Inflammatory bowel disease

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Improving IBD outcomes in the era of many treatment options

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Key studies published in 2022 highlight the emergence of several novel drugs for inflammatory bowel disease. Head-to-head trials and network meta-analyses have also been conducted to identify the sequencing of these treatments, but we still have a long way to go to achieve personalized medicine.

Inflammatory bowel disease (IBD), encompassing Crohn's disease and ulcerative colitis, is a chronic, immune-mediated, inflammatory disease of the digestive tract. Evidence suggests that its pathogenesis is closely related to immunological imbalances that result from genetic susceptibility and/or environmental triggers. This understanding has led to the development of novel therapies, but strategies for the use of these treatments have not yet been established. The introduction of the tumour necrosis factor (TNF) antibody infliximab was a major breakthrough in the field, as it can induce and maintain remission to a much greater degree than previous treatment options, such as 5-aminosalicylic acid and corticosteroids. Subsequently, various immunomodulatory therapies have been developed, including more TNF antibodies and IL-12/IL-23p40 antibody. Janus kinase (JAK) inhibitors and sphingosine 1-phosphate receptor modulators have also been shown to be effective. These therapies have been introduced into clinical practice, but several problems remain unsolved — remission rates are as low as 20–30%, a considerable proportion of patients develop secondary loss of response, some patients still require corticosteroids and safety concerns have not been completely addressed. However, 2022 may have brought new therapeutic breakthroughs in IBD.

First, the IL-23p19 antibody risankizumab was introduced into clinical practice on the basis of its efficacy for moderately to severely active Crohn's disease in the phase III ADVANCE and MOTIVATE trials[1]. Intravenous administration of risankizumab led to a statistically significant improvement in the co-primary endpoints of clinical remission and endoscopic response. The efficacy of risankizumab for maintaining remission for 1 year was confirmed in the phase III FORTIFY study[2]. The efficacy was the same in patients who were naive to treatment with biologics as in those who had previously received biologics. Similarly, the efficacy of another IL-23p19 antibody, guselkumab, was demonstrated in Crohn's disease in the phase II GALAXI-1 trial[3]. IL-23p19 has also been successfully targeted in moderately to severely active ulcerative colitis with the monoclonal antibody mirikizumab[4] — the phase III trial has been completed and regulatory authorities are considering mirikizumab for clinical approval.

The monoclonal antibody therapies require intravenous administration, and the convenience of oral treatments has been highlighted in the past 3 years, when the COVID-19 pandemic has hindered access to supervised treatments and shifted many consultations to telemedicine platforms. In 2022, novel JAK inhibitors have emerged that provide a patient-friendly, once-daily oral treatment. Following the positive trial of filgotinib published in 2021, the phase III trial of upadacitinib for ulcerative colitis was published in 2022 (ref. [5]). In this study, two cohorts received induction therapy with 45 mg upadacitinib once daily for 8 weeks, and this treatment significantly increased the proportion of patients who achieved remission when compared with placebo (26% versus 5% and 36% versus 4% in the two cohorts). The treatment was associated with an increased risk of herpes zoster virus infection, as reported with the first-generation JAK inhibitor tofacitinib. Patients who responded to the induction therapy went on to receive maintenance therapy with 30 mg or 15 mg upadacitinib or placebo for 52 weeks. Both doses increased the proportion of patients who achieved clinical remission when compared with placebo[5].

Beyond JAK inhibitors, other oral small molecules are being developed for the treatment of IBD, including oral anti-integrin agents. In 2022, results of a phase III trial of the integrin α4 inhibitor carotegrast methyl (AJM300) demonstrated its efficacy as an induction therapy in mildly to moderately active ulcerative colitis. At week 8, a significantly greater proportion of patients who received AJM300 (45%) had a clinical response than those who received placebo (21%). On the basis of these results, AJM300 is now approved for clinical use in Japan[6]. The safety profile of AJM300 was good in the trial, but this profile needs to be confirmed in real-world use owing to concerns that treatment could increase the risk of progressive multifocal leukoencephalopathy, which is a serious adverse effect of the integrin α4 antibody natalizumab.

Key advances

- Clinical trials of the IL-23p19 antibodies guselkumab and risankizumab have demonstrated that they are safe and effective for induction and maintenance of remission in moderately to severely active Crohn's disease[1–3].
- A phase III trial of the novel Janus kinase inhibitor upadacitinib demonstrated its efficacy in patients with moderately to severely active ulcerative colitis who either had or had not previously received biologic therapy[5].
- A phase III trial of the oral integrin α4 inhibitor carotegrast methyl (AJM300) demonstrated its efficacy as an induction therapy in mildly to moderately active ulcerative colitis; the drug is now approved for clinical use in Japan[6].
- Head-to-head comparison of adalimumab and ustekinumab in moderately to severely active Crohn's disease in the SEAVUE study showed that their efficacy is similar[8].

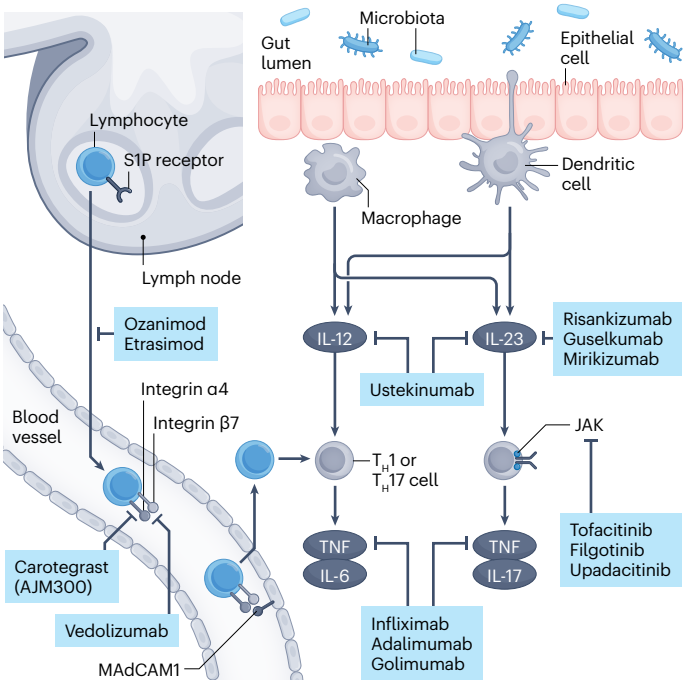

Fig. 1 | Mechanism of action of immunomodulatory drugs in inflammatory bowel disease. Drugs are shown in blue boxes. JAK, Janus kinase; S1P, sphingosine 1-phosphate; T_H cell, T helper cell; TNF, tumour necrosis factor.

The emergence of these novel therapeutic options means that we have a large number of available therapies for IBD with different mechanisms of action (Fig. 1), necessitating discussion about the sequencing of these treatments. The appropriate usage of each of the available therapies cannot be easily determined on the basis of their mechanism of action. In most trials of novel therapies, subgroup analyses have been included to compare efficacy in patients who have and have not previously received therapy with biologics. These analyses suggested that ustekinumab and tofacitinib might be the favourable options for people who have previously received anti-TNF therapy for ulcerative colitis. However, these data are not sufficient to draw firm conclusions about which treatment to use when, and head-to-head studies have been conducted to more directly compare efficacies.

In the CYSIF study, infliximab and cyclosporine were compared for the treatment of severely active ulcerative colitis, and the efficacy was the same for both drugs. In the VARSITY study, the efficacy and safety of vedolizumab and adalimumab in moderately to severely active ulcerative colitis were compared, showing superiority of vedolizumab in achieving clinical remission and endoscopic improvement at week 52 (ref. [7]). In 2022, a new head-to-head study — the SEAVUE study — was published and demonstrated that ustekinumab and adalimumab were similarly effective for treatment of Crohn's disease[8]. Interestingly, not only was the primary endpoint of clinical remission at week 52 identical, but so was the speed of onset of action.

In addition to these head-to-head studies, multiple indirect comparisons have been performed using network meta-analysis. One such network meta-analysis published in 2022 indicated the superiority of upadacitinib over all other biologic therapies for ulcerative colitis, both in patients who had and in patients who had not previously received biologic therapy[9]. In another similar analysis, infliximab and risankizumab were ranked most highly for the treatment of Crohn's disease[10].

Regardless of the findings of these studies, whether such comparisons are an appropriate basis for personalization of treatment is questionable. Even if we start treatment with the option that was superior in a head-to-head study, the possibility that remission will not be achieved is still considerable. In that case, we would need to try the second-line therapy and then possibly the third. The more options we have, the greater the possibility that we take a 'detour' to identify the most appropriate treatment for each patient. In this context, factors that predict outcomes of each therapy are needed to enable their appropriate use and selection in the real world. For example, some evidence suggests that measurement of oncostatin M expression and HLA-DQ5 genotyping can help to predict the outcomes of treatment with TNF antibodies, although confirmation is needed in large clinical studies and whether the findings apply to other treatments is unclear.

Despite substantial efforts to characterize IBD at the molecular level, we do not have the required evidence to identify the right treatment for the right patient at the right time. Furthermore, the safety of long-term use has not been established for several treatment options. Whether or not the novel treatments can improve the lives of patients depends on how well we can develop and establish appropriate individualized treatment. To facilitate this process, unbiased, fair and high-quality clinical studies are awaited.

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Competing interests

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