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Review

A review of the therapeutic management of ulcerative colitis

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Nasar Aslam, Sheng Wei Lo, Rafid Sikafi, Tom Barnes, Jonathan Segal, Philip J Smith and Jimmy K Limdi

***Abstract*:** Ulcerative colitis (UC) is a chronic relapsing and remitting gastrointestinal disorder of uncertain aetiology. The last two decades have seen an expansion in the therapeutic arsenal used to treat UC. This has resulted in improved clinical remission and response rates. Nonetheless, staples in our current medical management originate from trials conducted in the early 20th century. In this review article, we aim to outline the key milestones in the history of the medical management of UC in addition to highlighting promising therapeutic developments for the future.

Keywords: anti-TNFs, biologics, corticosteroids, inflammatory bowel disease, ulcerative colitis

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Correspondence to:
Nasar Aslam
Department of Gastroenterology, University College London Hospitals, 235 Euston Road, London, NW1 2BU, UK
nasar.aslam@nhs.net

Sheng Wei Lo
Northern Hospital, Epping, VIC, Australia

Rafid Sikafi
St Mark's Hospital, London North West University Healthcare NHS Trust, London, UK

Tom Barnes
Section of IBD – Division of Gastroenterology, Northern Care Alliance NHS Foundation Trust, Salford, UK

Jonathan Segal
Northern Hospital, Epping, Melbourne, VIC, Australia

Department of Medicine, University of Melbourne, Parkville, VIC, Australia

Philip J Smith
Department of Gastroenterology, Royal Liverpool Hospital, Liverpool University Hospitals Foundation NHS Trust, Liverpool, UK

Jimmy K Limdi
Section of IBD – Division of Gastroenterology, Northern Care Alliance NHS Foundation Trust, Manchester, UK

Manchester Academic Health Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK

Introduction

Ulcerative colitis (UC) is a chronic, relapsing and remitting and potentially progressive form of inflammatory bowel disease (IBD) of uncertain aetiology, characterised by inflammation localised in the mucosa of the rectum and colon.[1] A number of aetiological factors, such as genetic predisposition, environmental triggers, perturbations in the gut microbiome and immune dysregulation, have been implicated.[1] The term 'ulcerative colitis' was first coined by Sir Samuel Wilks in 1859, distinguishing it as a separate entity from infectious diarrhoeal illnesses, a condition that would, in fact, be called Crohn's disease today.[2] Until the realisation that corticosteroid therapy induced remission, surgery was the mainstay of management.[3] There has been an evolution in therapies since the 1950s, and conventional management evolved into the use of broad spectrum anti-inflammatory drugs, such as amino-salicylates and corticosteroids, or immunomodulators, such as thiopurines, often sequentially with the aim of relieving symptoms and achieving remission to prevent long-term complications.[1]

Unprecedented advances in the understanding of the aetiopathogenesis of IBD in the last 2–3 decades have translated into a dramatic increase in our therapeutic armamentarium with biological and 'small molecule' therapies intercepting and abrogating the immune-inflammatory cascade. Consequently, we have seen clinical response and remission rates that have emboldened our definitions of meaningful disease control.[4] In this paper, we undertake a journey in the pharmacological therapy of UC from corticosteroids to modern biological, small molecule and other novel therapies.

Corticosteroids

The first clinical use of corticosteroids was in 1948 when cortisone was used successfully in a patient with rheumatoid arthritis (RA).

Truelove and Witts first demonstrated the efficacy of corticosteroids for the treatment of active UC in a preliminary report in 1954,[5] followed in 1955 by a full report describing the immediate and long-term progress of patients.[6] In a double-blind placebo-controlled trial involving 210 patients with pan UC, patients were categorised according to whether they had an index *versus* relapse presentation of UC alongside the severity

of their illness at the start of treatment. In all, 109 patients were treated with oral cortisone and 101 patients received placebo. Cortisone was superior to placebo with improvement in clinical, endoscopic and radiological parameters. This remained true across all grades of severity and irrespective of whether the patient had an index or relapse presentation. Cortisone did however seem to have more favourable results in treating index cases. 22.2% of index cases had no change or worsening in their outcomes in the cortisone group with 37.5% of cortisone-treated relapse cases showing no change or worsening in their outcomes. Deaths were also reported to be less frequent in those treated with cortisone (4.6%) in comparison to placebo (9.9%). At the time, the group highlighted their concerns about cortisone increasing the risk of 'pyogenic complications' and advocated 'antibiotic prophylaxis' in those treated with cortisone. Current guidelines advocate caution for opportunistic infections in UC patients treated with immunomodulators, especially in combination with biologic therapies and steroids, and with malnutrition.[7]

Seven decades later, corticosteroids remain the cornerstone for inducing remission for patients presenting with moderate-to-severe active UC. Baron *et al.* established the initial dose for outpatient treatment at prednisolone 40 mg/day in 1962, finding comparable remission rates with doses of 60 mg/day, and superior rates compared with 20 mg/day.[8] Subsequently, administering high-dose intravenous (IV) hydrocortisone for acute severe UC (ASUC) as defined by the Truelove and Witts criteria was established in 1974,[9] with two-thirds achieving long-term remission. The landmark study by Travis *et al.* in 1996 further predicted the need for colectomy after 3 days of therapy, establishing the concept of steroid-refractory salvage therapy.[10] Numerous tapering regimens have since been utilised, typified by protocol-specified regimens in modern clinical trials for treatment of moderate–severe UC.[11] In general, a regimen comprising of an initial dose of prednisolone 40 mg/day, with a gradual taper over a period of 8 weeks or 3 months has been utilised, as relapse is associated with shorter courses, and smaller doses are ineffective at achieving remission.[8]

A landmark population-based cohort study by Faubion *et al.* highlighted the efficacy of steroids in UC, identifying 185 patients with UC, with 63 (34%) receiving corticosteroids. At 30 days after the first course of steroids, 54% achieved complete remission, with a further 30% achieving partial remission. 1 year after the first course of steroids, 49% remained in prolonged response, with 22% dependent on corticosteroids and 29% requiring surgical management.[12] This highlights the efficacy of corticosteroid therapy in the treatment of UC; however, there still remains a substantial group that require further therapy.

Unfortunately, corticosteroids are plagued by a myriad of side effects due to their pleotropic physiological roles. This includes osteoporosis, myopathy, cataract formation, weight fluctuations, neuropsychiatric side effects and glucose intolerance.[13] The advent of Budesonide multimatrix (MMX), a topically acting corticosteroid with high first-pass metabolism and few systemic side effects proved to be a comparable alternative.[14] Pooled analysis from the CORE I and II studies examining budesonide MMX 9 mg, 6 mg and placebo shows significantly greater rates of combined clinical and endoscopic remission of budesonide MMX 9 mg compared to placebo (17.7% *versus* 6.2%, $p = 0.0002$).[15] This was further confirmed in a Cochrane review of the efficacy for induction of remission, particularly in left-sided disease, without significant adrenal suppression.[16] In a recent study in UC refractory to 5-aminosalicylic acid (5-ASA) therapy, 5-ASA was continued, and the addition of budesonide MMX, 9 mg for 8 weeks was superior at achieving clinical and endoscopic remission compared to placebo ($p = 0.049$).[14] Budesonide MMX is associated with fewer systemic side effects than classical corticosteroids (33% *versus* 55%) but not associated with either adrenal suppression[17] or significant reduction in bone mineral density.[18] Oral beclomethasone diproprionate is another alternative corticosteroid with reduced systemic absorption, and has been shown to be non-inferior to conventional prednisolone in treating active mild–moderate UC, with a non-significant reduction in steroid-related adverse events (AEs).[19]

Although there are no adequately powered comparative studies comparing second-generation corticosteroids (budesonide MMX and beclomethasone diproprionate) and prednisolone, they could be positioned as alternatives to conventional corticosteroids in mild to moderate UC.[20]

Sulphasalazine and 5-ASA

The side effect profile associated with corticosteroids negated their use as a long-term treatment option. For patients with mild to moderate UC, 5-ASA compounds play a fundamental role in the treatment strategy to induce and maintain remission.[21] The introduction of 5-ASAs into the treatment armamentarium for UC began with the discovery of sulphasalazine.

The combination of an antibacterial and anti-inflammatory compound bound by an azo bond prompted the interest in sulphasalazine as a potential therapeutic option in UC. In 1942, Svartz first demonstrated the therapeutic efficacy of sulphasalazine in patients with UC and RA through an observational case series.[22] The first double-blind controlled trial of sulphasalazine against placebo was conducted by Baron *et al.*, at a dose of 4 g/day for a week then de-escalated to 2 g/day for the following 2 weeks.[23] The trial selected 30 patients with both clinical and endoscopic evidence of mild to moderate UC with limited systemic symptoms, and randomly allocated them to one of three treatment arms (placebo, sulphasalazine or salicylazosulphapyridine). Salicylazosulphapyridine had no benefit over placebo and was subsequently discontinued. A further 10 patients were recruited and allocated in a double-blind manner to receive either placebo or sulphasalazine. Over a 3-week period, the results showed a statistically significant benefit from treatment with sulphasalazine. 80% of patients benefited from treatment with sulfasazaline compared to 35% in the control group ($p < 0.02$).

The notable side effect profile associated with sulphasalazine, which include gastrointestinal, central nervous system and haematological disturbances,[24] prompted further work to clarify its mode of action and identify how it actually yields an anti-inflammatory effect on the colon.

Sulphasalazine reaches the colon intact and colonic bacteria split it into sulphapyridine and 5-ASA. In 1977, Khan and Truelove[25] conducted a series of experiments to try and determine the active moiety and administered sulphasalazine, sulphapyridine or 5-ASA retention enemas to patients in a double-blinded manner daily over a period of 2 weeks. They noted that 30% of patients who received sulphasalazine and 5-ASA had histological improvement in contrast to only 5% who received sulphapyridine. They determined through this that 5-ASA delivers the anti-inflammatory effect with sulphapyridine as the vehicle ensuring its delivery into the large bowel.

This left an unmet need for the development of oral preparations that ensure adequate delivery of 5-ASA to the colon without sulphapyridine which was deemed to be responsible for the adverse effects associated with sulphasalazine use such as nausea, vomiting, blood dyscrasia and rashes.

In 1983, Asacol® was developed which fulfilled this unmet need.[26] Mesalazine was coated with an acrylic-based resin [eudragit-S (Rohm Pharma GMBH)] coating. Following the passage of Asacol into the terminal ileum and colon, the resulting pH change (>7) would break down this coating, releasing mesalazine in the colon.

This paved the way for development of other compounds using similar delivery systems and leaves us now with more formulations with subtle pharmacokinetic differences and topical versions for distal colitis.

The ASCEND (delayed-release oral mesalamine for the treatment of mildly to moderately active UC) trials[27] investigated the dose response effect of 5-ASA for induction of response in UC. In ASCEND I, patients with mild to moderate active UC were randomised to 2.4 g or 4.8 g of mesalazine. At week 6, the proportion of patients experiencing improvement in either group was similar (51% *versus* 56%, p = not significant).[27] Patients with moderate active UC responded better to 4.8 g daily, but those with mildly active disease did not. The ASCEND II study showed that patients with moderately active UC had a better response to 4.8 g daily than 2.4 g daily (72% *versus* 59%, $p = 0.036$).[28] *Post-hoc* analysis of ASCEND I and II showed greater mucosal healing in the 4.8 g/d group as compared with 2.4 g/d.[29] The ASCEND III trial randomised patients with moderate active UC to receive 2.4 g daily or 4.8 g daily mesalazine.[30] The primary endpoint of treatment success was defined as complete clinical remission or partial response showed no differences between the groups. A small but significant difference in remission with 43% of patients on 4.8 g/d *versus* 35% on 2.4 g daily was observed at 6 weeks. In a subgroup analysis, patients receiving oral 5-ASA and rectal therapies had a greater likelihood of response to 4.8 g/d.

Topical steroids and 5-ASA

Prior to 1965 when the first placebo-controlled trial for rectal suppositories in UC was performed, rectal instillation of hydrocortisone was done at the discretion of the treating physician.[31] Subsequently, the advent of steroid and 5-ASA topical therapies in the form of suppositories, foam and liquid enemas have introduced another facet into management of UC.

Rectal 5-ASA therapy at a dose of ⩾1 g/day is currently the preferred initial treatment for mild or moderately active proctitis,[20] with Cochrane reviews concluding rectal 5-ASA therapy is superior to placebo and rectal corticosteroids for induction of remission,[32] and effective at maintaining remission[33] in mild to moderate distal UC. The mucosal concentration of 5-ASA has a direct effect on its efficacy in UC,[34] and rectal preparations allow delivery of the drug directly to the inflamed segment of the colon. Suppositories are preferable over enema preparations as they may be better tolerated, and enemas may pool higher up in the sigmoid.[35] When oral 5-ASA is combined with topical therapies, response rates are higher.[36] Furthermore, topical 5-ASA is more effective than topical hydrocortisone, beclomethasone and prednisolone enemas or suppositories.[37]

Recent Cochrane reviews and network meta-analysis in 2020 and 2021 have shown that there is significant evidence that 5-ASA is superior to placebo in both inducing and maintaining remission of UC,[38–40] with data to suggest that high oral doses of 5-ASA had more evidence for inducing remission than combined therapy with topical and oral 5-ASA, or low-dose 5-ASA therapy. Furthermore, oral therapy combined with topical treatment seemed to fare best for patients with left sided or extensive disease.[40]

Thiopurines

5-ASA agents proved effective for mild–moderate active UC but it became rapidly apparent that corticosteroids had no role in the maintenance of remission and also, that patients with moderate–severe active disease needed a steroid sparing agent, capable of maintaining remission.[41–43] Trials have suggested between 40% and 30% of patients do not respond to 5-ASA therapy.[28] The steroid sparing nature of azathioprine alongside its immunogenic properties propelled azathioprine as a promising therapeutic option.

Azathioprine has been used in the treatment of IBD for over 30 years. The results from the first controlled trial using azathioprine in UC were published in 1974 by Jewell and Truelove.[42] In all, 80 patients with ASUC were given corticosteroids as well as azathioprine (at a dose of 2.5 mg/kg) or placebo. The trial was conducted over 1 year with monthly endoscopic, histological, clinical and biochemical assessments. Azathioprine yielded some benefit with fewer relapses, albeit without clinical significance ($p = 0.055$). This trend was only noted in patients admitted with a relapse of established disease.

Despite the study not reaching clinical significance, it laid the foundations for future studies of thiopurine use in the management of UC. Thiopurines are not effective for induction of remission. In a meta-analysis of three randomised studies, thiopurine maintenance favoured placebo [relative risk (RR): 0.6; 95% confidence interval (CI): 0.37–0.95).[43] In a subsequent meta-analysis, treatment with thiopurine was associated with an absolute risk reduction of 23% (number needed to treat = 5) to prevent one recurrence (odds ratio (OR): 2.59; 95% CI: 1.26–5.3).[44] Results from subsequent clinical trials have yielded mixed results but a Cochrane review of four thiopurine maintenance studies *versus* placebo showed a benefit of AZA (44% *versus* 65% failure, respectively, RR: 0.68; 95% CI: 0.54–0.86).[45]

However, there are numerous downsides to thiopurine usage, with significant adverse effects including pancreatitis, bone marrow suppression and long-term risk of lymphoproliferative disorders, with up to one-third of patients discontinuing therapy due to adverse effects.[46] Determination of thiopurine S-methyltransferase activity to guide dosage (between 1 and 2 mg/kg of azathioprine), and close monitoring during uptitration to target dose, should be undertaken.[47]

Despite these downsides, and its modest effect in prevention of relapse, there has been a resurgence in its role after the advent of salvage therapy. Azathioprine use after cyclosporin rescue therapy has been associated with a lower relapse rate.[48] Combination of thiopurine and infliximab use has also been shown in a prospective randomised controlled trial (RCT) to improve clinical outcomes, with a greater percentage achieving corticosteroid-free remission at week 16.[49] As such,

thiopurines still remain an integral part in our arsenal to combat UC in the biologic era.

Ciclosporin

Following the discovery of corticosteroids, many years passed with limited therapeutic options for patients presenting with ASUC.[50,51] Ciclosporin is a calcineurin inhibitor, initially used in organ transplant patients, and as its mechanism of action was elucidated it was noted that ciclosporin inhibits T-helper lymphocyte production of interleukin-2.[51] This is one of the key cytokines involved in propagating UC inflammation; hence, the subsequent interest in its application for UC treatment. Early controlled studies in the 1990s revealed the potential for ciclosporin to be added to the therapeutic arsenal.

In 1994, Lichtiger *et al.* conducted the first randomised double-blind controlled trial using ciclosporin for patients with steroid refractory ASUC.[52] Patients were administered either ciclosporin (4 mg/kg/day) or placebo after failing to respond to 7 days of IV corticosteroids.

Nine of the 11 patients (82%) treated with ciclosporin showed a response, defined as improvement in symptoms and discharge from hospital, in contrast to 0 of the 9 who received placebo ($p < 0.001$). Given the striking results, the trial was stopped early and those in the placebo group who had not had a colectomy were also given ciclosporin ($n = 5$) and they all responded. In an RCT comparing 4 mg/kg with 2 mg/kg IV ciclosporin, both groups showed equal efficacy for severe steroid-refractory UC.[53]

Ciclosporin rapidly asserted its relevance in the management of ASUC. The advent of infliximab (IFX) at the turn of the century, demonstrating a rapid effect on symptom control and with a relatively favourable safety profile as also ease of administration made ciclosporin less appealing. There have been two head-to-head trials comparing ciclosporin and infliximab in ASUC.

The open-label CySIF (ciclosporin *versus* IFX in patients with severe UC) trial included 115 patients previously naive to IFX and ciclosporin with a Lichtiger score > 10 points (range 0–21) with ASUC refractory to at day 5 of IV steroids.[54] The patients were 1:1 randomised to receive IV ciclosporin (2 mg/kg per day for 1 week, followed by oral ciclosporin until day 98) or IFX (5 mg/kg on days 0, 14 and 42). AZA was commenced in both groups at day 7 in patients with a clinical response. Treatment failure defined by the absence of a clinical response at day 7 was the primary endpoint as was relapse between day 7 and day 98, absence of steroid-free remission at day 98, any severe AE leading to treatment discontinuation, colectomy or death. There were no statistically significant differences in treatment failure in patients given ciclosporin (60%) and those on IFX (54%) ($p = 0.52$). Nine (16%) patients in the ciclosporin group and 14 (25%) in the IFX group had severe AEs but not statistically different. Mucosal healing was similar in both groups (47% in the ciclosporin group and 45% in IFX-treated patients) and colectomy rates (17% in the ciclosporin group and 21% in IFX-treated patients) were also comparable. Long-term follow-up of patients treated in the CySIF trial showed no difference in colectomy-free survival at 1 year and 5 years in patients treated with either ciclosporin or IFX.

The CONSTRUCT (Infliximab *versus* ciclosporin for steroid-resistant ASUC) trial was a mixed methods, open-label, pragmatic randomised trial including 270 patients. Patients were randomly allocated (1:1) to receive either IFX (5 mg/kg IV at baseline and again at 2 and 6 weeks after the first infusion) or ciclosporin (2 mg/kg per day by continuous infusion for up to 7 days, followed by twice-daily (BD) tablets delivering 5.5 mg/kg per day for 12 weeks). The primary outcome was quality-adjusted survival. There was no statistically significant difference between groups for the primary endpoint or for the secondary endpoints of colectomy rates, time to colectomy, serious AEs, or death. IFX, however, was associated with a greater treatment cost.[55]

Ciclosporin may be associated with significant AEs which may include serious infections, hypertension, nephrotoxicity, tremor and gingivial hyperplasia. Frequent monitoring of patient physiological parameters and blood levels means that there is a general preference for infliximab use. In current practice, ciclosporin remains a valid option in treatment of ASUC; however, the ease of administration has seen infliximab supersede ciclosporin as the drug of choice.[47] Oral ciclosporin should subsequently be continued as bridging to thiopurine maintenance therapy, with a case series showing reduced colectomy rates at 5-year follow-up if patients are on thiopurine maintenance after ciclosporin salvage therapy.[56]

Anti-tumour necrosis factors

Infliximab

Despite the introduction of ciclosporin, there had been no significant reduction in observed short-term colectomy rates in patients with ASUC.[57]

During the 1990s, a greater appreciation of the immunogenic basis of UC led to the introduction of biologic compounds. It was noted that levels of tumour necrosis factor alpha (TNFα) in stool was elevated in patients with active UC and dropped when the disease became inactive.[58] Furthermore, an increased density of TNFα immunoreactive cells was found in the lamina propria of patients with UC.[59] This led to the use of anti-TNF agents in UC.

Infliximab was the first biological agent for the treatment of UC. Infliximab was first introduced to the wider medical community in 1993 as a chimeric monoclonal IgG1 antibody that acts against TNF.[60] The landmark ACCENT 1 trial demonstrated the successful use of infliximab in the treatment of Crohn's disease.[61] Early pilot studies also suggested promise for the use of infliximab in the treatment of severe steroid refractory UC.[62] This culminated in two meta-analyses exhibiting the effectiveness and safety of infliximab in severe steroid refractory UC. A significantly higher rate of treatment response (OR: 2.96, 95% CI: 2.12–4.14) and lower colectomy rate (OR: 0.42, 95% CI: 0.22–0.83) was identified among 13 non-randomised studies comparing ciclosporin and infliximab; however, when three randomised trials were analysed, the difference was not statistically different.[63] Similarly, long-term colectomy-free survival was not statistically different between the ciclosporin and infliximab salvage from 4 years onwards.[64] No significant difference in AEs was noted in either study for ciclosporin and infliximab. However, the ease of administration of infliximab has established it as a firm alternative to ciclosporin in the management of ASUC.

The first large-scale RCTs conducted to explore the efficacy of infliximab in patients with moderate-to-severe UC were published in 2005.[65] In the ACT-1 and ACT-2 studies, patients with moderate-to-severe UC failing corticosteroids and/or thiopurines (and/or 5-ASA for ACT-2) received 5 mg/kg or 10 mg/kg IFX or placebo at 0, 2 and 6 weeks and were followed through week 54 (ACT-1) or week 30 (ACT-2). Patients in both 5 mg/kg and 10 mg/kg had a similar clinical response at week 8 with pooled data showing 67% for 5 mg/kg *versus* 33% for placebo. Clinical remission rates at week 30 were 30% for 5 mg/kg (placebo 13%) with remission sustained through week 54. Corticosteroid-free remission rates were 22% for 5 mg/kg by week 30 and sustained through week 54.

Thereafter, the UC SUCCESS (efficacy and safety of infliximab monotherapy *versus* combination therapy *versus* AZA monotherapy in UC) study showed that the combination of IFX and AZA was more effective with higher corticosteroid-free remission rates at week 16 (40%) compared to IFX alone (22%).[49] Based on these results, IFX and the combination with AZA became mainstays in the treatment algorithm of steroid-dependent UC.

The advent of biosimilars has once again sparked further interest in infliximab, with current approved biosimilars including CT-P13 and SB2. Furthermore, CT-P13 is also available in a subcutaneous (SC) preparation, offering more options to patients with UC. Numerous studies based upon real-world experience have been described, with two recent systematic reviews for CT-P13[66] and SB2[67] having shown comparable effectiveness in clinical and endoscopic outcomes, with consideration for multiple switches and therapeutic drug monitoring taken into consideration.

Infliximab remains a mainstay in UC management, with further interest in accelerated dosing, therapeutic drug monitoring and immunogenicity highlighting the complexity of this drug.

Adalimumab

For over half a decade, infliximab remained the only biologic choice for UC. Over this period, it was noted that some patients receiving infliximab as maintenance therapy would go onto to lose response, which was thought to be primarily mediated by anti-infliximab antibodies.[68] Furthermore, those with antibodies were at higher risk of developing drug-mediated reactions.[69] This prompted the research into alternative treatment options.

Adalimumab is a recombinant human monoclonal antibody that targets TNFα. Early studies had already shown it to be efficacious in inducing

and maintaining remission in Crohn's disease.[70,71] The ULTRA 1 trial was conducted to assess the efficacy of adalimumab in inducing remission in patients with moderate-to-severe UC.[72]

The trial was conducted over 8 weeks as a randomised double-blind placebo-controlled design over multiple centres in North America and Europe. In all, 186 patients were randomised to receive either adalimumab or placebo. Two separate dosing schedules were used in the adalimumab group, ADA 160/80 (160 mg at week 0, 80 mg at week 2 and 40 mg at weeks 4 and 6) or ADA 80/40 (80 mg at week 0, 40 mg at weeks 2, 4 and 6).

At week 8, 18.5% ($p = 0.031$ *versus* placebo) of patients treated with ADA 160/80 regime and 10% of those treated with ADA 80/40 regime ($p = 0.833$ *versus* placebo) were in remission (placebo 9.2%). The high placebo response rate likely contributed to the failure to reach statistical significance. The ULTRA 2 trial served the purpose of gathering longer-term data on efficacy and safety[73] and found remission rates of 22% at week 52 in those receiving adalimumab (placebo 12.4%). An open label extension study (ULTRA 3) has shown that up to 25% of patients remain in clinical remission 4 years on.[74]

Numerous ADA biosimilars have been approved in recent years, with real-life data limited to observational cohort studies. However, there has been no significant difference in clinical, biochemical and endoscopic outcomes noted in these studies,[75–77] thus providing patients with a much larger variety in therapeutic options moving forwards. Interestingly, patients that were intolerant on one biosimilar, were subsequently switched to another biosimilar successfully,[78] further cementing the role of biosimilars in the therapeutic armamentarium of IBD.

Golimumab

Golimumab is a subcutaneously delivered human monoclonal antibody targeted against TNFα. *In vitro* and *in vivo* studies have demonstrated golimumab as having higher affinity to TNFα then both infliximab and adalimumab suggesting the possibility of a more potent clinical response.[79]

The PURSUIT-SC trial evaluated golimumab response in patients with moderate-to-severe UC who were naïve to anti-TNF agents, but had failed to respond to one or more of the other conventional medical therapies.[80] PURSUIT-SC was conducted as a combined double-blind phase II dose-finding and phase III dose confirmation study. The phase III component of the trial involving 774 patients reported that 51% of patients receiving 200 mg/100 mg golimumab (200 mg followed by 100 mg 2 weeks apart) and 54.9% receiving 400 mg/200 mg golimumab (400 mg followed by 200 mg 2 weeks apart) met the primary endpoint of clinical response at week 6 (as assessed by the Mayo score) *versus* 30.3% in the placebo group ($p \leq 0.0001$). The secondary endpoints of clinical remission were achieved at week 6 in both groups 17.8% (200 mg/100 mg) *versus* 17.9% (400 mg/200 mg) *versus* placebo 6.4% ($p < 0.0001$). Mucosal healing and improved quality of life markers as assessed by IBD questionnaire (IBDQ) scores were also met by patients receiving golimumab ($p \leq 0.0014$ for all comparisons).

The PURSUIT-maintenance trials followed on from PURSUIT-SC with the aim of assessing long-term clinical efficacy and safety.[81] The study involved patients who had responded to induction therapy in PURSUIT-SC ($n = 464$). These patients were randomly assigned to receive placebo, 50 mg or 100 mg golimumab injections every 4 weeks for 1 year. The trial found that golimumab maintained clinical response until week 54 in 47% ($p = 0.010$) of patients who received 50 mg golimumab and 49.7% ($p < 0.001$) who received 100 mg golimumab (placebo 31.2%). Serious AEs were noted in 7.7%, 8.4% and 14.3% of patients given placebo, 50 mg or 100 mg golimumab, respectively, with serious infections reported in 1.9%, 3.2% and 3.2%.

Anti-TNF therapy has revolutionised the treatment of UC offering options for both medical rescue in the setting of ASUC and as a maintenance strategy in those where conventional medical strategies have already failed them. Unfortunately, anti-TNFs are not universally effective with a significant proportion of patients not responding to treatment or losing response, in part due to immunogenicity.[82] Furthermore, concerns regarding the anti-TNF side effect profile, namely infection risk, malignancies, worsening heart failure and demyelinating disorders, open the opportunity for the development of biological agents that mitigate these issues.[83]

Anti-integrin agents

Although anti-TNF agents have transformed the treatment landscape for UC, it was noted that up to 10–30% of patients did not respond to anti-TNF therapy (primary non-response).[84] Furthermore, a significant proportion lose response and while antibody formation or pharmacokinetic issues were seen as the likely causal factor it has also been postulated that a proportion of patients may have an adaptive change in their immunopathogenesis from one which is TNFα mediated to one that is not primarily mediated by TNFα.[85,86] This has fuelled research to find additional treatment options that exploit and target distinct aspects of the immune cascade.

Vedolizumab

Vedolizumab is a gut-selective humanised monoclonal antibody that inhibits the interaction between the $\alpha_4\beta_7$ integrin and mucosal addressin cell adhesion molecule-1. This interaction leads to a gut-specific blockade of memory T cells into the gastrointestinal submucosa.[86]

In 2013, the GEMINI1 study group demonstrated the efficacy and safety of vedolizumab as induction and maintenance therapy for UC. This was a phase III randomised, double-blind placebo-controlled trial of vedolizumab in patients with moderate-to-severe UC.[87]

The primary outcome for induction therapy was a clinical response at week 6 with secondary outcomes of clinical remission and mucosal healing. Patients were randomly assigned a single dose of vedolizumab or placebo on days 1 and 15. At week 6, the vedolizumab group was superior to the placebo group with regard to clinical response (47.1% *versus* 25.5%, $p < 0.001$), clinical remission (16.9% *versus* 5.4%, $p = 0.001$) and mucosal healing (40.9% *versus* 24.8%, $p = 0.001$).

Clinical responders at week 6, in addition to patients who responded to open-label vedolizumab induction therapy, were enrolled in the maintenance trial and received vedolizumab or placebo every 4 or 8 weeks until week 52. The primary outcome for maintenance therapy was clinical remission at week 52. The vedolizumab groups showed statistically significance difference to the placebo group in terms of clinical remission in both vedolizumab groups (8 weekly 41.8%, $p < 0.001$, 4 weekly 44.8%, $p < 0.001$) compared to 15.9% of the placebo group. Secondary measures of durable clinical response (response at both weeks 6 and 52), durable clinical remission, mucosal healing and glucocorticoid-free remission at week 52 were significantly higher among patients assigned to the vedolizumab regimens than among those assigned to placebo.

VDZ was noted to be superior to placebo for clinical response (RR: 0.82, 95% CI: 0.75–0.91), induction of remission (RR: 0.86, 95% CI: 0.80–0.91), endoscopic remission (RR: 0.82, 95% CI: 0.75–0.91) and remission at 52 week in week 6 responders (RR: 2.73, 95% CI: 1.78–4.18) in a Cochrane review.[88]

In the GEMINI open label extension, patients with ⩾248 weeks of cumulative VDZ treatment were included ($n = 154$). Among patients responding to induction therapy who completed the maintenance study, 40.9% of patients had 248 weeks of treatment; 98% achieved clinical response and 90% had clinical remission. *Post-hoc* analysis noted improvements in patient reported outcomes of reduction in rectal bleeding and stool frequency (SF) by 2 weeks,[89] reflecting the rapid onset of action of vedolizumab compared with placebo. However, further analysis correlating higher trough serum concentrations with improved clinical outcomes suggests peak effect for vedolizumab would be expected closer to week 14, suggesting a slower inductive onset of vedolizumab, compared to other biologic therapy.[90]

The VICTORY Consortium registry performed a retrospective review of adults with follow-up after starting vedolizumab for clinically active UC.[91] The majority of the patients had prior anti-TNF exposure (71%). The 12-month cumulative rates of clinical remission, endoscopic remission, corticosteroid-free remission and deep remission were 51%, 41%, 37% and 30%, respectively. In this real-world cohort, vedolizumab was well tolerated and effective in achieving key clinical outcomes.

The EVOLVE (Retrospective Real-World Comparative Analysis Highlights Safety of Vedolizumab and Anti-TNFα Therapies in Biologic-Naive Patients study for UC) was a retrospective study of the safety and effectiveness of VDZ compared with anti-TNF agents in a real-world cohort of biologic naive patients. At 24 months, clinical response (91% *versus* 86%),

clinical remission (79% *versus* 66%),and mucosal healing (92% *versus* 84%) were high in VDZ and anti-TNF patients, respectively, with no real differences between groups. Treatment persistence (75% *versus* 54%; $p < 0.01$) was greater with VDZ than anti-TNF, while more anti-TNF-treated patients required dose escalation than the VDZ group (25% *versus* 31%; $p < 0.05$).[92] Further head-to-head comparisons have been undertaken in biologic-naïve,[93] and biologic-experienced cohorts,[94] with similar efficacy found in comparison to infliximab. The VARSITY trial comparing vedolizumab and adalimumab will be discussed later in this review.

SC preparations of biologic treatments offer advantages in terms of patient preference and reduced healthcare-associated cost. SC vedolizumab was investigated as a maintenance treatment option in patients with moderate to severely active UC.[95] Patients with moderate–severe UC received open-label treatment with IV vedolizumab 300 mg at weeks 0 and 2. At week 6, patients with clinical response were randomly assigned maintenance treatment with SC vedolizumab 108 mg every 2 weeks, IV vedolizumab 300 mg every 8 weeks, or placebo. Clinic remission at week 52 was achieved by 46.2%, 42.6% and 14.3% of patients in the SC vedolizumab, IV vedolizumab and placebo group, respectively. This demonstrated that SC vedolizumab is effective as maintenance therapy in patients with moderate to severely active UC who had a clinical response to IV vedolizumab induction therapy.

Considering the gut selectiveness of vedolizumab, as well as clinical trials showing a safety profile comparable to placebo, it may have advantages over other treatments if safety profiles need to be taken into consideration.[20]

Anti-interleukin agents

Ustekinumab

IBD appears to be mediated through an imbalance between the Th1 and the Th2 immune cells, but it is now known that another subset called Th17 and related cytokines are crucial mediators of inflammation independent of anti-TNF drive. Furthermore, IL-12 has been noted to induce a predominant Th1 response in humans and IL-23 has been shown to upregulate Th17-driven inflammation. This knowledge has fuelled research into IL-12 and IL-23 and the development of an agent targeting the common p40 subunit of anti-IL12/23, namely Ustekinumab.[96] Following successful trials for ustekinumab in the treatment of moderate to severely active Crohn's disease,[97] the UNIFI trial was established to determine the effectiveness of ustekinumab in patients with moderate to severely active UC.[98]

The trial was conducted in a double-blind randomised placebo-controlled manner in two phases involving an induction and maintenance phase.

In the induction phase, 961 patients with moderate–severe active UC, who had failed conventional medical therapy and/or anti-TNF and/or vedolizumab were assigned to receive placebo, weight-based IV ustekinumab dosing (6 mg/kg) or 130 mg IV ustekinumab. Patients were assessed for clinical remission at week 8. This was defined according to the Mayo score (total score $\leqslant 2$, with no subscore >1 across the four domains of the Mayo scale).

Those who had a clinical response at week 8 to ustekinumab were then randomised to the maintenance phase of the trial to receive placebo, 90 mg SC ustekinumab at 12 weekly intervals or 90 mg SC ustekinumab at 8 weekly intervals.

In the induction phase, both groups receiving ustekinumab showed significant clinical response, 130 mg (15.6%), 6 mg/kg (15.5%) in comparison to 5.3% in the placebo group ($p < 0.001$ for both comparisons).

In the maintenance phase of the trial, clinical response was assessed at week 44 and was found to be significantly higher in those receiving ustekinumab 90 mg at 8 (43.8%) and 12 (38.4%) weekly intervals in comparison to the placebo group (24%) ($p < 0.001$ and $p = 0.002$, respectively).

Both active treatment groups had a significant improvement in IBDQ, mucosal healing and histological healing ($\leqslant 5\%$ neutrophils in epithelium, no crypt destruction, and no erosions, ulcerations or granulations) was 20.3, 18.4 and 8.9%, respectively, at week 8. AEs were comparable to placebo, with no malignancies, opportunistic infections or tuberculosis reported. In the maintenance study, 523 week-8 responders were

re-randomised to placebo, 8-weekly or 12-weekly dosing, with week 44 remission rates of 24%, 38.4% and 43.8%, respectively ($p = 0.002$ for 8 weekly and $p < 0.001$ for 12 weekly *versus* placebo). A very small proportion (4.6%) of patients developed anti-drug antibodies to UST demonstrating low immunogenicity like vedolizumab.

The UNIFI trial long-term extension data show that clinical remission in ustekinumab responders is durable with 78.7% patients maintained on 12 weekly dosing in clinical remission at 92 weeks and 83.2% with 8 weekly dosing.[99] Five-year data from the IM-UNITI trial have shown that of all patients randomised to receive UST, 34.4% of those in the 8-weekly dosing group and 28.7% in the 12-weekly dosing group were still in remission at week 252. Furthermore, long-term data have shown low antibody formation with only 5.8% of patients developing antidrug antibodies.[100]

The efficacy, similar onset of action to infliximab,[101] safety profile and low immunogenicity of ustekinumab make it an appealing option for those with refractory UC who have already failed conventional treatment and one or more biological agent.[20]

Janus kinase inhibitors

Better understanding of the pathogenesis of IBD has revealed several different cytokine-driven inflammatory pathways that trigger and perpetuate the inflammatory cascade, underpinning the need to develop further therapeutic targets. The development of new molecules with the potential to target a myriad of cytokine targets such as the Janus kinase (JAK)-signal transducer and activator of transcription pathway have been shown to be effective in IBD.[102]

Tofacitinib

Tofacitinib is a first-in-class JAK inhibitor that had demonstrated efficacy in the treatment of RA and psoriatic arthritis.[102] It primarily inhibits JAK1 and JAK3 proteins, leading to downstream inhibition of cytokines that are implicated in the pathogenesis of UC. The OCTAVE trials were three distinct phase III randomised double-blind placebo-controlled trials evaluating the safety and efficacy of tofacitinib in patients with moderate-to-severe UC despite previous conventional therapy or treatment with an anti-TNF agent.[103] OCTAVE 1 and 2 were induction trials conducted over 8 weeks comparing tofacitinib 10 mg BD to placebo. The primary endpoint of the OCTAVE 1 and 2 was clinical remission as defined by the Mayo score (total Mayo score of ≤ 2, with no subscore > 1 and a rectal bleeding subscore of 0).

The induction trials (to week 8) included 598 and 541 patients for OCTAVE Induction 1 and 2, respectively, who were randomly assigned, in a 4:1 ratio, to receive induction therapy with oral tofacitinib (10 mg BD) or placebo for 8 weeks. The primary endpoint of clinical remission at 8 weeks (MCS ≤ 2, with no individual sub score > 1), was noted more frequently in the active treatment arm compared to placebo; in OCTAVE 1 – 18.2% *versus* 8.2% ($p = 0.007$) and OCTAVE 2 – 16.6% *versus* 3.6% ($p < 0.001$). A key secondary endpoint of mucosal healing was noted more frequently in the active treatment arm compared to placebo arm; OCTAVE Induction 1 – 31.3% *versus* 15.6% ($p < 0.001$), OCTAVE Induction 2 – 28.4% *versus* 11.6% ($p < 0.001$). The treatment effects for both primary and secondary endpoints were similar in both TNF-naïve and TNF-exposed patients. A *post-hoc* analysis of the OCTAVE 1 and 2 induction data showed a rapid onset of treatment effect. Significantly greater improvements in Mayo SF subscore and rectal bleeding score (RBS) were noted in the tofacitinib arm compared to placebo by day 3 [9.2% *versus* 2.3% ($p < 0.01$) and 14.4% *versus* 8.2% ($p < 0.05$), respectively] with consistent effects thereafter until day 15. These effects were uniformly observed in all subgroups.

Patients who had a clinical response to induction therapy ($n = 593$) were re-randomised 1:1:1 to receive oral 5 mg tofacitinib BD, 10 mg tofacitinib BD or placebo in the maintenance trial for OCTAVE Sustain trial with a follow-up period of 52 weeks.[78] Significantly higher clinical remission rates were noted in patients receiving tofacitinib 5 mg BD (34.3%) and tofacitinib 10 mg BD (40.6%) when compared with the placebo arm (11.1%) ($p < 0.001$ for both comparisons with placebo). Similarly, for the key secondary endpoint of mucosal healing significantly higher rates were noted in patients receiving tofacitinib 5 mg BD (37.4%) and tofacitinib 10 mg BD (45.7%) compared to placebo (13.1%) ($p < 0.001$ for both comparisons with placebo). Sustained and corticosteroid-free clinical remission (CFCR) rates

were also significantly higher in patients receiving tofacitinib 5 mg BD (35.4%) and tofacitinib 10 mg BD (47.3%) when compared with the placebo arm (5.1%) ($p < 0.001$ for both comparisons with placebo).

Patients who completed OCTAVE Sustain were eligible to enrol into the long-term extension follow-on study (OCTAVE Open). Of the 142 patients in remission at the end of OCTAVE Sustain, efficacy endpoints were maintained with ongoing tofacitinib 5 mg BD dosing in OCTAVE Open, with 68.3% achieving remission, 77.5% clinical response and 73.9% endoscopic improvement at 12 months; and 50.4%, 56.0% and 55.3%, respectively at 36 months.[104]

Tofacitinib as a small molecule has distinct advantages over biologic agents with no risk of immunogenicity, predictable pharmacokinetics and rapid clearance attributed to its short half-life (3–4 h) allowing for rapid discontinuation and resumption in the context of acute infections and surgery. Furthermore, as an oral compound, it simplifies the process of drug administration as well as reducing the healthcare costs associated with delivering parenteral biologics.

It is important to note however that the OCTAVE trials did identify infections as being more common in patients treated with tofacitinib, specifically a higher prevalence of herpes zoster infections.[105] Non-melanoma skin cancer also occurred more frequently in those treated with tofacitinib, but it is important to consider a number of patients had previously received thiopurines. Tofacitinib treatment was also associated with higher lipid levels and an increased number of adjusted cardiovascular events.

Trials of tofacitinib use in the treatment of RA have highlighted concerns that 10 mg BD dosing of tofacitinib resulted in a higher incidence of thromboembolic, cardiovascular, cancer risk and deaths.[106] Although these signals have not been detected in real-world trials in the IBD cohort, the Medicines and Healthcare Products Regulatory Agency (MHRA) recommends caution when prescribing tofacitinib to those with known thromboembolic risk factors.[107]

Additional real-world data are needed to establish long-terms risk, AEs and clinical efficacy when using tofacitinib in the UC cohort.

Upadacitinib

Even as the potential of non-selective JAK inhibition is being realised, newer (and more selective) JAK inhibitors are undergoing evaluation.

Upadacitinib (UPA) is an FDA-approved JAK1 selective inhibitor that has demonstrated clinical efficacy for inducing clinical remission after 8 weeks of treatment in phase IIb clinical trials for patients with moderate to severely active UC. Among 250 adults randomised to receive either placebo or induction therapy with once-daily (OD) UPA (7.5, 15, 30 or 45 mg), at week 8, 8.5% ($p = 0.052$), 14.3% ($p = 0.013$), 13.5% ($p = 0.011$) and 19.6% ($p = 0.002$) of patients respectively, achieved clinical remission (placebo 0%). Similar rates of AEs and related discontinuation were noted across the UPA groups with numerically higher events in the placebo group. Furthermore, elevation is serum lipid and creatine phosphosphokinase levels was also noted.[108]

In the phase III U-ACCOMPLISH study, a significantly higher proportion of patients receiving UPA 45 mg daily achieved clinical remission (33.5% *versus* placebo 4.1%) at 8 weeks.[109] All ranked secondary endpoints (symptomatic, endoscopic histologic improvements) were achieved in a significantly higher proportion of patients receiving UPA 45 mg daily *versus* placebo ($p < 0.001$).

The efficacy and safety of UPA maintenance therapy was reported recently from the randomised phase III study.[110] Both UPA 15 mg and 30 mg met the primary endpoint of clinical remission at week 52, and all secondary endpoints. Significantly greater percentages of patients receiving 15 mg and 30 mg *versus* placebo achieved clinical remission (42.3% and 51.7%, *versus* 12.1%), endoscopic improvement (48.7% and 61.6%, *versus* 14.5%), maintenance of clinical remission (59.2% and 69.7%, *versus* 22.2%), CFCR (57.1% and 68.0%, *versus* 22.2%), maintenance of endoscopic improvement (61.6% and 69.5%, *versus* 18.9%), endoscopic remission (24.2% and 25.9%, *versus* 5.6%), maintenance of clinical response (63.0% and 76.6%, *versus* 18.8%) and histo-endoscopic mucosal improvement (34.8% and 49.3%, *versus* 11.8%) ($p < 0.001$ for all endpoints). UPA 15 mg and 30 mg were both well tolerated and no new safety signals were observed.

Filgotinib

Filgotinib is another selective JAK-1 inhibitor with OD oral dosing and has been evaluated in the SELECTION study (phase IIb/III) with an induction and maintenance phase.[111] In the induction trial, a total of 1348, biologic-naïve (induction study A, $n=659$) or biologic-experienced (induction study B, $n=689$) patients with moderately-to-severely active UC were randomised and treated with filgotinib (200 mg or 100 mg OD) or placebo. A significantly higher proportion of patients achieved clinical remission at week 10 (primary endpoint) compared with placebo in both biologic-naïve (26.1% *versus* 15.3%, $p=0.0157$) and biologic-experienced (11.5% *versus* 4.2%, $p=0.0103$) arms. In the maintenance trial, patients achieving clinical response or remission at week 10 in the filgotinib arm ($n=664$) were re-randomised 2:1 to receive an induction dose of filgotinib or placebo and treated for total of 58 weeks. At week 58, significantly higher proportion of patients on filgotinib 100 mg (19.1% bionaive and 9.5% biologic experienced) and 200 mg (26.1% bionaive and 11.5% biologic experienced) were in clinical remission compared to placebo (15.3% bionaive and 4.2% biologic experienced) and a significantly higher proportions of patients on 200 mg filgotinib achieved key secondary endpoints including CFCR, sustained clinical remission, MCS remission, endoscopic and histological compared with placebo.[111]

Overall, the incidence of ARs, serious AEs and discontinuations due to AEs were similar in the filgotinib and placebo arms for both the induction and maintenance studies. Filgotinib is under regulatory review for use in UC.[112]

Sphingosine-1-phosphate receptor modulators

Similarities between the pathomechanism of relapsing multiple sclerosis and UC, *via* trafficking and accumulation of lymphocytes in inflamed tissue, have led to the development of sphingosine-1-phosphate (S1P) receptor modulators as a viable oral option for UC.[113]

Ozanimod

Ozanimod is a S1P receptor modulator that binds to S1P subtypes 1 and 5. Specifically, the internalisation of S1P subtype 1 receptors prevents lymphocyte trafficking to inflamed bowel. A phase III trial was completed with 645 patients randomised to receive either ozanimod hydrochloride 1 mg (equivalent to 0.92 mg of ozanimod) or placebo, and a further 367 receiving open-label ozanimod at the same dose.[114] Participants were adults with moderate-to-severe UC, completed varicella vaccination, with at most one previous biological attempt. Primary endpoints were assessed at 10 weeks for induction, and 52 weeks for maintenance, with Mayo score, clinical, endoscopic and histological endpoints recorded. Ozanimod was superior to placebo during induction (47.8% *versus* 25.9%, $p<0.001$) and maintenance (60.0% *versus* 41.0%, $p<0.001$). Safety data showed no difference in AEs during induction, but saw a higher rate of infection in the ozanimod group during maintenance (23% *versus* 11.9%). Elevated liver transaminases were also more common with ozanimod therapy than placebo (2.6% *versus* 0%), and bradycardia was another feature of induction (0.5% *versus* 0%), but not maintenance. Due to the requirement of varicella vaccination, the rates of herpes zoster infection were comparable to placebo (2.2% *versus* 0.4%). Ozanimod has been approved in various countries for use in UC.

Head-to-head trials

With an increasing number of therapeutic options available for the treatment of UC head-to-head trials can provide us with valuable information regarding clinical and cost effectiveness, although there is a distinct paucity of RCTs available. Real-world studies are available; however, currently there is insufficient evidence available to determine superiority of one therapy over another.[115]

VARSITY trial

The VARSITY (vedolizumab *versus* adalimumab for moderate-to-severe UC) trial was the first head-to-head study that compared vedolizumab against adalimumab in a double-blind, double-dummy randomised multisite international clinical trial involving 769 patients with moderate to severely active UC.[116] Vedolizumab was noted to be superior to adalimumab at week 52 with regard to clinical remission (31.3% *versus* 22.5%, $p=0.006$) and endoscopic improvement (39.7% *versus* 27.7% $p<0.001$) but not for corticosteroid-free remission (12.6% *versus* 21.8%).

Infection rates were also lower in the vedolizumab group (23.4 *versus* 34.6 events per 100 patient years). Further high-quality head-to-head trials are needed to help define the standard of care for patients with UC. Meanwhile, a systematic review and network meta-analysis found infliximab to be ranked highest in biologic-naïve patients, and ustekinumab and tofacitinib were ranked highest in patients with prior exposure to TNF antagonists, for induction of remission and endoscopic improvement in patients with moderate-to-severe UC.[117]

Aurora comparison study

The Aurora comparison trial was a retrospective multicentre study comparing 416 UC patients treated with adalimumab ($n=90$), infliximab biosimilar ($n=105$), golimumab ($n=79$) or vedolizumab ($n=142$) over a 5-year period. The primary endpoint was continuous clinical remission defined by relapse free, steroid-free clinical remission after 1 year of treatment. The primary endpoint was met by 33%, 37%, 28%, 37% of patients, respectively. All biologics had similar efficacy in biologic-naive patients; however, vedolizumab was more effective than other anti-TNF options in those patients that had previous anti-TNFα failure (primary endpoint met by 36% *versus* 18%, $p=0.004$).[118]

What is in the pipeline and what is coming

Modern biological and now small molecule therapies have emboldened our definitions of disease control, with improvements in clinical response and remission rates. Endoscopic mucosal healing has been shown to correlate with a sustained clinical response and reduction in important surrogates associated with morbidity such as corticosteroid use, hospitalisation, surgery and colorectal cancer complications.

However, remission rates range between 30% and 40% with most advanced therapies and data suggest that colectomy rates are not decreasing despite biologics.[119] A prospective population-based cohort study has also shown similar 5-year surgery, hospitalisation and disease progression rates compared to cohorts from 20 years ago, despite earlier biologic therapy.[120] Taken together with the complex, incompletely understood and evolving immunobiology of IBD, it highlights a major unmet need for other therapeutic targets to abrogate the inflammatory response.

A number of novel targets and therapeutic agents have shown promise in phase II trials with phase III trials underway and provide hope to fulfil this requisite in the future. A brief overview of these agents is provided in Table 1.

Table 1. Overview of novel therapeutic agents in development.

Name	Mechanism of action	Administration	Trial phase	Current results	Ref/clinical trials ID
Abrilumab	Anti-integrin	Subcutaneous	2B	Superior to placebo	Sandborn et al.[121]
AJM300	Anti-integrin	Oral	3	Ongoing	NCT03531892
Mirikizumab	Anti-IL-23	Intravenous/ subcutaneous	3	Superior to placebo	NCT03518086 NCT03524092 NCT03519945
Risankizumab	Anti-IL-23	Intravenous/ subcutaneous	2/3	Ongoing	NCT03398148
Guselkumab	Anti-IL-23	Subcutaneous	2b	Superior to placebo	[122]
Etrasimod	Sphingosine-1-phosphate receptor modulator	Oral	3	Ongoing	NCT04176588 NCT04607837 NCT03996369 NCT03950232
Cobitolimod	Oligonucleotide therapy	Topical	3	Ongoing	NCT04985968

Faecal microbiota transplant

A number of trials have yielded promising results when faecal microbiota transplant (FMT) is conducted in patients with recurrent and refractory *Clostridium difficile* infection (CDI).[123] A recent real-world observational study incorporating 259 patients from an FMT national registry in North America has demonstrated a 90% one-month cure rate for patients with CDI with a 4% recurrence rate.[124]

Trials are underway exploring its application in a number of other fields such as autoimmune, neurological and metabolic disorders.[125]

The gut microbiome has been shown to impact on our physiology, forming a symbiotic relationship with the host.[126] Research has shown it to influence intestinal immunity as well as gut function, with dysbiosis felt to be a contributing factor in promoting intestinal inflammation and propagating IBD.[127] However, it remains undetermined whether immune-mediated damage to the gut leads to gut dysbiosis or vice versa.

An evolving area in the field of UC treatment is the use of FMT. Given variable study protocols, preliminary findings into FMT use in cohorts of patients with UC have yielded conflicting results. A systematic review by Paramsothy *et al.* showed that the four RCTs of FMT in UC to date demonstrated a significant benefit in clinical remission in patients treated with FMT.[128] Most recently, lyophilised oral FMT has been shown to induce CFCR in 53% of participants, compared with 15% in placebo at 8 weeks. Clinical, endoscopic and histological remission were also achieved at week 52 for all four patients that continued with FMT, suggesting a potential role orally administered FMT could have in treatment of UC.[129] However, there are still numerous variables in FMT that remain unanswered, including other routes of administration, dosing and donor selection; further larger trials are needed to establish clinical efficacy as well as the place of FMT in current treatment algorithms.

Conclusion

The history of UC is flagged by several clinical trials that underpin and influence our current clinical practice (Figure 1). The biological era is considered the fulcrum that is propelling current and anticipated developments in the field. Given the associated drawbacks with immunosuppressive therapies, additional treatment options are being explored and progressing to clinical trials. With this in mind, we anticipate the therapeutic landscape and current treatment paradigms to undergo marked transformation over the proceeding decade.

The biological era

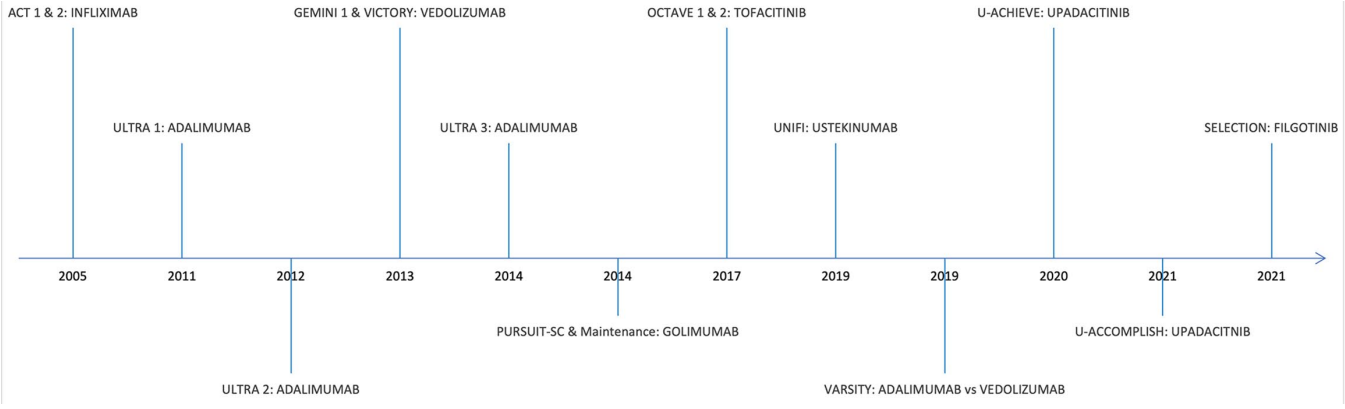

Figure 1. Milestone studies from the biological era of UC treatment.
UC, ulcerative colitis.

Declarations

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Not applicable.

Consent for publication
Not applicable.

Author contribution(s)
Nasar Aslam: Conceptualisation; Methodology; Visualisation; Writing – original draft; Writing – review & editing.

Sheng Wei Lo: Formal analysis; Resources; Validation; Writing – review & editing.

Rafid Sikafi: Writing – original draft; Writing – review & editing.

Tom Barnes: Writing – original draft; Writing – review & editing.

Jonathan Segal: Conceptualisation; Supervision; Writing – review & editing.

Philip J Smith: Conceptualisation; Supervision; Writing – review & editing.

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ORCID iDs
Jonathan Segal https://orcid.org/0000-0002-9668-0316

Jimmy K Limdi https://orcid.org/0000-0002-1039-6251

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