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Review Article

Enhancing treatment success in inflammatory bowel disease: Optimising the use of anti-TNF agents and utilising their biosimilars in clinical practice

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ABSTRACT

Anti-tumour necrosis factor (TNF) agents such as infliximab and adalimumab have greatly altered the treatment landscape in inflammatory bowel disease (IBD). However, there are remaining unmet needs and opportunities to optimise their use. Recent data suggest that proactive therapeutic drug monitoring may lead to more efficient usage of these agents, with potential for higher rates of corticosteroid-free clinical remission than with reactive monitoring. Expanded application of faecal calprotectin measurements may also be valuable, given the ease of use of the assay and its proven effectiveness as a diagnostic tool and predictor of relapse risk. From a practical viewpoint, improved multidisciplinary working may be essential to optimise patient care, with IBD nurse specialists playing an increasingly central role within this model. Finally, the availability of biosimilars of the anti-TNF agents allow drug costs to be reduced without compromising safety or efficacy – thereby providing opportunities to improve accessibility. Alongside extensive data on originator to biosimilar infliximab switch, new studies are beginning to demonstrate the safety of biosimilar to biosimilar switch, as well as adalimumab biosimilar transitions. The risk of a nocebo effect when switching to a biosimilar can be reduced through improved patient education and preparation.

1. Introduction

The worldwide incidence of inflammatory bowel disease (IBD) is rising [1], with more than a million people in the USA and around 2.5 million in Europe estimated to have the condition. Moreover, the prevalence is increasing rapidly in developing parts of Asia, South America and the Middle East [1]. The impact on patients and the associated costs on public healthcare systems and the wider economy create a substantial societal and disease burden.

The advent of biological therapies over the past two decades – in particular the anti-tumour necrosis factor (TNF) agents – has changed the management landscape of IBD [2]. These therapies have improved quality of life, decreased hospital admissions and reduced side effects from the use of corticosteroids and/or immunomodulators [2].

However, there are important issues with these treatments, not least in the risk of loss of response. This has been estimated at 13% and 20% per patient-year of follow-up with infliximab and adalimumab, respectively [3,4]. Treatment plan optimisation is therefore a key priority that may be improved through the use of novel strategies in monitoring and taking a multidisciplinary approach to management. Furthermore, increasing experience and confidence with biosimilars of originator biological molecules have created fresh potential to expand biosimilar drug use. In this review, we discuss key challenges and opportunities with anti-TNF agents in the biosimilar era.

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2. Optimising the use of anti-TNF agents in IBD

2.1. Therapeutic drug monitoring

Therapeutic drug monitoring (TDM) has an established role as a decision guidance tool following loss of response to an anti-TNF agent, and possibly also when considering de-escalation [5]. The association between serum drug levels and outcomes was first demonstrated with infliximab in 2006. A prospective study of 105 patients with moderate–severe Crohn's disease (CD) found that higher trough serum concentrations of infliximab correlated with significantly increased rates of clinical remission and endoscopic improvement [6]. Higher infliximab trough levels were also associated with mucosal healing in patients with CD [7]. Similar associations have been observed in ulcerative colitis (UC). For example, in a cohort study of 115 patients with moderate–severe disease, detectable trough serum levels of infliximab were predictive of clinical remission, endoscopic improvement, and reduced risk of colectomy [8].

Comparable associations have also been seen with another anti-TNF agent, adalimumab. Increased serum concentrations were linked with lower C-reactive protein levels and reduced endoscopic inflammation [9]. Furthermore, in an assessment of 168 CD patients, adalimumab trough concentrations of $>$ 0.33 μg/mL were a significant predictor of sustained clinical response [10].

More recently, the question was raised as to whether proactive TDM should be used in all patients initiating an anti-TNF agent as a means to optimise dose and improve clinical outcomes. The first study to assess this possibility with infliximab was a retrospective analysis of 48 IBD patients [11]. These individuals were found to have a significantly greater likelihood of remaining on infliximab than a control group of 78 patients who did not receive proactive TDM. The probability of remaining on infliximab was highest in patients with a trough level $>$ 5 μg/mL versus $<$ 5 μg/mL ($p < 0.0001$) [11].

Data were subsequently reported from a prospective, randomised trial of proactive infliximab TDM [12]. Patients with CD or UC who had stable responses to maintenance infliximab therapy first had their dose adjusted based on a prespecified algorithm to reach a target trough level of 3–7 μg/mL (the optimisation phase); they were then randomised 1:1 to receive continued infliximab dosing based on trough concentrations or infliximab dosing based on clinical features (the maintenance phase). In the optimisation phase, the targeting of infliximab trough levels resulted in more efficient use of the drug – in particular, increased remission rates in those who had their dose increased, and reduced drug costs in those who had their dose decreased. However, during the maintenance phase, continued trough level-based infliximab dosing was not superior to clinically based dosing with regard to remission rates at 1 year (although there were significantly fewer flares) [12]. Inadequate follow-up time may at least partially explain this negative result.

Meanwhile, in the prospective TAILORIX trial, biological-naive patients with active CD were initiated on infliximab and subsequently randomised at week 14 to infliximab dose increases based on a combination of symptoms, biomarkers and/or serum drug levels or based on symptoms alone [13]. There was no difference between the two groups in the primary endpoint of sustained corticosteroid-free clinical remission.

A subsequent meta-analysis based on nine studies in IBD (three randomised; six observational) found that neither proactive nor reactive infliximab TDM was associated with improved clinical remission rates versus empirical dose optimisation, although there was evidence of improved durability of response and cost benefits [14].

However, a recently reported prospective trial showed that proactive adalimumab TDM may lead to improved outcomes. In this study, 78 paediatric patients with CD and no prior exposure to biological agents, who had responded to adalimumab induction therapy, were randomised to receive proactive TDM (at weeks 4 and 8; then every 8 weeks thereafter) or reactive TDM after loss of response [15]. Rates of sustained corticosteroid-free clinical remission were significantly higher with proactive TDM than with reactive monitoring (82% vs 48%, respectively; $p = 0.002$) (Fig. 1). Moreover, the proactive monitoring group was significantly more likely to receive adalimumab intensification than the reactive group (87% vs 60%, respectively; $p = 0.001$) [15]. There were some limitations to this study, including that it was not blinded. Nonetheless, it marks an important milestone, being the first prospective, randomised, controlled trial to demonstrate improved outcomes with proactive TDM of an anti-TNF drug in patients with IBD [16].

Hence, overall, there are now data to suggest that proactive TDM can lead to more efficient use of anti-TNF agents and higher rates of corticosteroid-free clinical remission than reactive monitoring [12,14,15]. This has led some clinicians to advocate proactive assessment of anti-TNF concentrations in all patients after induction and at least once during maintenance [17]. However, data from large, blinded trials are still lacking, and the optimal scheduling of proactive TDM remains to be fully elucidated. In addition, it should be noted that when TDM is not available, the addition of an immunosuppressant after loss of response to anti-TNF monotherapy may result in treatment success [18].

2.2. Faecal calprotectin

Faecal calprotectin (FC) is an important marker of intestinal inflammation with potentially valuable roles in the diagnosis and management of IBD [5,19–21]. With regard to diagnosis, a meta-analysis of 30 studies showed that FC had high sensitivity and specificity for discriminating IBD from non-IBD diagnoses, including irritable bowel syndrome (IBS) [22]. Diagnostic precision was found to be better at a cut-off of 100 μg/g versus 50 μg/g [22]. In normal clinical practice, FC measurement may be particularly valuable when it averts the need for more invasive diagnostic techniques such as colonoscopy.

FC levels can also be used as a predictor of relapse risk. In a study of IBD patients in clinical remission, 12-month relapse rates were significantly higher in patients with an FC concentration $>$ 50 μg/g at the time of inclusion than in those with FC $<$ 50 μg/g ($p < 0.0001$) [23]. Furthermore, in a prospective analysis of adult UC patients in clinical remission under infliximab maintenance therapy, FC levels were already high (median $>$ 300 μg/g) up to 3 months in advance in those patients who went on to flare [24]. Two consecutive FC levels of $>$ 300 μg/g measured 1 month apart were found to be the best predictor of flare. By contrast, FC levels typically remained low amongst individuals in sustained deep remission (median $<$ 40 μg/g, all time points) [24].

A recent prospective study of UC patients attempted to define FC thresholds that could act as a surrogate for endoscopic (Ulcerative Colitis Endoscopic Index of Severity [UCEIS]) and histologic (Nancy index) disease activity [25]. Strong correlations were observed between FC and UCEIS or the Nancy index, with FC $\geq$ 72 μg/g indicating histologic inflammation (i.e. Nancy index $\geq$ 2) and FC $\geq$ 187 μg/g revealing endoscopically active disease (UCEIS 0$\geq$ 4) [25].

The CALM trial showed that FC level can provide treatment guidance [X]. In this trial conducted in patients with early CD, patients who were in a 'tight control' group underwent dose optimization when met one of failure criteria including FC $\geq$ 250 μg/g (as well as Crohn's disease activity index $\geq$ 150, C-reactive pro-

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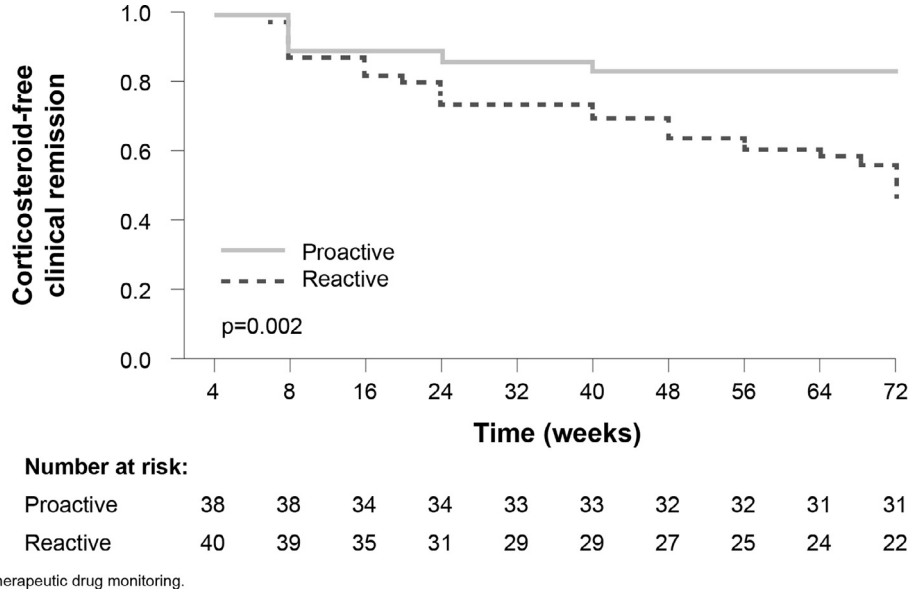

TDM, therapeutic drug monitoring.

Fig. 1. Cumulative incidence of sustained corticosteroid-free clinical remission with proactive versus reactive TDM in a randomised adalimumab trial [15] TDM, therapeutic drug monitoring.

tein ≥ 5 mg/L, and prednisone use) achieved better endoscopic and clinical outcomes compared to 'clinical management' group who treated based on symptoms alone [26].

Overall, in routine practice, FC may now be considered as an important diagnostic tool for differentiating between IBD and IBS [5,20]. Furthermore, it is becoming increasingly clear that FC correlates with endoscopic and histologic activity (in UC at least [25]), and that high levels are predictive of relapse risk whereas low levels predict sustained remission [23,24]. FC measurement also can contribute to treatment optimization for better clinical outcomes [26]. From a practical standpoint, the test is easy to perform and is typically cheap, reliable and safe [27]. More work is needed to define the optimal cut-off(s) – both in diagnosis and management of established IBD – which is a key focus of ongoing research.

2.3. Multidisciplinary working

Multidisciplinary working is increasingly becoming the gold standard in the long-term management of many complex diseases, including IBD [28]. In simple terms, a multidisciplinary team (MDT) may be defined as a group of healthcare professionals from different disciplines, working together to provide specific services to patients as part of a unified approach. In IBD, MDT meetings should ideally take place every 1–2 weeks, with a key focus on patients with complicated needs. Indeed, these meetings may provide a particularly valuable forum for discussing the most complex and difficult cases, and ensuring that all potential management strategies are explored. They can also provide learning opportunities for more junior members of the team.

Many different specialties are required to form an optimal MDT in IBD, and these may vary in different countries and healthcare environments. However, broadly, key members should include: a gastroenterologist with specific IBD training; a colorectal surgeon with specific IBD training; an IBD nurse specialist; a radiologist with an interest in IBD; a histopathologist with an interest in IBD; a dietician; a psychologist or counsellor; a pharmacist; and an administrator [29,30]. All team members should routinely be involved in MDT meetings, and all decisions should be recorded in appropriate hospital notes.

More specifically, proactive interaction between medical and surgical teams is essential to good disease management, and thus senior gastroenterologists and colorectal surgeons should play central leadership roles within the MDT. amongst the other specialties, patients are increasingly conscious of the value of dieticians within their care, and they can play a particularly important role in the management of severely ill individuals with nutritional failure. A frequently underestimated member of the optimal MDT is the administrative coordinator, who has a pivotal function to ensure smooth running of the meetings, the correct patients are discussed, and that the relevant patient information and test results to be discussed are collated ahead of each meeting.

However, the key lynchpin of multidisciplinary care is the IBD nurse specialist, who often plays a central linking role between all of the different healthcare service providers within the medical team, and of course with individual patients. In some countries, IBD nurses are now recognised as a separate speciality within the healthcare system. The responsibilities of these nurse specialists have continued to grow as IBD care has become more complex, and now incorporate functions across patient assessment, diagnosis, treatment planning, evaluation, monitoring, surveillance, education, and practical and emotional support [31]. This diversity of roles will continue to grow as drug choices increase and management becomes ever-more complicated. There is also a mounting burden of patient education that frequently falls upon nurse specialists.

3. Anti-TNF biosimilars in IBD management: growing confidence and key questions

Biological drugs have had a very positive impact on patient outcomes in IBD but have also presented some major challenges to healthcare systems, particularly with regard to cost and accessibility. For example, in a US study of CD health-plan costs between 2011 and 2013 – before the advent of biosimilars – almost 50% of the overall burden related to pharmacy costs [32,33]. This was almost twice as much as inpatient hospital costs. At that time, around 60% of pharmacy costs related to anti-TNF agents [32,33]. This trend towards high drug prices is set to continue as novel therapies come to market following complex and expensive discovery and development processes.

Biosimilars offer substantial potential to mitigate cost issues. In Denmark, the near total switch from originator to biosimilar inflix-

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imab in 2015 has been associated with an approximate halving of total monthly drug costs despite substantially increased infliximab use since that time [34]. However, their value lies not just in financial savings, but also in the potential for improved patient outcomes – by increasing accessibility and facilitating treatment with anti-TNFs earlier in the disease course.

Furthermore, biosimilars can be allied with other strategies as part of a unified cost control and accessibility improvement programme. For example, increased use of anti-TNF TDM can help to optimise dose and give better outcomes with reduced costs [35,36]. In a recent Italian study of infliximab-treated patients experiencing loss of response, clinical management according to a TDM algorithm resulted in fewer dose escalations than with empirical adjustment, without any loss of efficacy; cost savings were estimated at around 15% [36].

Cost savings with biosimilars may also support long-term use of these drugs by allowing patients to be treated for longer (if needed) with less pressure to discontinue therapy for non-medical, financial reasons. Ultimately, this may facilitate eventual *elective* withdrawal of treatment for patients in long-term remission – with resulting patient and cost benefits if remission can be maintained while drug-free. Available evidence suggests that around half of patients withdrawn from anti-TNF therapy after sustained remission do not experience a disease flare within the first 2 years [37]. However, further data are needed to better understand the implications of this approach for long-term outcomes.

With regard to biosimilars themselves, there was initial scepticism when the first approval was granted in 2013 by the European Medicines Agency. In particular, at that time, the available data related primarily to non-IBD indications, and approval in IBD was therefore based on extrapolation. The evidence base in IBD has grown substantially in the intervening years. Indeed, a recent randomised phase 3 trial definitively showed the non-inferiority of a biosimilar infliximab to the originator product in IBD [38], and this has been supported by data from multiple 'real-world' studies [39–42].

Nonetheless, there remain some important clinical issues to resolve with biosimilars and recent studies have begun to provide answers. These questions are discussed in detail below.

3.1. How should the nocebo effect be managed?

The 'nocebo effect' does not currently have a single consensus definition but may be broadly defined as the development of adverse events or disease worsening in response to treatment, which cannot be attributed to the specific therapy used. In other words, it involves negative consequences resulting from negative expectations [43] – the opposite of the placebo effect.

Anxiety around transitioning from an originator to a biosimilar anti-TNF may contribute to a nocebo effect after the switch has taken place. A recent systematic review attempted to analyse this effect based on data from 31 studies in which patients were switched from originator to biosimilar infliximab (or etanercept in 3 studies) [43]. The review found that median discontinuation rates for any reason were 14.70% in open-label studies compared with 6.95% in double-blind trials; discontinuation rates for adverse events were 5.60% versus 2.85%, respectively. Although these data alone do not confirm a biosimilar nocebo effect, they are supportive, and suggest that this phenomenon may indeed affect biosimilar adoption [43].

A recent consensus report on prevention and management of the nocebo effect suggested that a strong relationship between patient and healthcare provider (HCP) is essential [44]. In addition, they noted the need for greater knowledge about the safety and effectiveness of biosimilars amongst both HCPs and patients – with education tailored to individual patient needs, based on positive framing [44]. IBD nurses may play a critical role in this, particularly with regard to [45]:

- Enhancing patient knowledge about IBD, such as disease pathology and symptomatology;
- Improving general understanding of biosimilars, including the developmental process and underlying clinical data;
- Providing specific information prior to switching; and
- Delivering information on the particular biosimilar being used, including product storage, device handling and adverse event management.

Adequate preparation time is also important to ensure that patients do not feel rushed. In addition, offering product switch as a choice rather than a compulsory substitution – with the opportunity to switch back to the originator if desired – may help to make patients feel more comfortable.

Table 1
Preliminary results from the iBISS study of biosimilar to biosimilar infliximab switch [47].

	Week 0	Week 16/18	p value
Disease activity			
mHBI score	3.13 ± 3.31	3.15 ± 3.17	0.32
Partial Mayo score	1.53 ± 1.75	0.91 ± 1.64	0.15
Overall disease control component of the IBD control PROM			
Crohn's disease	74.99 ± 23.40	78.09 ± 19.27	0.66
Ulcerative colitis	76.22 ± 23.80	81.57 ± 21.21	0.49

Data are mean ± standard deviation. IBD, inflammatory bowel disease; iBISS, IBD Biosimilar to Biosimilar Infliximab Switching Study; mHBI, modified Harvey Bradshaw Index; PROM, patient-reported outcome measure.

3.2. Is biosimilar to biosimilar infliximab switch safe?

Transitioning from originator to biosimilar infliximab has been extensively studied, but less is known about biosimilar to biosimilar switching. Biosimilar to biosimilar switch may not be ideal for patients yet because the data is not robust enough, and cost saving may be less compared to the switching from the originator. In terms of pharmacovigilance, it is difficult to keep track of which drug causes what effect especially for patients undergoing multiple switch within short intervals. Given that several biosimilar infliximab products are now available, however, it is inevitable that patients undergo biosimilar to biosimilar switch in some cases due to a government or hospital policy, and etc. Studies are needed to evaluate effectiveness and safety of biosimilar to biosimilar switch, and four recent studies have attempted to address this issue [46–49].

In a retrospective analysis of 31 IBD patients who switched between biosimilar formulations (from CT-P13 to SB2), no adverse events were recorded [46]. All participants who were in remission/mild activity at baseline maintained that level of response after switching, and there was no additional risk of loss of response amongst those who had undergone a prior switch from originator to biosimilar infliximab [46].

The IBD Biosimilar to Biosimilar Infliximab Switching Study (iBISS) was a single-arm observational study with the aim to assess the outcomes of transitioning IBD patients from one biosimilar infliximab (CT-P13) to another (SB2) in a real-world setting [47]. In total, 133 adult participants ($n = 105$ CD; $n = 28$ UC) were recruited, with a mean disease duration of almost 10 years and a mean duration of infliximab treatment of 3 years. Preliminary data collected at week 16/18 showed that the switch had no effect on disease activity or the overall disease control component of the IBD control patient-reported outcome measure (Table 1) [47]. Qualitative analysis of patient interviews on the switch process and experience highlighted some important themes. Most importantly, lev-

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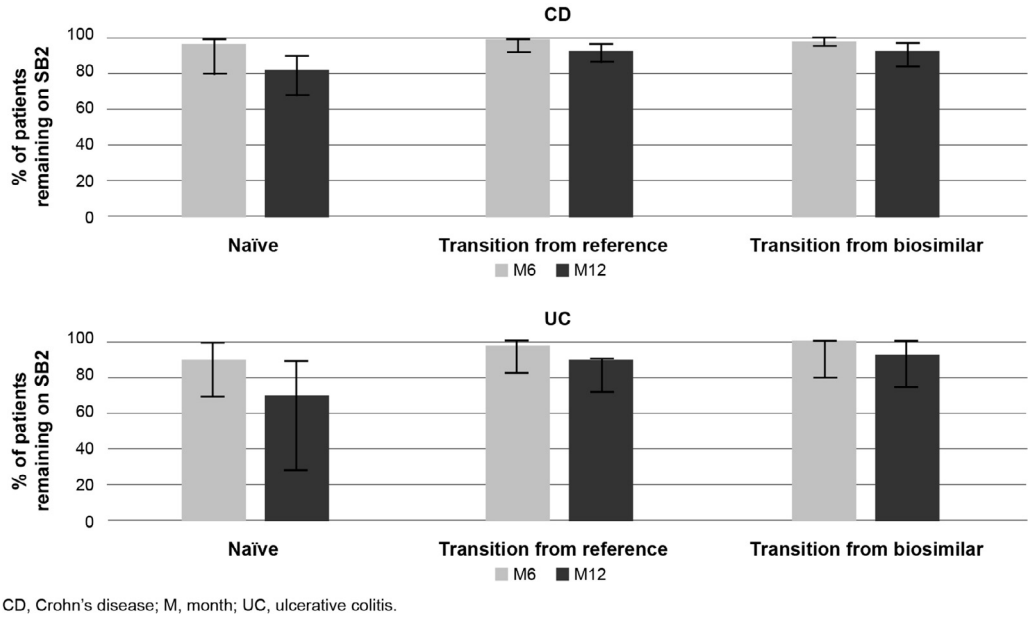

Fig. 2. Persistence with SB2 biosimilar infliximab in the PERFUSE study according to prior infliximab therapy [48] CD, Crohn's disease; M, month; UC, ulcerative colitis.

els of patient trust in the medical team, as well as overall confidence and reassurance, appeared to be high. Furthermore, their key motivators were largely altruistic – such as saving money for the healthcare system.

Data also recently became available from a French cohort study known as PERFUSE [48], conducted in patients initiating biosimilar infliximab (SB2) for any indication. An interim analysis was conducted, including 578 patients with CD and 174 with UC; mean duration of disease was relatively long in both groups (CD, 13.1 years; UC, 9.4 years). One-year persistence with SB2 treatment – the primary outcome measure – was 92.2% (95% confidence interval [CI]: 88.9, 94.8) and 89.9% (95% CI: 82.2, 95.0) in CD and UC patients, respectively. Most patients in the study had switched to SB2 either from the originator infliximab (CD, $n = 362$; UC, $n = 157$) or from another biosimilar infliximab (CD, $n = 88$; UC, $n = 53$). Persistence with SB2 at 1 year was similar irrespective of whether prior infliximab had been the originator or a biosimilar (Fig. 2). No clinically relevant changes in disease scores were observed at 1 year amongst patients switching to SB2. Thus, it appears that patients with IBD can be successfully transitioned to SB2 from either the originator or biosimilar infliximab [48].

Another one of the most recently published data came from The SPOSIB SB2 Sicilian Cohort [49]. It is a multicentre, observational, prospective study performed amongst the cohort of the Sicilian Network for IBD which included 276 patients (CD: 49.3%, UC: 50.7%). 43 (15.6%) and 24 (8.7%) out of those patients underwent biosimilar to biosimilar (CT-P13 to SB2) switch and multiple switch (originator to CT-P13 and then SB2), respectively. Overall, the safety and efficacy of the infliximab biosimilar SB2 were similar to those reported for the infliximab originator and CT-P13, which switching patients who were in stable status showed relatively favourable clinical outcomes than those of naïve to infliximab patients. The study results also showed that biosilmilar to biosimlar switch or multiple switch groups were not significantly different in terms of treatment persistency compared to infliximab naïve or single switch groups [49].

In summary, clinical data published as of May 2020 may suggest that biosimilar to biosimilar switch does not significantly affect patient outcome. However, it should be carefully interpreted as data so far are limited in sample size and follow-up duration. Further studies and vigorous pharmacovigilance activity would increase knowledge regarding this switch. Finally, biosimilar to biosimilar switch should be taken with the supervision of the physicians.

3.3. What about adalimumab switching?

The recent patent expiry of originator adalimumab, allied to the approval of several adalimumab biosimilars, has led to many patients being switched. Indeed, there is now a developing body of work showing that these biosimilars offer comparable efficacy and safety to originator adalimumab, both through extrapolation from other indications and from data in patients with IBD [50]. For example, in a recent analysis of 87 IBD patients who had responded to maintenance therapy with the originator adalimumab, switching to a biosimilar (SB5) had no impact on clinical effectiveness as measured by symptom activity indexes and inflammatory markers [51]. Some national IBD societies now support adalimumab biosimilar switch based on the scientific background of these drugs [52,53].

The ongoing PERFUSE study will likely add substantially more information to current data. It will assess the efficacy and safety of a biosimilar adalimumab in a mixed cohort of patients in routine clinical practice, including adalimumab-naive individuals, as well as those switching from the originator or from another biosimilar. As with the infliximab arm of this study, the primary outcome measure will be persistence at 1 year.

The key challenge with adalimumab biosimilars is likely to be around practical issues. As a subcutaneous drug, transitioning onto a biosimilar may also mean changing the delivery device and home care process, which may lead to patient anxiety [54]. Patient reassurance and education are essential to manage these concerns to ensure that individuals do not feel pressured into switching and are comfortable with how to use any new devices [52].

4. Conclusions

Biological drugs, and in particular the anti-TNF agents, have played a major role in improving patient outcomes in IBD. However, there are still unmet therapeutic needs and opportunities to further optimise care. Expanding the use of TDM and FC measure-

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ment may play an important role, alongside increased utility of a MDT approach to IBD management.

Biosimilars, which are by definition equivalent to the originator in their efficacy and safety, but with reduced cost, can offer a number of additional opportunities. These include increased accessibility and use in earlier treatment stages (with potential to reduce the risk of intestinal damage). This window of opportunity requires further study. Allying biosimilars to greater use of TDM could lead to further improvements in outcomes at a more reasonable cost. Savings from biosimilars may also allow patients to be treated for longer if needed, with fewer discontinuations due to non-medical (financial) reasons.

Alongside the extensive literature on transitioning from originator to biosimilar infliximab, more data are now becoming available on the safety of biosimilar to biosimilar switch, and also on adalimumab biosimilar transitions. The potential for a nocebo effect when switching to a biosimilar may be circumvented with more attention to patient education and preparation, allowing the full clinical value of these drugs to be realised.

Declaration of Competing of interest

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