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Review

A review on the use of prebiotics in ulcerative colitis

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The gut microbiome in the inflammatory bowel disease, ulcerative colitis (UC), is different to that of healthy controls. Patients with UC have relative reductions in abundance of Firmicutes and *Bifidobacterium* in the colon, and an increase in sulfate-reducing bacteria. Prebiotics are dietary substrates which are selectively metabolised by the human colonic microbiota to confer health benefits to the host. This review explores our current understanding of the potential benefits of prebiotics on various clinical, biochemical, and microbiological endpoints in UC, including new perspectives gained from recent studies in the field. This review looks to the future and highlights the need for appropriately designed trials to explore this potentially exciting new avenue for the treatment of UC.

Highlights

Ulcerative colitis (UC) is an inflammatory bowel disease which is associated with a disruption of the gut microbiota. Prebiotics may be used to restore a healthy microbiota and reduce inflammation in UC.

Three major classes of prebiotic are fructooligosaccharides (FOS), galactooligosaccharides (GOS), and human milk oligosaccharides (HMOs).

Three recent key clinical trials have been carried out with each of these classes of prebiotics in UC. The FOS 1-kestose was shown to improve clinical and endoscopic parameters. B-GOS has been shown to improve stool consistency, but not other inflammatory nor clinical parameters. The HMO 2′-fucosyllactose improved gastrointestinal quality of life and increased abundance of *Bifidobacterium longum* and *Faecalibacterium prausnitzii*, as well as increasing the concentration of faecal short-chain fatty acids, including butyrate.

Prebiotics in UC – an exciting new horizon

The effect of prebiotics to positively modulate the human gut microbiome has been demonstrated to support many gut health aspects, such as improving bowel habit, inhibiting pathogen growth, and improving gut barrier function [1]. This article reviews recent advances in the current evidence for prebiotics in UC, a form of inflammatory bowel disease. The demand by both patients and healthcare practitioners for a food-based intervention in UC is apparent, and modulation of the gut microbiota to benefit patients living with gastrointestinal disease is very much a therapy of interest at the moment. The field of gut microbiota modulation in UC is gathering pace rapidly, and with a number of key studies looking at prebiotic use in UC, this review offers a timely reflection on where the field is currently, and what the future potentially holds.

The gut microbiome and its role in health and disease

The human gut is home to a diverse multitude of microorganisms, collectively known as the gut 'microbiota', with the broader term gut 'microbiome' being used to describe the habitat, including the microorganisms themselves, their genetic material, and conditions in which they exist [2]. In health, the gut microbiota is critical for metabolism, homeostasis, and immune function [1]. When disrupted, 'dysbiosis' (alteration of the microbiome with negative consequences for the host) is associated with a number of pathological conditions, including inflammatory bowel disease (IBD), metabolic syndrome and obesity, irritable bowel syndrome (IBS), liver disease, colorectal cancer, and immune-checkpoint-inhibitor-related adverse events [3]. Moreover, the gut microbiome has been associated with certain cognitive states and respiratory infections, including with pathogens such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [4–6]. This has led to an expansion of research intended to mitigate symptoms of these conditions by fortifying health-promoting properties of the gut microbiota.

A logical extension of knowing key differences in the gut microbiota in health and disease is that we may be able to intervene to alter this in a bid to help prevent disorder, to reduce disease burden, or reverse the pathological process altogether. Any differences observed in the gut microbiota would need to be implicated in the disease process and not merely a consequence of

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it. One way might be to introduce microorganisms to the gut that somehow support health by complementing or competing with the existing microbiota to produce benefits (probiotics). Another may be to change nutrients received by the microbiota in order to induce qualitative and quantitative changes in its indigenous composition.

What is a prebiotic?

A prebiotic has been defined by the 2017 International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics as 'A substrate that is selectively utilised by host microorganisms conferring a health benefit' [7]. This definition has evolved over time from the original conception of the term by Gibson and Roberfroid in 1995 as 'a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health' [8]. The refined 2017 definition recognises what has been learned over the intervening two decades about the composition of prebiotics, their mode and anatomical location of action.

Although the vast majority of studies to date investigating prebiotics focus on nondigestible oligosaccharides (fructans and galactans), candidate prebiotics also include other fermentable carbohydrates, polyphenols, and polyunsaturated fatty acids [9,10]. Molecule size seems to be a key determinant of prebiotic status, with *Bifidobacterium* exhibiting a predilection for substrates with a degree of polymerisation (DP) of between 4 and 30 [11,12]. Similarly, structure drives function in that fructooligosaccharides (FOS) and galactooligosaccharides (GOS) are liberated by microbial enzymes, namely β-galactosidase for GOS and β-fructanofuranosidase for FOS. Both enzymes are found in bacteria of the genus *Bifidobacterium*, seemingly making them adept at competitively metabolising these prebiotics [13].

One requirement for a prebiotic is that it exerts its effect via the microbiota, and selective metabolism by one or more microbial groups. It is accepted that although the common end point is likely to involve stimulation of *Bifidobacterium* ('bifidogenesis') and production of beneficial metabolites such as short-chain fatty acids (SCFAs), the mechanism of action of a given prebiotic may be more complicated, with 'cross-feeding' of one beneficial class of microorganisms by the product(s) of another.

Throughout this review, the term prebiotic will be used in the context of the gut microbiota, but it should be borne in mind that substances may exert a prebiotic effect in a number of other anatomical locations, such as the skin, mouth, and urogenital tract, and substances which may be prebiotics in one location may not be in another.

A contrast must be made at this point between prebiotics and probiotics, with the latter defined as 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host' [14]. Conversely, synbiotics are a combination of the two: 'a mixture comprising live microorganisms and substrate(s) selectively utilised by host microorganisms that confers a health benefit on the host' [15].

The microbiome and UC

UC is a form of IBD defined by chronic inflammation affecting the mucosal layer of the colon resulting in bloody and profuse diarrhoea. It affects three in every 1000 people in the western world and has a rising incidence in lower- and middle-income countries [16]. It follows a relapsing–remitting clinical course, with most patients requiring some form of pharmacotherapy, ranging from salicylate-based medications to immunosuppression, with around 20% of patients requiring surgery during their lifetime [17].

The aetiology of UC is complex and not comprehensively understood, but the gut microbiota undoubtedly plays a role. Patients with UC have a significantly different microbiota composition to healthy controls. Members of the phyla Firmicutes and Bacteroidota comprise over 90% of the human gut microbiota [18]. One of the most common species of Firmicutes, *Faecalibacterium prausnitzii*, has a crucial role in butyrate production and controlling colonic inflammation [19]. Various studies have identified reduction in abundance of the Firmicutes *F. prausnitzii* and *Roseburia hominis* in patients with UC [20–23]. Furthermore, while *F. prausnitzii is less abundant in patients with UC in remission, there is an inverse correlation between UC disease activity and F. prausnitzii counts, suggesting* that a reduction in abundance in this bacterium may be linked to gut inflammation [20].

Bifidobacterium spp. produce lactate and acetate, and through crossfeeding effects of other commensal bacteria (such as *Faecalibacterium)* can produce butyrate, reducing gut inflammation [1]. It is not therefore a surprise to find that reductions in *Bifidobacterium* have been noted in UC [20,24].

One key observation in UC is an increased presence of sulfate-reducing bacteria (SRB), such as *Desulfovibrio* [24–29]. These bacteria result in higher hydrogen sulfide concentrations in the colon, which is cytotoxic and disrupts the oxidation of butyrate as fuel by colonocytes.

Whereas the majority of studies to date have examined relative abundances of different bacteria in the colonic microbiota, focus has shifted towards a functional view of the gut microbiome in IBD, using metagenomics and metatranscriptomics [30]. The Inflammatory Bowel Disease Multi'omics Database is comprehensively examining the functional aspect of human microbiome interactions, and demonstrates that there is more to the picture than just whether certain bacteria are depleted or increased. An example is the differential altered expression profiles of certain bacteria in IBD, which alter dependent on disease severity [31].

How might a prebiotic work to reduce inflammation in UC?

Bearing in mind the aforementioned changes observed in UC, manipulation of the dysbiotic gut microbiota in UC using prebiotics could be used to reduce gut inflammation to target increases in certain bacteria and reduction in others. Indeed, *Bifidobacterium* given as a probiotic in UC significantly reduced clinical and endoscopic disease activity indices [32]. Prebiotics with bifidogenic effects could boost Firmicutes populations through cross-feeding effects. Well established prebiotics such as FOS and GOS are bifidogenic [19]. GOS has been shown to decrease *Desulfovibrio* and increase *Bifidobacterium* in healthy elderly and overweight adults [33,34]. Mechanistically, this could reduce luminal hydrogen sulfide in the colon, which is directly toxic to colonocytes, and increase butyrate, a known fuel for colonocytes.

The landscape of evidence to date

In the current review, 12 articles have been identified detailing human intervention trials of prebiotics in patients with UC. The characteristics of each study are presented in Table 1. Heterogeneity existed in type of prebiotic used, study design, choice of primary outcomes, prebiotic dosage, and duration of treatment. Only two trials used a randomised, double-blind placebo-controlled design. Three key recent studies performed – using a prebiotic from each of the major classes of FOS, GOS, and human milk oligosaccharides (HMOs) – are highlighted, and studies performed using other prebiotic types discussed, with an overview of possible future directions and research priorities outlined.

Inulin-type fructans

Inulin-type fructan is a generic term to cover all β(2→1) linear fructans, including short- and long-chain FOS, and have been a central focus of prebiotic research. Previous studies have found

Table 1. Publications meeting criteria for human trials of prebiotics in ulcerative colitis[a]

Publication (first author, year, country)	Trial type	Intervention	Comparison	Duration of intervention	Study tion	popula	*n*	Primary outcome
Casellas, 2007, Spain [35]	RCT with parallel group design	12 g oligofructose-enriched inulin (Synergy 1)	Placebo 12 g day^{-1} maltodextrin	14 days	Mild to moderately active UC		10 intervention, 9 placebo	Reduction of calprotectin and human DNA
Faghfoori, 2011, Iran [49]	RCT, open label, single centre	30 g day^{-1} GBF (with standard drug therapy)	Standard drug therapy	2 months	Mild to moderately active UC		41 (20 intervention, 21 control)	Change in serum TNF-α, IL-6 and IL-8
Fujimori, 2009, Japan [50]	RCT, three-arm, single centre	Probiotic (Bifidobacterium longum), prebiotic (4 g day^{-1} of psyllium), syn- biotic (simultaneous probiotic and pre- biotic therapy)	Synbiotic vs prebiotic vs probiotic	4 weeks	UC in remission, or mildly active dis- ease		120 (31 probiotic, 31 prebiotic, 32 synbiotic)	Change in IBDQ score
Hafer, 2007, Ger-many [51]	RCT	Lactulose 10 g day^{-1}	Standard medication	4 months	Active IBD		14 with UC (7 in-tervention, 7 con- trol)	Improvement in CAI (Rachmilewitz CAI)
Hanai, 2004, Japan [48]	RCT	20 g day^{-1} GBF plus conventional therapy	Conventional therapy	12 months	UC in remission		59 (22 intervention, 37 control)	CAI (Rachmilewitz CAI)
Ikegami, 2023, Japan [37]	RCT	10 g day^{-1} kestose powder containing 98% 1-kestose	Placebo (5 g day^{-1} maltose)	8 weeks	Mild to moderately active UC		40 (20 intervention, 20 control)	CAI (Lichtiger method) at week 8 in intention to treat analysis
Kanauchi, 2002, Japan [46]	Multicentre, open label, RCT	20–30 g day^{-1} GBF (and baseline anti-inflammatory therapy)	Baseline anti-inflammatory therapy	4 weeks	Mild to moderately active UC		18 (11 intervention, 7 control)	CAI (Lichtiger method)
Kanauchi, 2003, Japan [47]	Multicentre, open label, uncontrolled trial	20–30 g day^{-1} GBF (and baseline anti-inflammatory therapy)	No comparison	24 weeks	Mild to moderately active UC		21	CAI (Lichtiger method)
Ryan, 2021, USA [44]	Single arm, open label	4 g day^{-1} 2′-FL	Nil	6 months	UC activity not specified		12 total, 4 with UC	GIQLI
Suzuki, 2006, Japan [53]	Nonrandomised, open-label, prelimi- nary trial	4.5 g day^{-1} bifidogenic growth stimula-tor comprising 20% lyophilised milk whey medium	Nil	Up to 4 weeks	Mild to moderately active UC		12	CAI score (authors' own)
Valcheva, 2018 [36], Canada	Dual arm, ex-ploratory study	15 g day^{-1} or 7.5 g day^{-1} β-fructans inulin plus FOS (Synergy 1)	High vs low dose	9 weeks	Mild to moderately active UC		31 (15 to high dose, 16 to low dose)	Decrease in the Mayo score ≥3 or an induction of clinical remission (Mayo score <2)
Wilson, 2021, UK [39]	Single arm, open label	2.8 g day^{-1} GOS (Bimuno)	Nil	6 weeks	Active UC		18	Changes in peripheral expression of immune-related genes

[a]Abbreviations: CAI, clinical activity index; GILQI, Gastrointestinal Quality of Life Index; IBDQ, Inflammatory Bowel Disease Questionnaire; RCT, randomised controlled trial.

significant improvements in clinical activity indices, decreases in faecal calprotectin, and increases in SCFA production in patients with mild to moderate UC given oligofructose-enriched inulin [35,36].

The most recent study included in this review, a 2023 single-centre randomised, double-blind placebo-controlled trial, compared the effect of 9.8 g day^{-1} of the trisaccharide FOS 1-kestose versus placebo (5 g day^{-1} maltose) [37]. Intention-to-treat analysis was carried out on 20 patients in the 1-kestose group, and 20 patients in the placebo group; two and one patients discontinued the intervention in each arm, respectively. The primary endpoint was improvements in the Lichtiger Clinical Activity Index (CAI), with secondary endpoints being the proportion of patients achieving clinical remission (CAI ≤3) and clinical response (clinical remission, or decrease in CAI of 3 or more from baseline to week 8), as well as endoscopic activity at week 8 and changes in gut microbiota and faecal metabolites. The trial met its primary endpoint, with a significant improvement in CAI in the intervention group compared with placebo, 3.8 ± 2.7 versus 5.6 ± 2.1, $P = 0.026$. Clinical remission in the intervention group was significantly higher than the placebo group (55% versus 20%, $P = 0.048$), but no significant difference between the groups was seen in clinical response ($P = 0.054$), nor endoscopic response as measured by the Ulcerative Colitis Endoscopic Index of Severity, or UCEIS ($P = 0.145$). No change in individual nor combined SCFAs was seen between groups, and interestingly, observed species – but not the Shannon Index – fell in the 1-kestose group, suggesting a reduction in alpha-diversity. Increases in *Bifidobacterium* and *Faecalibacterium* which might have been expected in the 1-kestose group were not seen however. The safety profile of 1-kestose was favourable, with one patient in the intervention arm needing to discontinue the study due to symptoms which were attributed to an exacerbation of UC rather than the 1-kestose itself.

Acknowledging that this was a pilot study, whose small sample size means that it was likely underpowered, these results are potentially exciting. An absence of change in SCFAs does not necessarily exclude changes in SCFA production as only the minority of SCFAs produced by the gut microbiota are found in the faeces. In addition, although alpha-diversity seemed to paradoxically decrease with FOS use, and no change was seen in *Bifidobacterium* nor in *Faecalibacterium*, the authors point to a reduction in *Ruminococcus gnavus*, associated with Crohn's disease, as an indicator of a reduction in harmful bacteria by the use of 1-kestose [38].

Galactooligosaccharides

Another major family of saccharides with prebiotic properties are GOS. In a single-arm open-label trial from 2021 by Wilson *et al.*, 2.8 g day^{-1} of GOS (B-GOS) was given to 18 patients with active UC, and at least one of - a C-reactive protein (CRP) above normal, faecal calprotectin greater than 150 μg (g faeces)$^{-1}$, or endoscopic evidence of active disease [39]. After 6 weeks, there was no difference in the primary outcome of immune gene expression between baseline and post-prebiotics following adjustment for false discovery rate ($P = 0.979$). There was also no difference in calprotectin ($P = 0.354$), SCFAs ($P = 0.733$), or pH ($P = 0.815$) before and after intervention. Decreases in the Firmicutes *Dialister* ($P = 0.016$), *Anaerostipes* ($P = 0.041$), and *Oscillospira* ($P = 0.046$) were observed, but no change in *Bifidobacterium* ($P = 0.272$) following prebiotic intervention in the per protocol population was seen. There were no differences in Simple Colitis Clinical Activity Index ($P = 0.438$) following prebiotics, but the proportion of normal stools as per the Bristol Stool Form Scale increased ($P = 0.026$).

The dose of B-GOS used in this trial was lower than has been used in previous human intervention trials, and the question remains whether a higher dose would have resulted in a greater bifidogenic effect and thus biochemical and clinical improvements. The bifidogenic effect of

B-GOS has previously been shown to be more favourable at 7 g day^{-1} compared with both 3.6 g day^{-1} [40] and 3.5 g day^{-1} [41], with high and low doses demonstrating broadly similar tolerance profiles.

Human milk oligosaccharides

Interest in HMOs and their prebiotic properties in health and disease has escalated in recent years. Their role in sculpting the immune system and reducing susceptibility to respiratory and gastrointestinal infectious diseases has been widely studied [42]. 2′-Fucosyllactose (2′-FL) is the most abundantly produced HMO in humans and is a trisaccharide with demonstrable bifidogenic effects in adults [43]. Ryan *et al*. [44] devised a 2021 pilot study on 2′-FL using batch cultures to assess the *in vitro* effect of 2′-FL alone and five candidate synbiotic combinations on the faecal microbiota from three healthy controls, three patients with IBS, and three with UC. They then progressed to an open-label, single-arm clinical trial which looked at the efficacy of a proprietary nutritional formula containing 2′-FL (along with a host of micro- and macronutrients, amino acids, and *iso*malto-oligosaccharide) in healthy controls and patients with IBS and UC. Participants consumed 4 g day^{-1} of 2′-FL for 42 days. Gastrointestinal Quality of Life Index (GIQLI) total score and gastrointestinal symptom domain score improved significantly over the course of the clinical trial (P <0.05), as did stool counts of *Bifidobacterium longum*, *F. prausnitzii*, *Anaerotruncus colihominis*, and *Pseudoflavonifractor* species. Faecal levels of butyrate, acetate, and total SCFAs significantly increased, which corroborated the group's *in vitro* findings.

This study needs to be interpreted with caution for a number of reasons. The small sample size in the clinical trial, high dropout rate, and lack of control group limits interpretability. In addition, the intervention was a formula containing a number of other nutrients alongside 2′-FL, which could cloud the effect of 2′-FL with a potentially confounding effect of these additives. Despite this, HMOs remain a promising avenue for future research, 2′-FL in particular.

Other prebiotic candidates in UC – hemicellulose, disaccharides, and non-saccharide prebiotics

Prebiotics which do not definitively fit into the class of FOS, GOS, or HMOs have also been studied in UC. Germinated barley foodstuff (GBF) is a hemicellulose comprising 34% dietary fibre and is derived from the aleurone and scutellum fractions from milled and sieved germinated barley [45]. GBF could be a promising intervention in inducing and maintaining remission in UC. It has been demonstrated to significantly reduce clinical disease activity at 4 weeks, 6 months, and 12 months [46–48]. In selected patients, an increase in *Bifidobacterium* and improvement in endoscopic parameters has been noted, although no significant difference in serum inflammatory indices was observed between groups, whilst this has been demonstrated since elsewhere [49].

Another hemicellulose-based prebiotic, psyllium, or ispaghula, has been studied in patients with UC in remission or with mildly active disease [50]. The primary endpoint of improvement in Inflammatory Bowel Disease Questionnaire (IBDQ) score was met in the group where psyllium was combined with a probiotic as a synbiotic, but not in the groups taking either prebiotic or probiotic alone.

The important role of the disaccharide lactulose in clinical practice in gastroenterology is undoubtable, having found widespread use as a laxative and in prevention and treatment of hepatic encephalopathy in patients with chronic liver disease. Supplementary lactulose in addition to standard care has been shown in a pilot trial to decrease UC disease activity and increase IBDQ, but endoscopic scores, need for corticosteroids, defaecation frequency, immunoglobulins, faecal pH, and faecal α-1 antitrypsin did not change [51].

Finally, although the overwhelming focus within the prebiotic field is on nondigestible carbohydrates, other non-saccharide compounds may have prebiotic qualities. One such example is the 1,4-dihydroxy-2-naphthoic acid component of 'bifidogenic growth stimulator' (BGS), derived from *Propionibacterium freudenreichii* ET-3 isolated from Swiss cheese [52]. BGS given to patients with mild to moderately active UC offered significant improvement in clinical disease activity at 2 and 4 weeks, as well as endoscopic improvement and an increase in butyrate levels [53]. No changes in stool bacteria (including *Bifidobacterium*) were observed.

Concluding remarks and future perspectives

Prebiotics offer an exciting novel dietary management approach for gastrointestinal diseases, UC included. The relatively few studies looking at prebiotics in UC, along with heterogeneity of study design, prebiotic choice, dosing and duration, all make it very challenging to draw conclusions which can influence clinical practice. Existing studies are often limited by the absence of placebo control and small sample sizes. Insufficient data currently exist as yet to carry out a meaningful meta-analysis on prebiotic interventions in UC, but as is clear from this review, there is scope for clinical benefit with this food-based approach.

Well-controlled studies are vital to address the benefits of prebiotics in UC. The nature of UC as a relapsing–remitting condition means that clinical effects of a treatment under investigation can both be lost and exaggerated in the absence of a control arm. The placebo effect in clinical trials of UC is considerable; for example, response to placebo in trials looking at induction of remission showed a pooled estimate of placebo response of 33% and placebo remission of 12% [54].

The dose-dependent impact on clinical and microbiological outcomes identified in one study is interesting, as it highlights that, provided the prebiotic is well tolerated, higher doses may reap higher benefits, up to a point. Valcheva *et al.* found a significant decrease in Mayo score (P <0.05) and faecal calprotectin (P <0.05), and significant increase in Bacteroidaceae (P = 0.015) in the group taking higher dose oligofructose-enriched inulin compared with those taking the lower dose [36]. Dose-dependent increases in *Bifidobacterium* and *Lactobacillus* have also been seen with FOS in a randomised controlled trial (RCT) with healthy controls [55]. It is therefore important that a suitable prebiotic dose is chosen in trials such that no observed effect is lost due to underdosing.

In studies which performed microbial analysis, the effect of prebiotics on the gut microbiota varied. Trials have variously reported an increase or no change in *Bifidobacterium* [36,37,39,44,46,53]. None of the studies looked at SRB, and only the Ryan study [44] looked specifically at *F. prausnitzii*, a paucity of which has been suggested to define the microbiome in UC, and in which 2′-FL caused a significant increase in numbers [20]. An increase in SCFA levels identified in several studies, particularly butyrate, highlights this as an important potential mechanism for how prebiotics may exert positive effects in UC [36,44,53].

In general, it is important to move away from merely a compositional view of the effects of prebiotics in inflammation and towards a functional view. This has been already demonstrated in one study using FOS, whereby – through dividing the patients into responders and non-responders – the authors identified significantly higher butyrate production in responders but no significant compositional change in the colonic mucosal microbiota [36].

With respect to duration of prebiotic therapy in UC, trials to date have had a wide range of treatment durations, from 14 days to 12 months. Typically, human intervention studies have intervention periods of 2–3 weeks, with washout periods of 2–3 weeks, but some crossover design

Outstanding questions

Can a prebiotic dietary intervention improve clinical and biochemical endpoints in patients living with UC, as demonstrated in adequately powered, reproducible, randomised, double-blinded, placebo-controlled clinical trials?

Can a prebiotic dietary intervention alter the indigenous gut microbiota of humans living with UC towards a more beneficial community, as measured not only by microbial ecology but also by examining end products of bacterial metabolism and resultant modulations in host endogenous metabolism?

Can a prebiotic dietary intervention reduce numbers and activities of SRB in the gut microbiota of people living with UC?

What is the optimal class, dose, and duration of prebiotic intervention to achieve desired clinical improvements and reduce inflammation?

trials have shown beneficial effects after 7 days and used washout periods of 7 days [40,56,57]. A minimum treatment period of 14 days seems reasonable for studies going forward, yet mechanistically it would be logical for studies into maintenance of remission to involve longer periods of prebiotic use.

The therapeutic niche for prebiotics in UC is likely to be as an adjunct in patients with mild to moderately active disease. Clinical equipoise would not exist to trial prebiotics in patients with acute severe colitis at risk of colectomy requiring intravenous corticosteroids. Neither will prebiotics replace the need for immune modulating therapy with the array of advanced therapies available now for UC. Yet the role of prebiotics in reducing frequency and severity of flares, improving quality of life, and reducing the need for escalation of treatment in mild to moderately active UC is potentially exciting. Unlike most pharmacological options available to treat UC, prebiotics do not have an immunosuppressive effect and so would not expose patients to concomitant risks of infection and malignancy inherent with immunosuppressants.

One further consideration is the source of prebiotics used in future clinical trials. This review has described prebiotics derived from varied origins such as GBF, Swiss cheese, and human breastmilk [44,46–49,53]. For future prebiotic candidates to alleviate inflammation in UC researchers may look to novel sources such as algae-derived oligosaccharides [58].

What this review has demonstrated is a clear need for a multimodal combined approach to studying the effects of prebiotics in UC, with a robust, adequately powered RCT design and clinically meaningful endpoints (see Outstanding questions). Interest in the area is ongoing, with six trials enrolled with clinicaltrials.gov at the time of writing looking at either FOS or HMOs in UC. It is likely that there will not be a single prebiotic which has a positive impact in UC, but the 'best' choice will be dictated by tolerability, availability, function, efficacy, ease of use, and cost.

Declaration of interests

No interests are declared.

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