ranking categories used differed between studies, the majority of patients reported a neutral or positive switching experience across studies. In addition to the experience of switching, Scherlinger et al (2018) also

report that 15% of patients felt pressured to accept the switch;²⁷ however, it is not reported how this subset of patients eventually experienced the actual switch. No study on patients with UC presented data on patient experience from switching.

Table 2 Patient Experience of Switching

Author, Year	Switch	Patients (n)	Indication	Country	Patient-Reported Switching Experience				
					Excellent	Very good	Satisfactory	Poor	Very poor
Attipoe 2018 ³⁶	ETA biologic → ETA biosimilar	107	AS: 11% PsA: 16% RA: 68%	UK					
					45%		44%	9%	
Scherlinger 2018 ²⁷	Enbrel → SB4	52*	RA: 38% SpA (incl AS, PsA, and SAPHO): 62%	France	Good				
					86%				
Shah 2018 ⁷⁷	ETA biologic → ETA biosimilar	155	RA	UK	Pleased	Indifferent	Not sure	Not pleased	No answer
					43%	7%	8%	23%	18%
Hoque 2018 ⁵⁷	ETA biologic → ETA biosimilar	94	RA/PsA/SpA	UK	No problem with switch				
					62%				

Note: *44 patients switched treatment from Enbrel to SB4.

Abbreviations: AS, ankylosing spondylitis; ETA, etanercept; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SAPHO, synovitis-acne-pustulosis-hyperostosis-osteitis syndrome; SpA, spondyloarthritis; UK, United Kingdom.

Indirectly Reported Patient Experience of Switching

Among the studies including patients with IA, 21 studies included some form of PRO,^{18,20,21,23,24,27,29–31,36,48,49,54,57,59,65,75,77,78,80,84} of which 10 studies reported PROs prior to the switch only and therefore did not provide any information on the patient experience of switching treatment.^{20,21,23,24,29–31,49,59,78} The PRO measurement tools used are summarized in [Figure 3](#). The most commonly used tool was the Health Assessment Questionnaire (HAQ) (12 studies),^{18,20,23,24,31,48,49,54,65,75,77,84} while the least common measurement methods were Routine Assessment of Patient Index Data 3 (RAPID3) and Treatment Satisfaction Questionnaire for Medication (TSQM), each of which were used in one study only.⁴⁸ No study on patients with UC presented data on PROs before or after treatment switch.

Among the studies reporting PROs before and after treatment switch, Forejtova 2017 reported a decrease in post-switch HAQ scores compared to pre-switch (baseline) scores,⁴⁸ while Haugeberg 2018 reported a slight increase;⁵⁴ none of the changes in HAQ were statistically significant. Glintborg 2017, meanwhile, reported an unchanged mean HAQ score over time.¹⁸ Similarly, a post-switch visual analogue scale (VAS) score increase was reported by Haugeberg 2018,⁵⁴ while Forejtova 2017 reported a decrease.⁴⁸ Overall, patient global assessment (PGA) scores were mostly stable as reported by Glintborg 2017 and Valido 2018,^{18,80} although a slight increase was observed for patients with PsA in the former

study. Zengin 2018 reported a statistically significant decrease in mean PGA score at week 60 compared to baseline.⁸⁴

Investigator-Reported Reason for Switching

Investigator-reported reasons for patients switching were reported in 20 studies; 19 of these included patients with IA, while one included patients with UC. Reasons for treatment discontinuation were provided in 46 studies, 40 of which were performed in IA patient populations while the remaining six included patients with UC. The results from these studies are summarized in [Table 3](#). Overall, the most common reason for switching or discontinuing treatment was loss of efficacy, while the least common reason was patient preference. Of the four studies listed in [Table 2](#) reporting direct patient experience of switching treatment, two reported reasons for switching back to the originator biologic from the etanercept biosimilar; in both of these, the most common reason was adverse events.^{27,77} These two studies are included in [Table 3](#).

Risk of Bias Assessment

The detailed results of the risk of bias assessment are provided as a supplementary spreadsheet ([Supplementary Table 7](#)). An overview of the scores is shown in [Figure 4](#).

The scores for the included full-text publications ranged between 3 and 6; publications scoring 0, 1, or 2 – indicating high risk of bias – were all conference abstracts, for which the limited amount of information resulted in a reduced score. Among the four publications reporting patient experience with switching, two publications received a score of 2;^{36,57} one

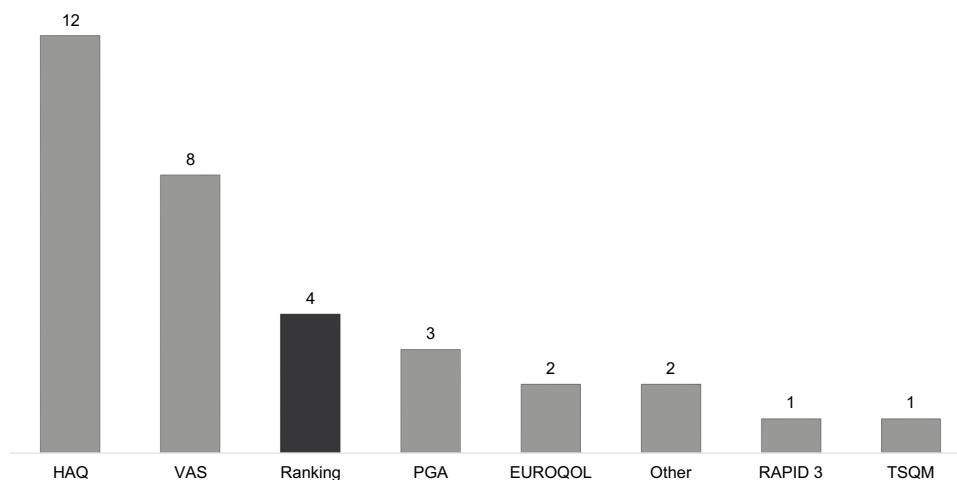


Figure 3 Patient-reported outcome measurement tools used. The number above each bar denotes the number of studies using each particular PRO measurement tool. The four studies reporting patient experience of switching treatment ("Ranking" bar) are highlighted in dark grey.

Abbreviations: HAQ, Health Assessment Questionnaire; VAS, Visual Analogue Scale; PGA, Patient Global Assessment; RAPID3, Routine Assessment of Patient Index Data 3; TSQM, Treatment Satisfaction Questionnaire for Medication.

Table 3 Reasons for Switching and/or Discontinuing Biologic Originator or Biosimilar Treatment

	Adverse Events	Loss of Efficacy	Remission	Patient Preference	Other
Reason for Switching Treatment					
Unweighted mean	23%	52%	N/A	14%	34%
Median	22%	53%	N/A	7%	34%
Range	2–63%	2.5–98%	N/A	1.9–44%	5–67%
Reason for Discontinuing Treatment*					
Unweighted mean	25%	48%	10%	10%	18%
Median	23%	50%	4%	9%	15%
Range	4.4–77%	6.3–92%	0–52%	4–16%	2–55%

Note: *These data may or may not include patients switching treatment; not always evident from the reported information.

Abbreviation: N/A, not applicable.

a score of 3,²⁷ and one a score of 4 points,⁷⁷ respectively; however, it is worth noting that, with the exception of Scherlinger 2018,²⁷ all were conference abstracts.

No publications were excluded as a result of the risk of bias assessment; this is due to the relatively large number of conference abstracts, indicating that the low scores found for some publications are likely to be due to missing information rather than true methodological or reporting flaws.

Discussion

This study systematically reviewed the literature on the patient experience of switching biologic treatment in IA

and UC. One of the main findings is that patient perspective on switching is poorly understood, with only four studies explicitly reporting patients' direct experience of switching. These four studies utilize a ranking exercise with slightly varying categories to assess the switching experience among the patient population. However, the scales used are not standardized and the number of categories differ between studies – Scherlinger et al (2018)²⁷ and Hoque et al (2018)⁵⁷ in particular only report the proportion of patients in the “Good” and “No problem with switch” category, respectively. The relatively sparse information provided is likely related to the fact that of

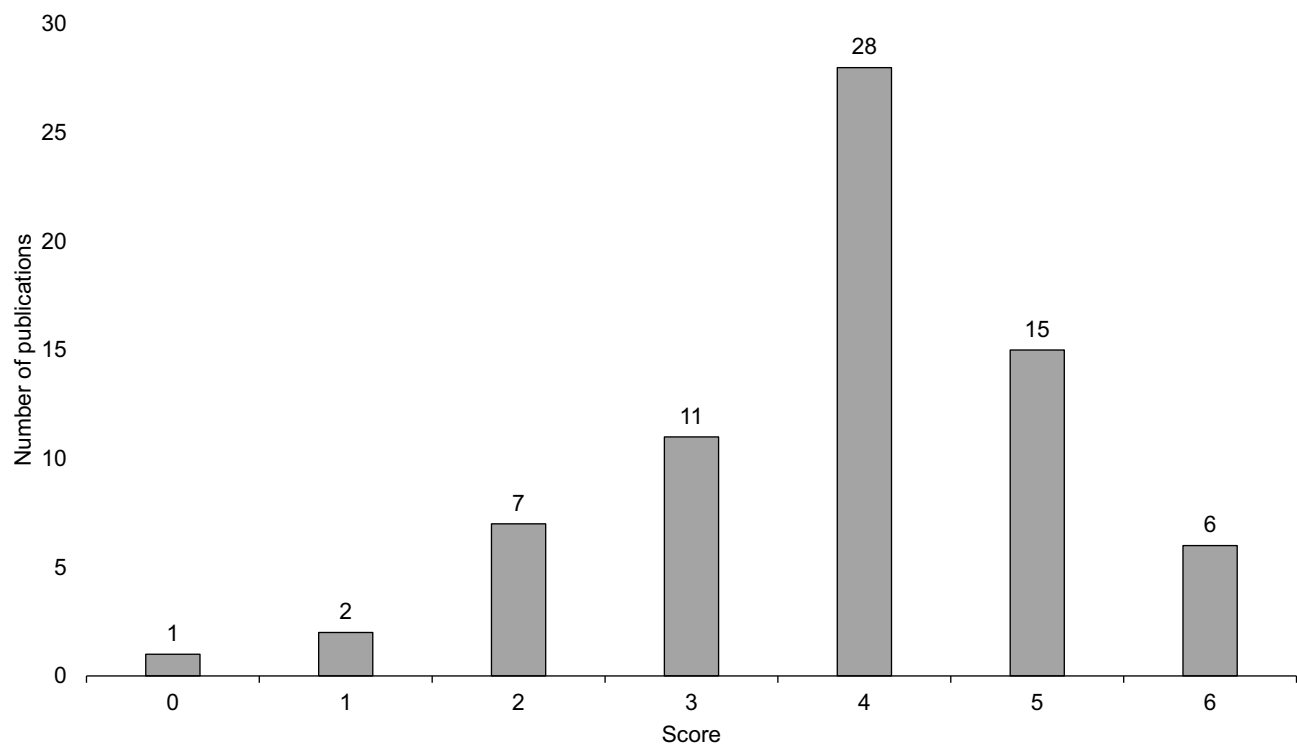


Figure 4 Risk of bias assessment scores. The number shown above each bar denotes the number of publications receiving a particular score.

these four publications, Scherlinger et al (2018)²⁷ was a full-text article while the remaining three were conference abstracts. Given the limited amount of available data regarding patient experience of switching, as well as the diversity in measurement methods between the studies that do report this outcome, the current literature does not allow for a meaningful comparison across studies.

A number of publications include indirect information pertaining to the patient experience of switching by reporting PROs before and after a treatment switch. While it is impossible to isolate and quantify the potential direct impact of the treatment switch on observed changes in these PROs, it can be noted that the results were heterogeneous: A few studies reported no change, or an improvement, in HAQ, VAS, and PGA scores following the switch, while others showed the opposite. One possible reason for this heterogeneity may be differences in follow-up time, which was reported in some, but not all, publications.

A majority of the studies included in this review provided investigator-reported reasons for switching and/or discontinuing treatment. While these do not provide the same level of insight into the patient experience of switching as the studies reporting PROs do, they nonetheless serve to illustrate the more common reasons underlying changes in treatment. Notably, the least common reason for switching or discontinuing treatment was patient preference, which is in line with the finding that numerous studies included in this review state that the initial switch, in which patients cycle from originator to biosimilar products, was due to non-medical reasons and mandated by healthcare payers.^{18,31,32,43,44,49,50,54,55,62,80} This is in contrast to switching to a treatment with another MoA, which generally occurs due to medical reasons² and is less related to mandates issued by payers. In this context, it is of interest to note that an overall originator-to-biosimilar switching strategy has been recommended by several healthcare authorities^{3,85} and that this review found that the most commonly cited reason for switching back to the originator drug from biosimilar treatment was adverse events.^{27,77} This is in line with the observed association of treatment persistence with the effectiveness, safety, and patient satisfaction with treatment,^{8–10} maintaining patient persistence with the prescribed therapy is of interest from a payer perspective, as switching treatment has been associated with increased costs.^{5–7}

While the number of studies reporting patient experience of switching was low, they indicate that a majority of patients

have a positive or neutral switching experience. However, the reasons for the dissatisfaction reported among a minority of patients are not further explored.

The proportion of patients who switch back to their original treatment (“back-switch” proportion) ranged from a low 1%⁴³ to a quarter of the patients (26%).⁶³ Elucidating the reasons underlying this difference is of interest to promote an agreeable switching experience for the patients, thereby minimizing the risk of performing additional switches. This is of particular importance, not just from a cost perspective, but also since payer-mandated switches from originator to biosimilar treatments are being implemented by various healthcare authorities.^{3,85} Increased educational and informational efforts provided by healthcare professionals (HCP) prior to the treatment transition are doubtlessly important to increase patient satisfaction. This fact is highlighted by the finding reported by Attipoe et al, in which 21% of patients stated that their transition experience would have improved if having been given more information about the biosimilar treatment they were being switched to.³⁶ Furthermore, Al Tabaa et al conclude that the likelihood of patients transitioning to a biosimilar treatment was mainly related to the behavior of the physicians; and that, when using an open study design, a larger proportion of patients transitioning to a biosimilar treatment complained of lower efficiency and/or a worse safety profile.³⁴ Scherlinger et al also suggest that negative patient perceptions of biosimilars impact the persistence with biosimilar treatment, as shown by the lack of objective clinical disease activity among a large proportion of patients who requested to be transitioned back to the originator treatment.²⁶ Taken together, this points to the importance of considering a placebo effect when investigating patient satisfaction with treatment transition. While factors impacting patient experience of switching biologic treatment were not the primary objective of the current review, it remains an important area for future research. As the number of publications investigating patient-reported experiences continue to increase, the amount of data available will consequently allow for a statistically sound analysis to be conducted.

Furthermore, while several studies included information regarding the treatment history of patients (ie, naïve to, or experienced with, biologic treatment), none reported PROs related to switching experience by treatment line. As it is conceivable that previous experience with biologic treatment may have an impact on the experience of switching, stratifying analyses by treatment line should be an avenue of interest in future studies.

The use of treatment persistence as a proxy for efficacy and/or safety of the prescribed therapy is also highlighted by the finding that across the studies included in this review, loss of efficacy or adverse events were the most common reasons for switching or discontinuing treatment.

The current study has some limitations. Firstly, the number of conference abstracts compared to full-text articles is relatively large, which poses a restriction on the amount of available information for each study. Secondly, the limited data availability also meant that a meta-analysis was not feasible. As the four studies providing information regarding patient-reported experience of switching all used different ranking scales, this further hindered the possibility of performing a meta-analysis. The language restriction (English only) is also likely to have resulted in the exclusion of relevant studies; however, as the geographic scope was limited to Europe and North America, any studies performed in patient populations from other continents would have been excluded. It is also worth noting that the three studies by Glintborg et al all use the DANBIO registry and that the overlap of patients is therefore likely to be considerable.^{18,49,50} This is especially pertinent for the two conference abstracts, both of which focus on patients treated with etanercept. However, as the population size, patient baseline characteristics, and number of treatment switches differ between the two publications, both were included as it was not possible to discern the amount of overlap. Similarly, the two publications by DeCock et al^{43,44} investigate the same database and indication; however, since the reported variables available for extraction differed somewhat, the studies were considered to overlap and both were therefore included.

In summary, while patient experience and satisfaction are of great importance to achieve successful treatment outcomes, the current review of studies reporting patient experience of switching biologic and/or biosimilar treatment indicates that it is an area in need of further exploration. In addition, while ranking exercises may be an appropriate tool to investigate patient-reported experience of switching treatment, the research topic would benefit from the use of more standardized, or translatable, assessments to enable meta-analyses or easy comparison between studies.

Conclusion

This systematic literature review illustrates the current sparsity of information regarding patient-reported experience of switching biologic and/or biosimilar treatment in

IA and UC populations from real-world studies. Since patient preference and experience influence adherence and persistence with treatment, thereby affecting the clinical response, these factors should be considered in the treatment decision process. As the number of available treatments continue to increase, further research regarding patient preference and/or experience would benefit this therapeutic area.

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Disclosure

KL, JD, AS, and MD conducted this work as part of their employment with ICON plc. CMB and AP are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. The authors report no other conflicts of interest in this work.

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