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Current Opinion in
Pharmacology

Switching biologics used in inflammatory bowel diseases: how to deal with in practice?

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Inflammatory bowel disease patients do not all respond to biological treatment since several patients will initially respond but will lose response or develop side effects over time. In such cases, a switch from one biologic to another offers a valuable clinical solution. This requires to evaluate both patient and drug profiles in combination with the reason(s) for switching in order to adequately select the second-line biologic. Therapeutic drug monitoring is obviously a useful tool but is currently limited to the use of anti-TNF α . In this review paper, we provide overview and guidance on switching biologics in clinical practice, with the emphasis on the motivations for switching, the selection of the second-line biologic, as well as explanations on how and when to switch.

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Current Opinion in Pharmacology 2020, 55:82–89

This review comes from a themed issue on **Gastrointestinal**Edited by **Paul Declerck** and **Joanna Torres**<https://doi.org/10.1016/j.coph.2020.10.003>

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Introduction

Biologics represent a mainstay in the current therapeutic Inflammatory bowel diseases (IBD) armamentarium. They have revolutionized the management of IBD, especially when started early in the disease course, allowing to decrease IBD-related surgeries and complications [1,2]. Despite this growing therapeutic arsenal, IBD patients do not all respond to biologic since it is observed that some will respond initially, but will lose response or develop side effects over time. In these situations, a switch from one biologic to another is therefore required. Switching biologic is defined by the replacement of one biologic by another within the same class or outside the class of the previous biologic. In this latter situation, a switch out of class is called as a swap. Today, the switch also relates to

any change from the originator biologic ('reference' product) to its biosimilar, or to a conversion of the administration route (intravenous - subcutaneous) with the same biologic. In this review paper, we provide guidance by describing the reasons for switching as well as the practical aspects to carefully consider such as which second-line biologic to choose (sequential order, within or outside class), how to switch (premedication, with or without a concomitant immunomodulator) and when is the best timing to switch (wash-out period).

Reasons for switching in clinical practice

Primary non-response

Some patients do not experience any efficacy to the drug defining the primary non-response (PNR). Owing to differences in study designs (such as prospective or retrospective studies), endpoints (such as clinical or endoscopic response), and population characteristics (such as a refractory or a naïve population), there is not a unique definition of PNR and related rates are consequently variable in the literature. Table 1 describes rates of PNR reported by recent real-life studies. Different mechanisms have been suggested to explain this absence of efficacy [3]. One explanation could be that the main inflammatory pathway driving the overall inflammation is not targeted by the biologic. Up to now, very few biomarkers can help the clinician to assume which one is the main driver one for a patient. An interesting study demonstrated that treatment-naïve IBD patients who developed severe disease with primary non-response to anti-TNF α expressed higher oncostatin M protein than patients who responded to anti-TNF α [4]. Oncostatin M may therefore be a predictive marker of PNR and anti-TNF α resistance and paves the way to find new biomarkers which could guide the clinician in choosing the right biologic for the right patient. An insufficient exposure to the biologic represents another explanation. In addition, factors related to the patient (such as smoking, obesity, genetic predisposition) or factors related to the disease (such as longstanding disease or upper gastrointestinal involvement) may also contribute to this absence of efficacy [3].

Secondary loss of response

Apart from PNR, some patients with an initial response and/or remission develop a secondary loss of response (LOR) over time. In a same extent, it remains difficult to provide precise rates of LOR which are variable and

Table 1

Rates of primary non-response and loss of response for biologics used in IBD in real life studies.

Biologic	Crohn's disease	Ulcerative colitis	Timing for assessing PNR
Infliximab	PNR: 20% [56**] LOR: 15% PYF [29]	PNR: 20% [3] LOR: 20% PYF [57]	Week 14
Adalimumab	PNR: 25% [56**] LOR: 20% PYF [30]	PNR: 30% [3] LOR: 20% PYF [58]	Week 14
Golimumab	---	PNR: 34% [59] LOR: 23% PYF [59]	Week 14
Vedolizumab	PNR: 10–35–35% [46,60,61] LOR: 48 % PYF [28]	PNR: 10–35% [46,60,61] LOR: 40 % PYF [28]	Week 14 ^a
Ustekinumab	PNR: 5–24% [15,43] LOR: 8–27% PYF [15,43]	---	Week 12

PNR: Primary non response; LOR: Loss of response; PYF: patient-year of follow-up.

^a Due to its delayed therapeutic efficacy, there is no consensus on when to assess vedolizumab PNR.

broadly distributed (Table 1). With regards to anti-TNF α , pharmacokinetics can partly explain LOR through three different mechanisms (Table 2) [5]. Immunogenicity is a key driver of LOR for anti-TNF α but less involved for ustekinumab and vedolizumab, two drugs inducing infrequently an immunogenicity. For these latter ones, further studies are required to better investigate the exact mechanisms underlying this loss of efficacy. Otherwise, it has been suggested that chronic blocking of the TNF α pathway could promote the activation of other inflammatory pathways [6]. This mechanism, called immune shift, could also elicit LOR, whatever the biologic.

Adverse events

Adverse events (AEs) may occur in the same extent than any other drug. Their description and management have been the most largely documented for anti-TNF α [7,8]. Accumulating data on safety are progressively available for ustekinumab [9] and vedolizumab [10].

AEs can be specific to the biologic or related to the biological class. For instance, paradoxical psoriasis induced by anti-TNF α is a well-known class side effect with a risk of recurrence in half of patients when using another anti-TNF α [11]. On the other hand, acute infusion reactions, mainly due to specific antibody against the drug, are drug specific side effects rather than class-related. Finally, adverse events such as infections [12] or malignancy [13] may be the consequence of an overall immunosuppression and are considered as

Table 2

Clinical algorithm for managing a loss of response to anti-TNF α based on reactive therapeutic drug monitoring.

Mechanism	Pharmacokinetic Measurements ^a	Therapeutic options
Mechanistic failure	IFX TL > 5 μ g/mL ADA TL > 7.5 μ g/mL No interest to measure ADABs	Switch out of class
Non immune-mediated failure	IFX TL < 5 μ g/mL ADABs to IFX < 9 μ g/mL ADA TL < 7.5 μ g/mL ADABs to ADA < 4 μ g/mL	Optimize then switch within class (or out of class)
Immune-mediated failure	IFX TL < 5 μ g/mL ADABs to IFX > 9 μ g/mL ADA TL < 7.5 μ g/mL ADABs to ADA > 4 μ g/mL	Optimize (in case of low ADABs level) then Switch within class (or out of class)

TLs = Trough levels, ADA = Adalimumab, IFX = Infliximab, ADABs = antibodies against drug.

^a TLs and ADABs Cut-offs based on Vande Casteele N, Herfarth H, Katz J, Falck-Ytter Y, Singh S. American Gastroenterological Association Institute Technical Review on the Role of Therapeutic Drug Monitoring in the Management of Inflammatory Bowel Diseases. *Gastroenterology*. 2017;153(3):835–57 e6.

immunosuppression-related side effect. Besides, serious infections remain a common but important issue to consider when treating patients with biologics. A recent meta-analysis highlighted that anti-TNF α agents significantly increased the risk of serious infection compared with immunomodulators. Of note, further studies are urgently requested to compare safety of anti-TNF α agents with ustekinumab and vedolizumab [8].

While the rate of anti-TNF α discontinuation due to AE was 11 % over a six-year follow-up in a large prospective registry [14], vedolizumab had to be discontinued only in a minority of cases that is 3.6% and 0.4% of patients for serious infections and arthralgias, respectively in a large study although with a different design [10]. Likewise, in real-life cohort on ustekinumab, 3.6% of CD patients stopped treatment due to AE, mainly for severe arthralgia [15].

Switching to biosimilars

A change from an originator drug to its biosimilar represents a switch to some extent. The key driver for switching to a biosimilar is to improve the financial sustainability of health care system by delivering significant cost savings and investments for IBD management [16]. To support this kind of switch, NOR SWITCH trial was a pivotal

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study demonstrating the non-inferiority of CT-P13 infliximab biosimilar across six diseases including IBD [17^{**}]. Nonetheless, this key study was unpowered to demonstrate non-inferiority within each disease group which may explain that the subgroup analysis of Crohn's disease displayed a close to significant difference in favour of the originator infliximab. Since NORSWITCH publication, several cohorts fully dedicated to IBD patients confirmed comparable efficacy and safety of infliximab biosimilars. Regarding the CT-P13 infliximab biosimilar, a large prospective cohort including 155 switched patients did not report safety signals nor lower effectiveness after 12 months of follow-up [18]. Despite a smaller cohort, the SPOSIB study also reported comparable results for SB2, another infliximab biosimilar. More interestingly, this cohort described reassuring data among a subgroup of patients experiencing multiple switches, meaning a switch from originator infliximab to CT-P13 to SB2 [19]. This observation is not strong enough to change recommendations against multiple switches [20] but represents first data supporting this practice. With regards to pharmacokinetic parameters, both drug serum concentrations and concentrations of anti-drug antibodies were non-impacted by switch [21].

More recently, biosimilars of adalimumab came on the market with a confirmed bioequivalence [22]. However, further data are required to guide the clinician on an appropriate use of adalimumab biosimilars in the clinical practice [23].

Switching the mode of administration

The subcutaneous route often represents an attractive alternative to more invasive and time-consuming intravenous infusions for numerous patients. Switching from intravenous infliximab to subcutaneous adalimumab were described in the past to answer this patient convenience. However, a prospective randomised trial has demonstrated that this kind of switch was associated with loss of response and impairment of anti-TNF α tolerance [24]. For now, adalimumab, ustekinumab and golimumab offer this possibility as opposed to infliximab and vedolizumab. Recent studies confirmed the comparable clinical efficacy and safety of subcutaneous formulation for both vedolizumab and infliximab [25,26^{*}]. Regarding the switch of administration route, a randomized trial including 131 IBD patients compared the efficacy and safety of infliximab between patients treated with intravenous infliximab 5 mg/kg every 8 weeks and patients treated with subcutaneous infliximab 120 mg (<80 kg) or 240 mg ($\geq$ 80 kg) every two weeks. One year after switching, both efficacy and safety of infliximab were unaffected [27]. In a near future, this novel formulation would facilitate and broaden access to these convenient therapies for IBD patients as this specific case of switch seem safe and efficient.

Practical aspects for switching

Before switching, it is important to consider optimizing the current biologic to avoid a premature exhaustion of therapeutic alternatives. Hence, a LOR can be overcome with dose and/or interval optimization [28–30] and/or addition of an immunomodulator (IMM) [31–33] while taking into account potential side effects and contraindications. Overall, clinicians need to evaluate the risk-benefit ratio of optimizing a treatment versus switching to another treatment on a case by case basis.

Which biologic to choose

The best option for switching depends on many criteria (Figure 1) which cannot be extensively covered in this review [34,35]. More specifically related to the switch are the following questions: Does the reason for switching influence the choice of the next biologic? Is the choice of the second-line or third-line biologic is based on the use of previous biologic(s)?

Patient and drug profiles

The choice for the new biologic has to consider factors related to the drug, namely the drug profile, and factors related to the patient, namely the patient profile. Drug profile includes mechanism and speed of action, administration route and frequency, specific therapeutic indications (such as perianal disease or acute severe ulcerative colitis), and, cost and reimbursement conditions. Age, co-morbidities, IBD type and subtype (according to the Montreal classification), presence of extra-intestinal manifestations and concomitant inflammatory immune-mediated diseases, specific situations (such as pregnancy willingness) represent the patient profile.

The reason for switching influences the choice of the next biologic

When attempts to overcome LOR or PNR have failed [28–31], the switch may be required and relies on several aspects. Regarding use of anti-TNF α , therapeutic drug monitoring (TDM) is an important feature for the management of PNR or LOR [5,36]. An algorithm based of TDM might guide the clinician to explore the underlying mechanism (Table 3). Hence, in case of mechanistic failure, a swap is recommended by choosing a biologic with another mode of action such as vedolizumab or ustekinumab. In case of both immune-mediated and non-immune-mediated pharmacokinetic failures, after an appropriate optimization, either a switch within class or a swap could be adopted by considering patient and drug profiles. Of note, this current algorithm is based on a reactive approach and fails to manage all clinical situations. Evidence supporting this approach originates from prospective studies showing an association between pharmacokinetics measurements and outcomes [5,37] but validation in well-designed clinical trials is still missing. Likewise, this TDM approach is so far not recommended for ustekinumab and vedolizumab. Evidence supporting

Figure 1

Overview of aspects to consider for switching.

Table 3

Summary of half-life and wash-out for biologics used in IBD.

Biologic	Route	Half-life ^a	Wash-out ^b
Infliximab	IV	8–12 days	4 weeks
Adalimumab	SC	10–20 days	5 weeks
Golimumab	SC	12 days	5 weeks
Vedolizumab	IV	25 days	11 weeks
Ustekinumab	IV then SC	19 days	8 weeks

IV: intravenous, SC: subcutaneous.

World Health Organization. Multisource (generic) pharmaceutical products: Guidelines on registration requirements to establish interchangeability. Working document QAS/04.093/Rev.4 (2005). www.who.int/medicines/services/expertcommittees/pharmprep/QAS04_093Rev4_final.pdf.

^a Ref. [47].

^b Wash-out period is arbitrarily based on threefold to fivefold the biologic half-life but there is no clear consensus. Wash-out periods here listed are calculated on threefold biologic half-life.

the use of TDM in clinical practice is still limited for both of them [37], and a switch within class is for now impossible as vedolizumab and ustekinumab are unique by their mode of action although new biologics targeting common pathways will arrive soon [38].

When the decision to switch is related to the development of an adverse event, the identification of class-related, drug-related or immunosuppression-related side effect may help guide the decision to choose the therapeutic alternative. By considering both patient and drug profiles, a drug-related side effect may offer the clinician to switch to any another biologic, whether within or out of class, whereas a class-related side effect should incite the clinician to swap. Regarding immunosuppression-related side effects, ustekinumab or vedolizumab represent for now the most suitable alternatives due to their mode of action [13*,39*].

The choice of the second-line or third-line biologic is based on the use of the previous biologic(s)

Historically, patients were treated with infliximab or adalimumab because of commercial availability. Up until now, the majority of the literature is still based on patients exposed to anti-TNFα as first-line. It is well described that these patients previously exposed to anti-TNFα generally do not respond as well to the following second-line biologics (within class or out of class) as do biologic-naïve patients [15,40–43]. In a network

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meta-analysis evaluating the efficacy of biologics in anti-TNF α exposed CD patients, some evidence supported the use of ustekinumab for induction of clinical remission [44^{*}]. In UC patients with prior anti-TNF α exposure, tofacitinib, a small molecule, was ranked highest for inducing remission while vedolizumab was ranked second (of note, ustekinumab was not yet available for UC patients) [45^{*}]. Real-life data on efficacy of second-line biologic among patients primarily exposed to ustekinumab or vedolizumab are not yet available. These further data are eagerly waited to offer more information on influence of sequential use of biologics.

Interestingly, the reason for stopping the first biologic could have an impact on the efficacy of the second-line biologic. Recent data reported a higher likelihood of efficacy in case of switch for other reasons than LOR [40,42]. However, data are still conflicting with other ones showing no association between treatment outcomes and the clinical mechanism of failure of the first biologic (failure versus intolerance) [46]. Further data are required to evaluate the efficacy of a biologic according to its use in first, second, or even third line while considering the reason for stopping the previously used biologic(s).

For now, the practical message to keep in mind is that the efficacy of a biologic would probably be lower when used in second-line and third-line than in biological naïve populations. Nevertheless, in case of switch for another reason than biological failure, the clinician may expect similar efficacy of the biologics whether used in first or second line.

How and when to switch

Once the switch and the biologic have been decided, the following questions to be solved are: When to start the new biologic? Is combined treatment with an IMM indicated? Should we prescribe a premedication?

Best time to switch

PNR, LOR or occurrence of adverse events often require a rapid therapeutic intervention. The wash-out period is the time interval between the discontinuation of one biologic and the initiation of a second one. Very few data have been published on its relevance in clinical practice. The wash-out period is for now arbitrarily calculated on basis of threefold to fivefold the biologic half-life [47] but there is no clear consensus. We here report calculated wash-out periods in Table 3. In theory, shortening the wash-out period between two biologics could affect the pharmacokinetics of the second one, and may subsequently affect its efficacy and safety. On the contrary, increasing the wash-out period could have a deleterious impact on the disease evolution. Two studies have reported that direct switch or shorter wash-out periods had no impact on the efficacy of the second biologic [48,49] but safety concerns have been pinpointed

regarding possible higher rate of infections [48]. In the absence of robust recommendations, both direct switch or wash-out observance are valid options depending on the need for a rapid therapeutic intervention and the risk-benefit balance. Overall, the clinician has to be aware of possible safety issues in case of direct switch.

Adjunction of an immunomodulator

Azathioprine, mercaptopurine and methotrexate are IMM largely used in IBD field. Beside their use in monotherapy, these drugs may both synergistically improve the efficacy of anti-TNF α agents and reduce their immunogenicity. Whatever infliximab or adalimumab (although there is some persisting debate about adalimumab [50]), guidelines recommend to start these biologics on combotherapy for the management of CD [34]. Likewise, a combotherapy infliximab-azathioprine is recommended for the management of UC [35]. No combotherapy recommendation exists regarding golimumab and adalimumab in UC due to the absence of randomised controlled trials [35,51]. Regarding vedolizumab and ustekinumab, accumulating data confirm that adjunction of an IMM does influence neither efficacy nor pharmacokinetics data [51,52].

Premedication

Premedication is related to the use of anti-histaminic and/or steroids drugs administrated before intravenous administration of biologic to reduce the risk of infusion reactions. Premedication has been largely used for infliximab for which the risk of infusion reactions is 5–25% [53]. However, a recent meta-analysis showed no evidence related to this practice [53]. In case of switch to infliximab, instead of premedication, combining infliximab with an IMM is clearly more efficient for reducing the risk of infusion reactions [51]. Regarding ustekinumab, a recent study showed that only 0.8–3% of patients had reactions to the intravenous infusion with no impact on the following subcutaneous injections [54]. In GEMINI studies, infusion reactions occurred in $\leq 5\%$ of patients receiving vedolizumab and rarely resulted in treatment discontinuation [55]. Consequently, in case of switch to vedolizumab or ustekinumab, premedication is not recommended.

Conclusions

The growing therapeutic arsenal opens the way towards new switching possibilities that may be tailored to each patient. There is a move from a restricted situation where the switch was uniquely driven by drug availability to a situation where the switch relies on specific clinical motivations. To guide readers through these different options, we have discussed the ‘why, how and when’ to switch. In particular, the reasons for switching and the previous exposure(s) to biologics might influence on the choice of the following ones. Then, the patient and drug profiles have also to be considered. Finally, a better

understanding of the mechanisms of PNR and LOR, as well as the pharmacokinetics of biologics will definitely help clinicians in the art of switching.

Conflict of interest statement

C. Liefverinckx is supported by FNRS (Belgian National Fund of Scientific Research) and received grants from Fonds Erasme (Erasmus hospital, Belgium). She received honoraria fees for lectures or consultancy from Abbvie, Janssen, Takeda and Sandoz.

A. Cremer is supported by Fonds Erasme (Erasmus hospital, Belgium) and received honoraria fees for lectures or consultancy from Abbvie, Janssen, Takeda and Pfizer.

D. Franchimont is research director of FNRS (Belgian National Fund of Scientific Research), and has received educational grants from Abbvie, Takeda, MSD, and has received honoraria fees for lectures or consultancy from Ferring, Falk, Chiesi, Abbvie, MSD, Centocor, Pfizer, Amgen, Janssen, Mundipharma, Takeda and Hospira.

CRedit authorship contribution statement

Claire Liefverinckx: Conceptualization, Writing - original draft. **Anneline Cremer**: Writing - review & editing. **Denis Franchimont**: Writing - review & editing, Supervision.

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