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Positioning therapies for the management of inflammatory bowel disease

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A careful integration of the effectiveness and safety of the therapies for inflammatory bowel disease, considering patients' disease risks, treatment complications and preferences, is warranted to inform the positioning of therapies in clinical practice. Precision medicine might help choose the best option for an individual patient.

Over the past decade, treatment options for the management of inflammatory bowel disease (IBD) have expanded remarkably. After the regulatory approval of infliximab targeting tumour necrosis factor (TNF) in 1998, the regulatory approval of vedolizumab, an anti-α4β7 integrin, followed in 2014 (barring the approval of natalizumab, an anti-α4 integrin for Crohn's disease in 2005, which is used infrequently owing to risk of progressive multifocal leukoencephalopathy)[1]. Since 2014, three more classes of biologic agents and oral small-molecule drugs with unique mechanisms of action with varying efficacy and safety profiles have been approved for the management of IBD: IL-12 and IL-23 antagonists (IL-12p40 and IL-23p40 antagonist, ustekinumab, in 2016; IL-23p19 antagonist, risankizumab, in 2022 – Crohn's disease), Janus tyrosine kinase (JAK) inhibitors (a pan-JAK inhibitor, tofacitinib in 2019; selective JAK1 inhibitors, upadacitinib and filgotinib in 2022 – ulcerative colitis) and a sphingosine 1-phosphate receptor modulator (ozanimod, in 2021 – ulcerative colitis)[2]. These advances have brought into focus aspects of comparative effectiveness and safety of different therapies and precision medicine to choose the right drug, for the right patient, at the right time. This Clinical Outlook aims to highlight the current approach to positioning therapies for the management of moderate-to-severe IBD, relying on careful integration of the medication's effectiveness and safety in the context of a patient's risk of disease-related and treatment-related complications and preferences. In addition, it provides a glimpse of how precision medicine might help choose the best therapy for an individual patient.

In patients with moderate-to-severe Crohn's disease, the SEAVUE trial demonstrated that ustekinumab monotherapy is not superior to adalimumab monotherapy (Supplementary Table 1). Integrating data from this head-to-head trial with data from phase II and III trials of approved therapies, network meta-analyses suggested that infliximab, with or without immunomodulators, and adalimumab are probably the most efficacious therapies for induction of remission in patients who were biologic-naive[3]. For patients with prior exposure to TNF antagonists, risankizumab and ustekinumab are probably the most efficacious therapies, substantially more effective than vedolizumab[3]. Alternative TNF antagonists might be appropriate for patients who discontinued the first TNF antagonist due to intolerance or immunogenicity[3]. Given the chronic nature of IBD, the long-term safety of different immunosuppressive agents is another crucial consideration in choosing therapies. Two key factors determine the safety of a treatment strategy in patients with IBD: the intrinsic systemic immune suppression potential of the immunosuppressive agent and its effectiveness in controlling disease, achieving corticosteroid-free remission and improving functional status. Meta-analyses of head-to-head observational studies suggest that ustekinumab might be associated with a lower risk of serious infections compared with a TNF antagonist, and with vedolizumab, in patients with Crohn's disease[4]. Although vedolizumab is a gut-specific agent with a lesser degree of systemic immunosuppression potential, there is no difference in the risk of serious infections between vedolizumab and TNF antagonists, potentially because of lower rates of achieving disease control with vedolizumab. Other factors are involved in informed shared decision-making – comorbid conditions, speed of onset of action and a patient's values and preferences, such as the mode of administration, cost and access. In most jurisdictions, cost considerations upend these discussions, with a strong preference for using biosimilars for TNF antagonists and conventional immunosuppressive agents like thiopurines and methotrexate in resource-limited settings (Fig. 1).

Similar to Crohn's disease, there is a paucity of head-to-head clinical trials of advanced immunosuppressive therapies in patients with moderate-to-severe ulcerative colitis. Integrating data from the VARSITY trial comparing vedolizumab versus adalimumab (Supplementary Table 1) with data from phase II and III trials of approved therapies, network meta-analyses suggest that upadacitinib, infliximab and vedolizumab are probably the most efficacious therapies for induction of remission in patients who are biologic-naive, and are substantially more effective than adalimumab[5]. In patients with prior exposure to TNF antagonists, upadacitinib is probably the most efficacious agent, more effective than all other approved agents except ustekinumab. Comparative safety studies suggest a lower risk of serious infections with vedolizumab compared with TNF antagonists[4]. Based on the ORAL surveillance study on the comparative safety of tofacitinib versus TNF antagonists in 4,362 older patients with rheumatoid arthritis, the US Food and Drug Administration issued an advisory limiting the use of all JAK inhibitors across all indications only to patients who have failed, or are intolerant to, TNF antagonists[6] (Fig. 1).

These indirect approaches, relying on network meta-analyses and observational studies, have informed clinical guidelines to facilitate the mass personalization of therapy in routine clinical practice. However, personalized medicine at an individual level remains unclear. For example, which patient is at high risk of disease-related and treatment-related complications, which advanced immunosuppressive agent to choose, and in what order? Novel prognostic biomarkers and routine clinical factors that predict disease course can help strike a balance between potent immunosuppression and the risk of uncontrolled inflammation. However, no such biomarker is currently used in clinical practice. PredictSURE-IBD is a machine-learning-derived and validated 17-gene whole-blood

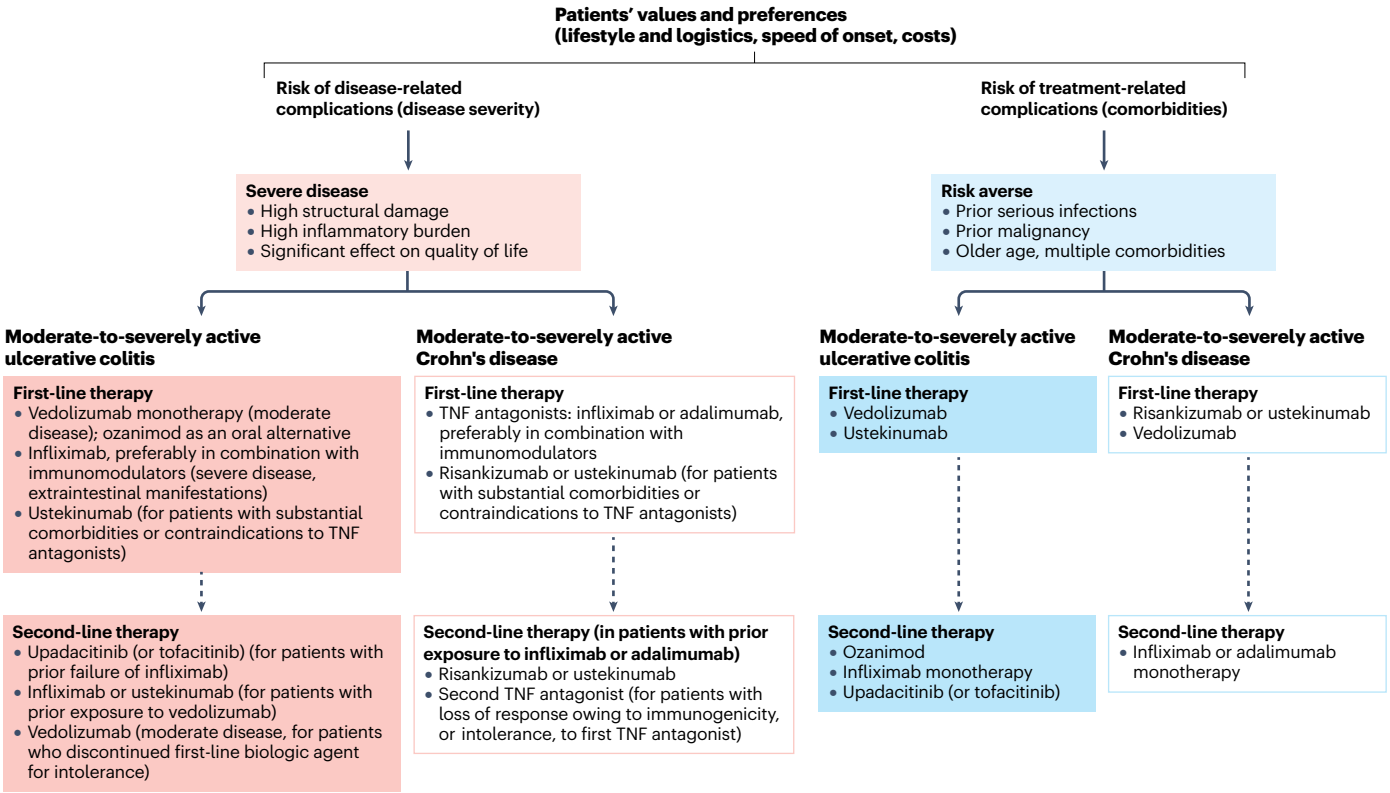

Fig. 1 | Proposed treatment algorithm for patients with moderate-to-severe Crohn's disease and moderate-to-severe ulcerative colitis. The algorithm integrates data on comparative effectiveness and safety of therapies in the context of an individual patient's risk of disease-related and treatment-related complications. TNF, tumour necrosis factor. Adapted with permission from ref.[10], Elsevier.

quantitative PCR classifier for separating patients with IBD with mild versus aggressive disease course at diagnosis[7]. It is currently being tested in the Predicting outcomes for Crohn's disease using a molecular biomarker (PROFILE) trial. Biomarkers predictive of therapeutic efficacy are also vital to identify potentially effective specific agents. Single-gene transcriptomic markers were associated with a high likelihood of failure of TNF antagonists, including mucosal IL-13Rα2 and mucosal oncostatin[8]. However, these biomarkers are not ready for prime time. *HLADQA1*05*, a genetic variant associated with a high risk of immunogenicity to TNF antagonists, is a commercially available pharmacogenomic biomarker being used in clinical practice to make decisions regarding the use of immunomodulators in combination with TNF antagonists[9]. Clinical prediction models relying on routine clinical factors have modest predictive ability in choosing between different therapies. However, they can help identify patients more or less likely to respond to treatment.

In summary, as treatment options for IBD expand rapidly, an integrated synthesis of risk benefits from diverse evidence sources, including head-to-head trials, real-world evidence, and patients' values and preferences, can inform the optimal positioning of therapies to improve patient outcomes. In the future, prognostic and predictive biomarkers in conjunction with clinical factors might help make precise decisions.

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Competing interests

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Additional information

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