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Review article

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Understanding the therapeutic toolkit for inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD), encompassing ulcerative colitis and Crohn's disease, is a group of chronic, immune-mediated disorders of the gastrointestinal tract that present substantial clinical challenges owing to their complex pathophysiology and tendency to relapse. A treat-to-target approach is recommended, involving iterative treatment adjustments to achieve clinical response, reduce inflammatory markers and achieve long-term goals such as mucosal healing. Lifelong medication is often necessary to manage the disease, maintain remission and prevent complications. The therapeutic landscape for IBD has evolved substantially; however, a ceiling on therapeutic efficacy remains and surgery is sometimes required (owing to uncontrolled disease activity or complications). Effective IBD management involves comprehensive care, including medication adherence and a collaborative clinician–patient relationship. This Review discusses current therapeutic options for IBD, detailing mechanisms of action, efficacy, safety profiles and guidelines for use of each drug class. We also explore emerging therapies and the role of surgery. Additionally, the importance of a multidisciplinary team and personalized care in managing IBD is emphasized, advocating for patient empowerment and involvement in treatment decisions. By synthesizing current knowledge and emerging trends, this Review aims to equip healthcare professionals with a thorough understanding of therapeutic options for IBD, enhancing informed, evidence-based decisions in clinical practice.

Sections

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Key points

- Comprehensive and effective inflammatory bowel disease (IBD) care integrates pharmacological therapies, surgical interventions and tailored lifestyle modifications to holistically address individual patient needs.
- Current treatment options for IBD span a range of agents, including aminosalicylates, corticosteroids, immunomodulators, biologic agents (anti-tumour necrosis factor agents, anti-integrins, anti-interleukins), and small molecules such as JAK inhibitors and S1P modulators.
- Emerging therapies for IBD, including anti-IL-23, JAK inhibitors, TL1A inhibitors and RIPK1 inhibitors, offer targeted approaches to mitigate inflammation, expanding options for patients with IBD.
- Non-pharmacological strategies, such as smoking cessation, healthy diets, regular physical activity, and mental health support, complement medical treatments for improved disease management.
- Multidisciplinary care is important in IBD management, collaboration between specialists and active patient engagement through education and shared decision-making enhance treatment adherence, satisfaction and long-term outcomes.
- Empowering patients by providing patients with accessible knowledge, self-management tools and resources fosters active involvement and more effective disease control.

Introduction

Inflammatory bowel disease (IBD), which includes ulcerative colitis and Crohn's disease, are chronic immune-mediated disorders of the gastrointestinal tract that can lead to impaired quality of life and disability. These conditions can present clinical challenges owing to their complex underlying pathophysiology, chronic nature and tendency to relapse[1]. The International Organization for IBD (IOIBD), through its Selecting Therapeutic Targets in IBD (STRIDE) initiative, recommends a treat-to-target approach[2]. This approach involves iterative treatment adjustments to achieve short-term goals of clinical response, medium-term goals of normalizing inflammatory markers and long-term goals of clinical remission, endoscopic healing, absence of disability and restoration of quality of life[2]. As outlined in the consensus of the Selecting End Points for Disease-Modification Trials (SPIRIT), continuous care aims to comprehensively manage the various manifestations of IBD, even after controlling inflammatory activity[3]. Consequently, patients with IBD often require lifelong medication to modulate the course of the disease, maintain remission, prevent debilitating complications (such as stricture, fistulas, bowel resection and colorectal cancer) and preserve their quality of life[4,5].

The therapeutic landscape for IBD has evolved substantially, driven by advancements in our understanding of the molecular mechanisms underlying intestinal inflammation. Despite an increasing availability of therapeutic options, medical therapies have reached a ceiling in their effectiveness[6–8], and surgical resection is sometimes the last option for patients who do not respond adequately to optimized treatments, in ulcerative colitis and Crohn's disease[9]. Current treatments primarily aim to inhibit immune activity by targeting specific inflammatory cytokines. However, there remains a substantial gap in strategies that directly promote mucosal healing and restore homeostasis[10]. A comprehensive management approach for IBD involves more than just specific treatments for IBD, it includes various tools and strategies. However, even with an extensive set of tools, the effectiveness of interventions is limited without an in-depth understanding of the diverse therapeutic toolkit to enable tailoring of treatment strategies to individual needs. Additionally, the success of these interventions heavily depends on the patient adherence to medical prescriptions and lifestyle recommendations, which underscores the importance of a collaborative approach in managing IBD, whereby clinicians and patients actively engage in the treatment process.

This Review provides a comprehensive overview of the current therapeutic toolkit for managing IBD in adult patients. We explore how each class of drugs interacts with the immune system and the inflammatory pathways involved in IBD, presenting clinical efficacy and safety profiles based on key studies (most studies cited are phase III trials unless stated otherwise) and usage guidelines for each class of medication. Surgery, along with a variety of procedures, will also be addressed, although the primary emphasis will be placed on drug treatment options. By synthesizing current knowledge and emerging trends, this Review seeks to provide a thorough understanding of the therapeutic options for IBD to inform evidence-based decisions in clinical practice.

Current therapies and landscape of new drugs

In the 1930s, no treatments were available for IBD. An initial breakthrough came in the 1940s when sulfasalazine was found to be effective in treating ulcerative colitis[11,12]. This discovery originated from Swedish physician Nanna Svartz, who observed that patients with rheumatoid arthritis treated with sulfasalazine (formed by the combination of sulfapyridine and 5-aminosalicylic acid (5-ASA)), who also had ulcerative colitis, experienced relief from their ulcerative colitis symptoms[12]. It was only later that 5-ASA was identified as the active therapeutic component of sulfasalazine[12,13]. In 1955, Truelove conducted the first blinded, controlled trial in patients with ulcerative colitis ($n = 213$), demonstrating that corticosteroids significantly ($P < 0.001$) improved outcomes and reduced mortality compared with individuals who received a 'dummy preparation' as controls[14]. The 1950–1970s saw the development of immunomodulators, initially used as chemotherapeutic agents: methotrexate in the 1950s in Crohn's disease, 6-mercaptopurine in the 1960s and azathioprine, a prodrug of 6-mercaptopurine, in the 1970s[15–18]. The approval of infliximab, a monoclonal antibody targeting the pro-inflammatory cytokine tumour necrosis factor (TNF) for Crohn's disease in 1998 marked the beginning of a new era of targeted 'biological therapies', revolutionizing the management of IBD[19]. Other anti-TNF drugs were subsequently developed, including adalimumab[20–24], certolizumab pegol[25,26], and golimumab[27,28]. Subsequent advancements led to the development of new biologic agents with distinct mechanisms of action: vedolizumab, an anti-integrin $\alpha_4\beta_7$ agent[29,30]; ustekinumab, which inhibits IL-12 and IL-23[31,32]; and risankizumab and mirikizumab, which specifically target IL-23 (refs. 33–36). In parallel, from the mid-2010s to 2020, innovative synthetic drugs, known as 'small molecules' emerged, demonstrating the efficacy of oral therapies with Janus kinase (JAK) inhibitors and sphingosine-1-phosphate (S1P) receptor modulators. Table 1 provides an overview of the current IBD drug classes, detailing the specific molecules within each class, their indications, modes of administration, pros and cons, and the potential clinical benefits of combining them

Table 1 | Summary of current inflammatory bowel disease drug classes and their indication

Drug	Indication	Method of administration and dose			Pros	Cons	Use in combination therapy with immunomodulator
		Induction	Maintenance	Optimization			
Aminosalicylates							
Sulfasalazine	UC	PO: ≥3 g/day	PO: ≥2 g/day	PO: 6 g/day	Effective for mild-to-moderate UC Generally well-tolerated Topical and oral option Potential cancer prevention Use in pregnancy	Limited efficacy for severe UC and in CD Sulfasalazine specific issues	NA
5-ASA	UC	Distal colitis: topical (rectal) 5-ASA ≥1 g/day Extensive colitis: topical (rectal) 5-ASA ≥1 g/day + oral 5-ASA ≥2 g/day	Topic: ≥1 g/day PO: ≥2 g/day	PO: >4 g/day			
Corticosteroids							
Prednisolone	CD, UC	PO or IV: 0.5–0.75 mg/kg	NA	NA	Rapid control of flares Versatile administration (oral, intravenously, topically)	Adverse effects Long-term use limitations Monitoring requirement (in particular blood pressure and blood sugar levels)	NA
Budesonide	CD	PO: 9 mg/day 2–3 months	NA	NA			
Budesonide MMX	UC	PO: 9 mg/day 2–3 months	NA	NA			
Immunomodulators							
Azathioprine	CD, UC	Thiopurines are not used for induction of remission	PO: 2.0–2.5 mg/kg/day	According 6-TGN level	Oral treatment for thiopurines Reduction of ADA when combined with anti-TNF agents Safety in case of cancer for methotrexate	Slow onset of action Regular monitoring required Adverse events, including risk of infections, cancers and sun sensitivity	NA
6-Mercaptopurine	CD, UC	Thiopurines are not used for induction of remission	PO: 1.0–1.5 mg/kg/day	According 6-TGN level			
Methotrexate	CD	Parenteral: 25 mg/week (during 12 weeks)	Parenteral: 15 mg/week	Parenteral: 25 mg/week			
Cyclosporine	UC	IV: 2 mg/kg/day	PO: 5 mg/kg/day (up to 3 months)	NA			
Anti-TNF agents							
Infliximab	CD FDA: August 1998 EMA: August 1999 UC FDA: September 2005 EMA: July 2004 Subcutaneous EMA: July 2020 FDA: October 2023	IV: 5 mg/kg at weeks 0, 2, 6 (infusion at week 6 is not required if SC administration is used thereafter)	IV: 5 mg/kg every 8 weeks SC: 120 mg every 2 weeks	IV: 10 mg/kg every 8 weeks (label) or 5 mg/kg every 4 weeks (off-label) SC: 240 mg every 2 weeks	Effective for moderate-to severe disease Indicated in perianal disease Indicated in stricturing and penetrating disease Effective on some extraintestinal manifestations Combination therapy benefit Choice between IV or SC Use during pregnancy	Adverse events (including infections and cancer risks) Infusion reaction The need to often combine an immunomodulator for 6–12 months	Yes
Adalimumab	CD FDA: February 2007 EMA: December 2006 UC FDA: September 2012 EMA: May 2012	SC: 160 mg at week 0, 80 mg at week 2, 40 mg at week 4	SC: 40 mg every other week	SC: 80 mg every 2 weeks or 40 mg weekly			
Certolizumab pegol	CD FDA: April 2008	SC: 400 mg at weeks 0, 2, 4	SC: 400 mg every 4 weeks	NA			
Golimumab	UC FDA: May 2013 EMA: October 2009	SC: 200 mg at week 0, then 100 mg at week 2	SC: 50 mg (<80 kg) to 100 mg (≥80 kg) every 4 weeks	<80 kg using 50 mg: 100 mg every 4 weeks			

Table 1 (continued) | Summary of current inflammatory bowel disease drug classes and their indication

Drug	Indication	Method of administration and dose			Pros	Cons	Use in combination therapy with immunomodulator
		Induction	Maintenance	Optimization			
Anti-integrins							
Natalizumab	CD FDA: November 2004	IV: 300 mg every 4 weeks	IV: 300 mg every 4 weeks	NA	Gut-selective action for vedolizumab Safety profile Choice between IV or SC Use during pregnancy	Risk of PML for natalizumab Lower efficacy in patients previously exposed to anti-TNF drugs Slower action in CD Limited efficacy in extraintestinal manifestations and perianal disease	No
Vedolizumab	CD, UC FDA: May 2014 EMA: May 2014 Subcutaneous FDA: September 2023 EMA: May 2022	IV: 300 mg at weeks 0, 2, 6. CD: an additional dose at week 10 might be indicated	IV: 300 mg every 8 weeks SC: 108 mg every 2 weeks	IV: 300 mg every 4 weeks			
Anti-interleukins							
Ustekinumab	CD FDA: September 2016 EMA: May 2018 UC FDA: October 2018 EMA: December 2020	Single IV dose: ≤55 kg: 260 mg; >55 to ≤85 kg: 390 mg; >85 kg: 520 mg	SC: 90 mg every 8 or 12 weeks	SC: 90 mg every 4 weeks (off-label)	Effective, regardless of the line of treatment Safety profile Use during pregnancy	Lower efficacy than risankizumab according to SEQUENCE head-to-head trial for ustekinumab	No
Risankizumab	CD FDA: June 2022 EMA: November 2022 UC FDA: June 2024 EMA: July 2024	CD - IV: 600 mg at weeks 0, 4, 8 UC - IV: 1,200 mg at weeks 0,4,8	SC: 180 mg or 360 mg at week 12 and then every 8 weeks	NA			
Mirikizumab	UC FDA: October 2023 EMA: May 2023	IV: 300 mg at weeks 0, 4, 8	SC: 200 mg every 4 weeks	NA			
Guselkumab	UC FDA: September 2024	IV: 200 mg at weeks 0, 4, 8	SC: 200 mg at week 12 and then every 4 weeks or 100 mg at week 16 and then every 8 weeks	NA			
JAK inhibitors							
Tofacitinib	UC FDA: May 2018 EMA: July 2018	PO: 10 mg BID for 8 weeks Possible induction extended for a further 8weeks	PO: 5 mg BID	PO: 10 mg BID	Oral administration Rapid onset of action Effective regardless of previous treatment line No immunogenicity Short half-life	Adverse effects Contraindications and precautions Regular monitoring requirements Prescription contraindicated for certain populations	No
Filgotinib	UC FDA: not approved EMA: November 2021	PO: 200 mg/day for 10 weeks Possible induction extended for a further 12 weeks	PO: 200 mg/day	NA			
Upadacitinib	CD FDA: May 2023 EMA: April 2023 UC FDA: March 2022 EMA: May 2023	CD - PO: 45 mg/day for 12 weeks UC - PO: 45 mg/day for 8 weeks Possible induction extended for a further 12 weeks for CD (30 mg/day) and 8 weeks for UC (45 mg/day)	PO: 15–30 mg/day	PO: 45 mg for patients on 30 mg and 30 mg for patients on 15 mg			

Table 1 (continued) | Summary of current inflammatory bowel disease drug classes and their indication

Drug	Indication	Method of administration and dose			Pros	Cons	Use in combination therapy with immunomodulator
		Induction	Maintenance	Optimization			
S1P modulators							
Ozanimod	UC FDA: May 2021 EMA: October 2021	PO: days 1–4: 0.23 mg/day PO: days 5–7: 0.46 mg/day From day 8: 0.92 mg/day	PO: 0.92 mg/day	NA	Oral administration Short half-life No immunogenicity Selectivity for etrasimod	Adverse effects and risk Need for regular monitoring Difficulty in obtaining an ophthalmological examination prior to initiation Possible drug interaction	No
Etrasimod	UC FDA: October 2023 EMA: February 2024	PO: 2 mg/day	PO: 2 mg/day	NA			

5-ASA, 5-aminosalicylic acid; ADA, anti-drug antibodies; BID, twice a day; CD, Crohn's disease; IV, intravenous; JAK, Janus kinase; MMX, multi-matrix system; NA, not applicable; PML, progressive multifocal leukoencephalopathy; PO, per os; S1P, sphingosine-1-phosphate; SC, subcutaneous; TGN, 6-thioguanine; TNF, tumour necrosis factor; UC, ulcerative colitis.

with an immunomodulator. The mechanisms of action of these drugs are illustrated in Fig. 1.

Anti-inflammatory drugs

Aminosalicylates are a class of drugs that includes sulfasalazine and 5-ASA. Sulfasalazine, which was developed earlier than 5-ASA, requires activation by azo-reductases that are produced by gut bacteria to be converted into sulfapyridine, which is responsible for most of its adverse effects, and 5-ASA, which provides direct local anti-inflammatory effects on the mucosa[12,37]. Subsequently, isolated 5-ASA formulations (mesalamine, olsalazine and balsalazide) were developed to provide similar efficacy with fewer adverse effects[38]. 5-ASAs act by decreasing the biosynthesis of prostaglandins and leukotrienes through the inhibition of the cyclooxygenase, scavenging free radicals, reducing chemotaxis of macrophages and neutrophils, and increasing the expression and nuclear translocation of peroxisome proliferator-activated receptor-γ (PPARγ)[39,40] This process inhibits the production of pro-inflammatory cytokines such as IL-1, IL-6 and TNF, as well as the activation of nuclear factor-κB (NF-κB)[40]. In addition to their anti-inflammatory properties, 5-ASAs might help prevent colorectal cancer, although further research is needed to confirm this effect[41–43].

5-ASAs have long been used in the treatment of IBD and remain the preferred first-line therapeutic option for mild-to-moderate ulcerative colitis, both for treating and for preventing relapses[44]. However, 5-ASAs are not effective for moderate-to-severe forms of ulcerative colitis and have no role in the contemporary management of Crohn's disease, regardless of disease location, owing to a consistent lack of evidence supporting their efficacy[45]. The additive benefit of continuing aminosalicylates alongside thiopurines or advanced therapies is still debated[46–50]. Patients with ulcerative colitis confined to the rectum or left colon could benefit from topical treatments (suppository or enema)[44]. Those with more extensive disease are advised to use oral therapy, ideally in combination with topical treatments[44,51,52]. All of the 5-ASA formulations can be considered therapeutically equivalent at equimolar doses[53]. According to findings from a Cochrane meta-analysis, a single daily dose of 5-ASA improves adherence without reducing efficacy, whereas irregular intake is associated with an increased risk of relapse[54].

Although 5-ASA is a safe and well-tolerated class of medication, adverse effects can occur. Severe but rare idiosyncratic reactions include fever, acute pancreatitis, hepatitis, myocarditis and pneumopathy, which necessitate discontinuation of the medication[55]. Headaches are one of the most experienced adverse events (approximately 5–10%)[54,56]. Paradoxically, some patients (around 3%) might report worsening diarrhoea[57], and interstitial nephritis is another rare adverse effect, justifying biannual blood creatinine and proteinuria checks[58,59]. Sulfasalazine has more adverse effects than other aminosalicylates owing to its sulfonamide component, sulfapyridine. Oral and/or topical aminosalicylates are generally considered safe during pregnancy, with folic acid supplementation recommended for those on sulfasalazine. However, formulations containing dibutyl phthalate have been associated with congenital anomalies as well as adverse effects on the male reproductive system in animal studies and should, therefore, be avoided during pregnancy[60–62].

Corticosteroids were the second class of therapeutic agents effective in treating IBD[63]. First-generation corticosteroids such as prednisone, methylprednisolone and hydrocortisone, are systemic corticosteroids whereas the second-generation corticosteroids such as budesonide, budesonide multi-matrix system and beclomethasone dipropionate, are considered locally acting[64,65]. These local agents primarily target the gastrointestinal tract, reducing the systemic effects and associated adverse events[64,65]. Mechanistically, corticosteroids operate through the glucocorticoid receptor in the cytoplasm, which is bound to the receptosome (a multi-protein complex)[66]. Binding induces conformational changes, enabling the receptor to translocate to the nucleus and either activate or repress gene transcription[66]. Additionally, the glucocorticoid-receptor complex can inactivate pro-inflammatory transcription factors (such as NF-κB and activator protein 1), thereby preventing the activation of inflammatory mediators such as leukotrienes and cytokines (for example, IL-1 and IL-6)[66]. Corticosteroids effectively induce remission and rapidly control disease flares in both ulcerative colitis and Crohn's disease. However, long-term use is not recommended owing to the high potential for adverse events and they should be taken in the morning, given the potential to cause sleep disturbance[67].

Adverse effects are relatively frequent, especially with systemic corticosteroids, and can manifest in various ways, including cutaneous (cushingoid appearance, acne, hirsutism, abdominal striae, impaired wound healing, skin thinning); psychiatric (sleep disturbance, psychosis, euphoria or hypomania); metabolic–endocrine (weight

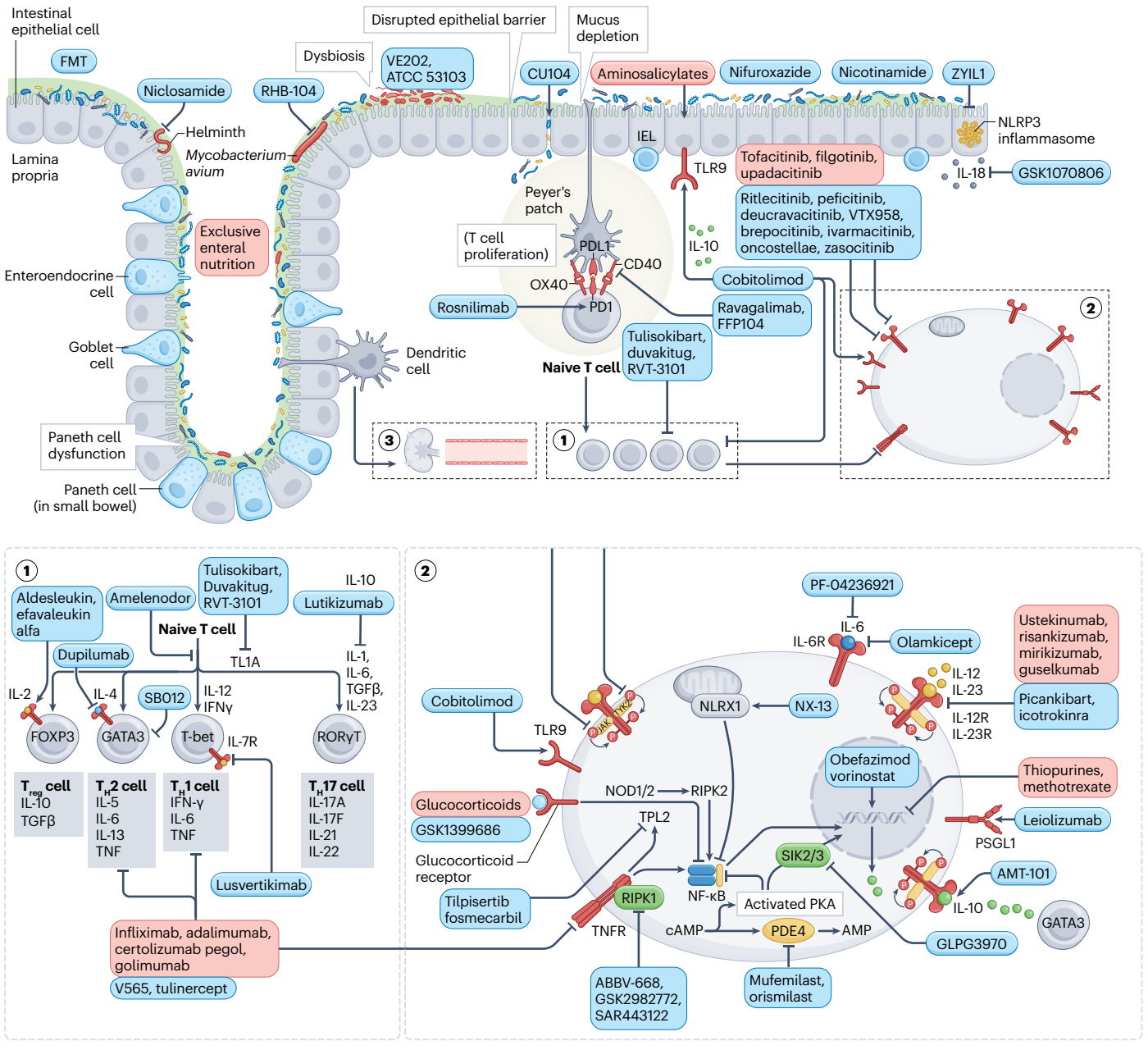

Intestinal epithelial cell
FMT
Niclosamide
RHB-104
Dysbiosis
VE202, ATCC 53103
Disrupted epithelial barrier
Mucus depletion
CU104
Aminosalicylates
Nifuroxazide
Nicotinamide
ZYIL1
NLRP3 inflammasome
IL-18
GSK1070806
Helminth
Mycobacterium avium
Lamina propria
IEL
TLR9
Tofacitinib, filgotinib, upadacitinib
Ritlecitinib, peficitinib, deucravacitinib, VTX958, brepocitinib, ivarmacitinib, oncostellae, zasocitinib
Peyer's patch
(T cell proliferation)
PDL1
CD40
OX40
PD1
IL-10
Cobitolimod
Rosnilimab
Ravagalimab, FFP104
Tulisokibart, duvakitug, RVT-3101
Naive T cell
Exclusive enteral nutrition
Enteroendocrine cell
Goblet cell
Dendritic cell
Paneth cell dysfunction
Paneth cell (in small bowel)
1
2
3
Aldesleukin, efavaleukin alfa
Amelenodor
Tulisokibart, Duvakitug, RVT-3101
IL-10
Lutikizumab
Dupilumab
TL1A
IL-1, IL-6, TGFβ, IL-23
IL-2
IL-4
SB012
IL-12 IFNγ
FOXP3
GATA3
T-bet
IL-7R
RORγT
T_reg cell IL-10 TGFβ
T_H2 cell IL-5 IL-6 IL-13 TNF
T_H1 cell IFN-γ IL-6 TNF
T_H17 cell IL-17A IL-17F IL-21 IL-22
Lusvertikimab
Infliximab, adalimumab, certolizumab pegol, golimumab
V565, tulinercept
PF-04236921
IL-6
IL-6R
Olamkicept
Ustekinumab, risankizumab, mirikizumab, guselkumab
IL-12 IL-23
Picankibart, icotrokinra
IL-12R IL-23R
NLRX1
NX-13
Cobitolimod
TLR9
JAK
TYK2
Obefazimod vorinostat
Thiopurines, methotrexate
Leiolizumab
PSGL1
Glucocorticoids
GSK1399686
Glucocorticoid receptor
NOD1/2
RIPK2
TPL2
SIK2/3
AMT-101
IL-10
GATA3
Tilpisertib fosmecarbil
RIPK1
NF-κB
Activated PKA
cAMP
PDE4
AMP
TNFR
GLPG3970
ABBV-668, GSK2982772, SAR443122
Mufemilast, orismilast
3 Lymph node
Ozanimod, etrasimod
Icanbelimod, tamuzimod, amiselimod
S1P
S1P gradient
Vasculature
Endothelium
CXCL8, CXCL1, CXCL3, CXCL10 for leukocyte recruitment
Alicaforsen
ICAM1
Natalizumab
Carotegrast methyl, milategrast
α4β1
CCR9
Vedolizumab
α4β7
Abrilumab, PN-943, MORF-057, GS-1427, ABBV-382
AZD7798
FKN
Quetmolimab
MAdCAM-1
VCAM1

Fig. 1 | Mechanism of action of drugs currently approved or in clinical trials for inflammatory bowel disease. Mechanisms of action for drugs currently approved (red box) or being tested in phase II and III clinical trials (blue box) for inflammatory bowel disease (IBD). Although not exhaustive, the intention is to showcase the breadth of mechanisms and targets. Many IBD treatments focus on inhibiting pro-inflammatory cytokines, which is particularly evident with anti-tumour necrosis factor (TNF) agents (such as infliximab, adalimumab, certolizumab pegol and golimumab), which are approved, and investigational therapies (such as V565 and tulinercept). Other therapies target specific interleukins, including: lutikizumab (targets IL-1α/β); aldesleukin and efavaleukin alfa (targets IL-2); PF-04236921 (inhibits IL-6); and olamkicept (targets IL-6 receptor). Additionally, lusvertikimab antagonizes the IL-7 receptor and GSK1070806 inhibits IL-18. IL-12/IL-23 inhibitors, such as ustekinumab (approved for both ulcerative colitis and Crohn's disease) and a range of anti-IL-23 agents are also an important part of the therapeutic arsenal. Other treatments focus on inhibiting TL1A (e.g., tulisokibart, duvakitug and RVT-3101), which promotes the differentiation of lymphocytes into T helper 17 (T_H17) cells, playing a pro-inflammatory part. Further treatments, such as amelenodor, reduce the differentiation of naive CD4 cells into T_H1 and T_H17 cells, whereas SB012 acts as a GATA3 antagonist to prevent the differentiation of lymphocytes into pro-inflammatory subsets. Other treatments currently in development target molecules involved in antigen presentation, such as rosnilimab (targets PD1); and ravagalimab and FFP104 (inhibits CD40). When pro-inflammatory cytokines bind to their receptors, they activate enzymes linked to the intracellular domains, specifically Janus kinases (JAKs) and tyrosine kinases (TYKs), triggering pro-inflammatory signalling cascades within immune cells. By inhibiting JAKs (a rapidly expanding drug class in IBD treatment), it is possible to disrupt multiple cytokine-dependent pro-inflammatory pathways simultaneously. Finally, other molecules target pro-inflammatory signalling pathways within immune cells, including receptor-interacting serine/threonine protein kinase 1 (ABBV-668, GSK2982772, SAR443122), as well as phosphodiesterase-4 (PDE4), such as mufemilast or orismilast and SIK2/3 inhibitors (GLPG3970). Several treatments inhibit lymphocyte migration, such as anti-integrin $\alpha_4\beta_7$ therapies (vedolizumab, approved, and others under evaluation such as abrilumab, PN-943, MORF-057, GS-1427 and ABBV-382) and anti-integrin α_4 therapies (including natalizumab, and investigational agents such as carotegrast methyl and milategrast). Lymphocyte migration is facilitated by binding of integrins on lymphocytes to endothelial adhesion molecules, which are also targeted by emerging therapies including alicaforsen (targets intracellular adhesion molecule 1 (ICAM1)), quetmolimab (acts on fractalkine) and AZD7798 (inhibits CCR9). Additionally, treatments such as sphingosine-1-phosphate receptor (S1PR) modulators (approved agents include ozanimod and etrasimod, with others such as icanbelimod, tamuzimod and amiselimod under investigation) prevent lymphocytes from leaving lymph nodes by internalizing their receptors, hindering their ability to reach the site of inflammation. Exclusive enteral nutrition can be used as induction therapy for patients with mild-to-moderate Crohn's disease who are motivated to adhere to dietary treatment and have access to dietetic support. Additionally, certain antimicrobial therapies are currently under investigation. Agents under investigation but not shown include: rosiglitazone (targets PPARγ); vixarelimab (oncostatin M R inhibitor); SPH3127 (renin inhibitor); PL-8177 (melanocortin 1R agonist). CCR, chemokine receptor; CXCL, chemokine ligand; FKN, fractalkine; FMT, faecal microbiota transplant; IEL, intraepithelial lymphocyte; IFNγ, interferon-γ; MAdCAM-1, mucosal vascular addressin cell adhesion molecule 1; NF-κB, nuclear factor-κB; NLRP3, NOD-like receptor family pyrin domain containing 3; NLRX-1, nucleotide-binding oligomerization domain leucine rich repeat containing X1; PDE4, phosphodiesterase-4; PKA, protein kinase A; PSGL1, P-selectin glycoprotein ligand-1; R, receptor; RIPK, receptor-interacting serine/threonine-protein kinase; S1P, sphingosine-1-phosphate; SIK2/3, salt inducible kinases 2/3; TGFβ, tumour growth factor-β; TLR9, toll-like receptor 9; TPL2, tumour progression locus 2; TNFR, tumour necrosis factor receptor; T_{reg} cell, regulatory T cell; VCAM1, vascular cell adhesion molecule 1.

gain, hyperglycaemia, suppression of the hypothalamic–pituitary–renal axis); cardiovascular (hypertension, venous thromboembolism); immunological (lymphocytopenia, immunosuppression and increased risk of infections, especially opportunistic infection); gastrointestinal (gastritis, gastric ulcer, pancreatitis, hepatic steatosis); musculoskeletal (osteoporosis/fracture, osteonecrosis and myopathy); and ophthalmic (cataract, glaucoma)[67–69]. During treatment, blood pressure and blood sugar levels should be monitored. The infection risk depends on the dose, duration of therapy and concurrent use of other immunomodulators. Additionally, screening for cataracts and glaucoma is necessary, and bone density should be monitored with prolonged corticosteroid use (oral corticosteroid therapy for at least 3 consecutive months in a dose ≥7.5 mg per day of prednisone-equivalent) or frequent courses of steroids[70]. Corticosteroids can also cause adrenal gland suppression (characterized by extreme fatigue, weight loss, loss of appetite, hypoglycaemia, nausea, diarrhoea or vomiting, and abdominal pain), so adrenal function should be checked when discontinuing treatment if symptoms arise. Corticosteroids should never be used as maintenance therapy[44,45,67]. Patients with IBD who are steroid-dependent should be managed with steroid-sparing treatments, and educating patients is crucial to prevent misuse. Corticosteroids can be used during pregnancy and lactation to induce remission when necessary, but they should be administered with caution, as they can increase the risk of complications, including pregnancy-related complications such as gestational diabetes and adverse pregnancy outcomes[62,71].

Immunomodulators

Azathioprine, 6-mercaptopurine, methotrexate, cyclosporine A and tacrolimus are immunomodulators that can be used in the treatment of IBD[72,73]. Azathioprine is a prodrug of 6-mercaptopurine and, although they are dosed differently, these agents have equivalent effects. Mechanisms of action include the integration of 6-thioguanine (in place of guanine nucleotides) into DNA or RNA, hindering replication, DNA repair and protein synthesis; inhibition of de novo purine synthesis by the metabolite 6-thioinosine 5′-monophosphate, disrupting replication of immune cells; and induction of T cell apoptosis via the mitochondrial pathway activated by 6-thioguanosine 5′-triphosphate[74]. Methotrexate inhibits folic acid, which is necessary for purine synthesis and suppresses the JAK–signal transducer and activator of transcription (STAT) pathway, mediating its immunomodulatory effects[75]. Cyclosporine A and tacrolimus are calcineurin inhibitors that work by blocking the nuclear translocation of the transcription factor NFAT, thereby preventing the initiation of T cell cytokine transcription[76].

Thiopurine monotherapy is not recommended as an induction therapy for either ulcerative colitis or Crohn's disease owing to its slow onset of action[44,45,77–79]. Typically, thiopurines are introduced alongside faster-acting drugs such as corticosteroids. In ulcerative colitis, thiopurine monotherapy is used for the maintenance of remission in patients with steroid-dependent ulcerative colitis or who are intolerant to 5-ASA[44,78]. In Crohn's disease, thiopurine monotherapy can be used as maintenance therapy or to prevent postoperative recurrence[45]. Thiopurine can also be used as concomitant treatment with anti-TNF agents in

ulcerative colitis and Crohn's disease[44,45,78,79]. Parenteral methotrexate can be used in both induction and maintenance of remission in patients with Crohn's disease[45,80,81]. However, use of methotrexate in ulcerative colitis is not supported by current evidence[44,82]. The prospective PANTS study showed that infliximab or adalimumab combination therapy with one of these immunomodulators (methotrexate or thiopurines) reduced the risk of developing anti-drug antibodies (ADAs), which is a frequent cause of loss of response to anti-TNF drugs[83]. Although thiopurines and methotrexate have demonstrated efficacy, they are less effective than biologic agents and small-molecule therapies in achieving endoscopic healing[84]. Cyclosporine is another immunomodulator used in cases of acute severe ulcerative colitis that are refractory to steroid therapy, provided that emergency colectomy is not required. However, its use is complicated by the need for regular monitoring of serum levels and concerns about its safety profile[85,86].

Common adverse effects of thiopurines include gastrointestinal intolerance (diarrhoea, vomiting), leukopenia, thrombocytopenia and anaemia, necessitating regular blood count monitoring. Thiopurine *S*-methyltransferase (*TPMT*) genotyping or research of nudix hydrolase 15 (*NUDT15*) polymorphisms before thiopurine initiation can help identify patients at risk of myelosuppression[87,88]. Other adverse events include allergic reactions (fever, rash, joint pain, flu-like symptoms) and pancreatitis. Liver monitoring is essential owing to the risks of hepatotoxicity and nodular regenerative hyperplasia. Immunomodulators slightly increase the risk of viral infections (cytomegalovirus, varicella-zoster virus, Epstein–Barr virus (EBV)) and serious lymphomas, particularly in young EBV-naive men and patients older than 65 years, as well as the risk of urinary tract cancer[89]. Consequently, long-term use in these patient categories requires careful, case-by-case evaluation[90]. Moreover, immunomodulators can increase skin sensitivity to sunlight, raising the risk of non-melanoma skin cancers[91]. Protection measures and regular full-body skin examinations are recommended for patients who currently are being treated with immunomodulators or have received such treatment in the past[92]. Methotrexate can cause early adverse effects such as nausea, vomiting, diarrhoea and stomatitis, which can be mitigated by taking folic acid[76]. Longer-term adverse effects include hepatotoxicity and pneumonitis[76]. Additionally, a case–control study has suggested that methotrexate can increase the risk of non-melanoma skin cancer[93]. With cyclosporine A, most common adverse effects are paraesthesia (especially of the hands and feet, sometimes associated with a tremor of the hands) and hypertrichosis (dense, pigmented hair growth predominantly occurring along the spine, upper arms and face)[94]. Additionally, there is a risk of nephrotoxicity, hepatotoxicity (cholestasis), hypertension, possibly malignant lymphoma, infectious complications, seizures, headaches, gingival hyperplasia and anaphylaxis (with intravenous cyclosporine administration only)[94]. Initiating thiopurine monotherapy during pregnancy is generally not recommended owing to its slow onset of action and potential risk of adverse events[95]. However, patients already on thiopurine monotherapy can safely continue maintenance treatment during pregnancy and lactation[95]. For those on combination therapy with biologic agents, discontinuing thiopurines can be considered if they are in long-term remission, with adequate anti-TNF serum levels offering helpful guidance in such cases[95]. Although data on the use of cyclosporine and tacrolimus in pregnant patients with IBD are limited[95], methotrexate is contraindicated during pregnancy due to safety concerns[96,97]. Methotrexate should be discontinued at least 3 months prior to attempting conception[95].

Anti-TNF agents

TNF is a key pro-inflammatory cytokine that contributes to IBD pathology by promoting the apoptosis of T cells[98–100], Paneth cells[101] and intestinal epithelial cells, thereby increasing epithelial permeability[102]. It also induces neoangiogenesis, facilitating the influx of inflammatory cells to the inflammatory site[98], activates the production of pro-inflammatory cytokines by macrophages and exacerbates tissue injury by activating matrix metalloproteinases whilst reducing their inhibitors[103,104]. Anti-TNF therapies bind to both soluble and transmembrane TNF, inhibiting its interaction with receptors and therefore regulating various signalling pathways involved in IBD pathophysiology[105,106].

Anti-TNF agents approved by the FDA (United States) and EMA (Europe) for the treatment of IBD include infliximab, adalimumab, certolizumab pegol and golimumab. Anti-TNF agents are recommended for moderate-to-severe corticosteroid-dependent or corticosteroid-resistant IBD, as well as for patients who have had an inadequate response to, or are intolerant of, 5-ASA or immunomodulator[44,45,51,79]. Additionally, anti-TNF agents are effective and often the best treatment option in cases of perianal involvement, penetrating or fistulizing disease, certain extraintestinal manifestations (such axial spondyloarthritis or uveitis), and acute severe ulcerative colitis[44,45,51,79]. Infliximab, the first approved anti-TNF agent, is a chimeric monoclonal antibody administered intravenously on an 8-week maintenance schedule after an initial 3-dose induction (weeks 0, 2, 6). Clinical trials ACCENT I and II confirmed the efficacy and safety of infliximab as induction and maintenance treatment for moderate-to-severe luminal and fistulizing Crohn's disease[107,108]. For ulcerative colitis, the ACT I and ACT II trials demonstrated that infliximab led to significantly ($P < 0.001$) higher rates of clinical response, remission and mucosal healing than placebo at 8, 30 and 54 weeks, respectively[109]. Adalimumab, a fully humanized monoclonal antibody administered subcutaneously every 2 weeks, has shown efficacy in inducing and maintaining remission in both Crohn's disease and ulcerative colitis. The CLASSIC I, CLASSIC II and CHARM studies demonstrated the effectiveness of adalimumab in moderate-to-severe Crohn's disease[20,21,110], whereas the CHARM post hoc analysis highlighted the role of adalimumab in healing perianal fistulas[111]. The ULTRA 1 and ULTRA 2 studies demonstrated the superiority of adalimumab over placebo in achieving and maintaining clinical remission and mucosal healing in patients with ulcerative colitis at weeks 8 and 52[22–24]. Certolizumab pegol, a PEGylated-conjugated Fab fragment of a recombinant humanized monoclonal antibody targeting TNF, is approved by the FDA for moderate-to-severe Crohn's disease only[25,26]. The PRECISE I and II studies demonstrated the safety and efficacy of certolizumab pegol in both induction and maintenance therapy, with a longer half-life (due to its PEGylated form) enabling subcutaneous administration every 4 weeks in maintenance therapy[25,26]. Finally, golimumab, administered subcutaneously every 4 weeks after induction phase, effectively induces and maintains clinical remission in moderate-to-severe ulcerative colitis, as demonstrated by the PURSUIT-SC and PURSUIT-M randomized controlled trials (RCTs)[27,28].

The high costs of anti-TNF therapies have led to the development of biosimilars, which have been shown to reduce healthcare costs, especially after the expiration of patents[112]. Biosimilars are biologic products developed to closely match approved biologic agents, designed to have comparable efficacy, safety and purity to the original products[113,114]. Regulatory agencies in the United States and Europe have approved several biosimilars for treating ulcerative colitis and Crohn's disease, including a subcutaneous form of infliximab, primarily based on efficacy

and safety data from other indications, such as rheumatological diseases[115,116].

Therapeutic drug monitoring (TDM), historically used for anti-TNF agents and now also applied to other biologic therapies, is a valuable tool for optimizing the management of patients with IBD[117–119]. TDM can be used in two ways: proactive or reactive. Proactive TDM involves regular, repeated monitoring of drug and ADA levels, regardless of disease activity, followed by dose adjustments of the biologic agent to achieve a predefined target concentration[45,120]. Currently, there is insufficient evidence to recommend the routine use of proactive TDM for patients receiving anti-TNF therapy, except in specific situations such as treatment de-escalation, dose reduction in patients in remission with higher-than-necessary drug levels, optimizing anti-TNF monotherapy as an alternative to combination therapy with immunomodulators in select patients and assessing ADA after restarting infliximab following a drug holiday[45,120]. By contrast, reactive TDM, endorsed by multiple gastroenterological societies, guidelines and expert consensus statements, involves assessing drug concentration and ADA levels in patients with active disease to help identify the underlying cause of primary non-response or secondary loss of response[45,120]. Indeed, a primary drawback of anti-TNF therapies is that up to 30% of patients do not respond to initial induction treatment (primary non-response), and 40% of initial responders eventually lose their response[121–123]. This secondary loss of response can result from pharmacodynamic or pharmacokinetic failure, which might be immune-mediated[124]. In pharmacodynamic failure, patients do not respond despite optimal drug levels, indicating the drug is not blocking inflammatory mediators, necessitating a switch to a different drug class[124]. Non-immune-mediated pharmacokinetic failure involves subtherapeutic drug levels due to rapid clearance, often requiring increased dosages to achieve therapeutic level[124]. Immune-mediated pharmacokinetic failure is characterized by low or undetectable drug levels and the presence of ADAs, leading to increased drug clearance, termed immunogenicity[125]. For low ADA levels, optimizing anti-TNF therapy by increasing the dose, shortening intervals or adding immunomodulator may help (by acting on ADAs and drug levels)[126,127]. High ADA levels necessitate switching within the drug class with combination therapy, using proactive TDM or changing to a different drug class[125]. Phase III RCTs have indeed shown that combination therapy with infliximab and azathioprine is superior in inducing corticosteroid-free clinical remission compared with monotherapy with either agent in both Crohn's disease and ulcerative colitis[84,128]. This combination therapy is probably the best strategy for patients at high risk of disease progression, but long-term studies are needed to understand its value in preventing bowel damage, permanent disability and serious drug-related adverse events or mortality[129,130]. In the REACT study, early anti-TNF and immunomodulator combination therapy was not associated with an increased risk of serious drug-related adverse events or mortality compared with 'conventional management'[131]. However, subcutaneous infliximab delivered markedly higher drug levels than intravenous administration, which might help prevent the development of ADAs and potentially dispense the need for adding an immunomodulator[132].

Anti-TNF therapies can lead to adverse events such as infusion reactions when given intravenously and increased infection rates. TNF has a role in immune responses to bacterial and fungal infections, and its inhibition can raise the risk of rare opportunistic infections such as candidiasis, *Legionella pneumophila* and tuberculosis[133]. Patients can experience paradoxical reactions with joint or skin manifestations, such as new-onset psoriasiform dermatitis lesions[134]. Additionally, rare cases of hepatitis, leukopenia, thrombocytopenia (necessitating blood sampling every 6 months), heart failure, demyelinating neurological diseases (requiring evaluation and additional examinations as per symptoms) and drug-induced lupus have been reported[133]. Combining anti-TNF with thiopurine increases the risk of lymphoma, although the role of anti-TNF alone in this condition is less clear[93,135–137]. Anti-TNF drugs can be safely continued during pregnancy and breastfeeding[62,95].

Anti-integrins

Integrins are leukocyte cell-surface adhesion molecules, activated via intracellular signalling triggered by chemokines and other stimuli, which enables leukocytes to migrate through the vascular wall and access tissues, such as the intestinal tract. Various integrins, including $\alpha_2\beta_2$, $\alpha_4\beta_1$, $\alpha_4\beta_7$ and $\alpha E\beta_7$, bind to specific ligands on the endothelium, such as addressins or adhesion molecules. Inhibiting these integrins prevents lymphocytes from binding to adhesion molecules and migrating into tissues.

Natalizumab, a recombinant humanized monoclonal IgG4 antibody targeting the integrin subunit α_4, blocks both $\alpha_4\beta_7$ and $\alpha_4\beta_1$ integrins. It was the first anti-integrin developed for Crohn's disease, following its approval for multiple sclerosis. Inhibiting integrin $\alpha_4\beta_7$ prevents its adhesion to the mucosal addressin cell adhesion molecule 1 (MAdCAM-1), predominantly expressed in the endothelial venules of the digestive tract, thereby preventing lymphocytes from migrating to the inflammatory site[138,139]. Conversely, inhibition of $\alpha_4\beta_1$ binding to the vascular cell adhesion molecule-1 (VCAM1), is not gut-selective and affects lymphocyte migration in the central nervous system[140,141]. Although natalizumab is effective in inducing and maintaining clinical remission in patients with Crohn's disease[142], its use is limited in many countries owing to the risk of reactivating the JC polyomavirus and causing often fatal progressive multifocal leukoencephalopathy[143,144].

Vedolizumab, a gut-selective humanized IgG1 monoclonal antibody that antagonizes $\alpha_4\beta_7$ integrin, is approved by the FDA and EMA as induction and maintenance therapy for patients with moderate-to-severe ulcerative colitis and Crohn's disease[29,30], and has also been shown to be effective in preventing postoperative recurrence[145]. Anti-integrin $\alpha_4\beta_7$ effectively induces and maintains remission in moderate-to-severe ulcerative colitis (GEMINI 1 study)[29] and Crohn's disease (GEMINI 2 study)[30]. Anti-TNF naïve patients have a better clinical remission rate than those previously exposed to anti-TNF agents[146,147] The treatment regimen for both conditions involves infusions at weeks 0, 2 and 6, followed by every 8 weeks, with an additional dose at week 10 for Crohn's disease if necessary[29,30]. A subcutaneous form of vedolizumab is also currently available, requiring an injection every 2 weeks. A meta-analysis showed that combining vedolizumab with an immunomodulator is no more effective than monotherapy in inducing or maintaining remission[148]. Vedolizumab has also proved effective in treating pouchitis[149]. However, its gut-selectivity could limit its effectiveness in treating perianal disease and extraintestinal manifestations, although the role of anti-adhesion therapies in these conditions remains uncertain[150].

Vedolizumab, whilst primarily targeting integrin $\alpha_4\beta_7$ in the digestive tract, is also expressed in the ear, nose, throat, bronchial and biliary tracts and can, therefore, be associated with upper respiratory infections (pharyngitis, angina, laryngitis)[29,30]. Rare cases of infusion reactions have been reported, with serious allergic events being very rare. Other adverse effects, such as headaches and joint pains, can occur after infusions but are usually temporary. At present, no cases

of progressive multifocal leukoencephalopathy have been observed with vedolizumab. Finally, despite being a continuing concern, vedolizumab initiation does not seem to cause new-onset arthritis, including spondylarthritis, in patients with IBD[151]. Vedolizumab can be safely continued during pregnancy and breastfeeding[62].

Anti-interleukins

In response to endogenous or exogenous signals associated with host defence and wound healing, dendritic cells and tissue-resident macrophages release IL-12 (composed of p40 and p35 subunits) and IL-23 (composed of p19 and p40 subunits), which are pro-inflammatory cytokines[152]. IL-12 promotes the differentiation of naive $CD4^+$ T cells into IFNγ–producing type 1 T helper (T_H1) cells[153]. IL-12 binds to the IL-12Rβ1 and IL-12Rβ2 subunits of the IL-12 receptor, stimulating the activity of JAK family enzymes, JAK2 and tyrosine kinase 2 (TYK2). This process leads to the phosphorylation of STAT family members STAT1, STAT3, STAT5 and particularly STAT4[154,155]. IL-23 promotes the differentiation of naive $CD4^+$ T cells into T_H17 cells, but indirectly, as naive $CD4^+$ T cells lack the IL-23 receptor (IL-23R)[153,156,157]. Exposure to cytokines such as transforming growth factor-β (TGFβ), IL-1 and IL-6 induces the expression of retinoic acid receptor–related orphan receptor-γt (RORγt), a transcription factor that promotes the expression of *Il23r* and *Il17a*[157,158]. IL-23 binds to the heterodimeric receptor complex (composed of IL-12Rβ1 and IL-23R) activating the JAK–STAT pathway as IL-12, but predominantly STAT3. IL-23 induces the production of IL-17A, IL-17F and/or IL-22 and stabilizes T_H17 cells[158].

Ustekinumab is a fully human $IgG1_K$ monoclonal antibody that binds p40 subunit shared by IL-12 and IL-23, which has been approved by the FDA and EMA for both Crohn's disease and ulcerative colitis[159]. Ustekinumab received approval for treating moderate-to-severely active Crohn's disease following proven safety and efficacy in induction (UNITI-1 in biologic agent-exposed and UNITI-2 in biologic agent-naive patients) and maintenance (IM-UNITI) studies in both TNF antagonist naive and failure patients[31]. The highest clinical efficacy was observed in patients who were anti-TNF naive[31]. In patients with moderate-to-severe active ulcerative colitis, the phase III clinical trial (UNIFI) demonstrated that ustekinumab was effective in inducing clinical remission at 8 weeks, both in biologic agent-exposed and biologic agent-naive individuals[32]. Ustekinumab was also effective in maintaining remission, when administered subcutaneously every 8–12 weeks after the intravenous induction infusion, in these two patient categories[32]. In addition to IL-12/IL-23, three specific IL-23 inhibitors have been approved in the past few years. Risankizumab is an IgG1 monoclonal antibody directed against the p19 subunit of IL-23, approved for patients with moderate-to-severe Crohn's disease and ulcerative colitis. The ADVANCE (including 42% of biologic agent-naive patients) and MOTIVATE (exclusively patients previously exposed to biologic agents) studies evaluated the safety and efficacy of therapeutic induction of risankizumab in Crohn's disease[33]. At week 12, the administration of risankizumab 600 mg at weeks 0, 4 and 8 resulted in a significantly ($P < 0.001$) higher rate of clinical and endoscopic remission rates than placebo[33]. The efficacy and safety of risankizumab in the maintenance treatment of Crohn's disease has been evaluated in the FORTIFY trials[34]. A markedly higher proportion of patients on risankizumab had achieved clinical remission (52% versus 41%) and endoscopic response (47% versus 22%), compared with placebo, by week 52[34]. In ulcerative colitis, a phase III RCT demonstrated that risankizumab resulted in a significantly ($P < 0.001$) higher rate of clinical remission in patients with moderate-to-severely active ulcerative colitis, both during the induction (INSPIRE study) and maintenance (COMMAND study) phases, than placebo[35]. Mirikizumab is a humanized monoclonal antibody that also targets the p19 subunit of IL-23. It has been approved by the FDA and EMA for the treatment of patients with moderate-to-severe ulcerative colitis. The efficacy and safety of mirikizumab has been demonstrated in the LUCENT-1 (induction) and LUCENT-2 (maintenance) studies[36]. In 2023 and 2024, preliminary results from the QUASAR and GALAXI studies showed that guselkumab, another IL-23p19 subunit antagonist, induced and maintained remission in patients with moderate-to-severe ulcerative colitis and Crohn's disease, respectively[160–162]. Guselkumab has just been approved by the FDA in September 2024 for the treatment of ulcerative colitis[160–162]. A meta-analysis has shown that combining ustekinumab with an immunomodulator is no more effective than monotherapy in inducing or maintaining remission[148] and at present there are no data for anti-IL-23 agents.

Cases of drug hypersensitivity associated with the administration of ustekinumab and anti-IL23 agents have been reported[163]. Common adverse effects of this class of drugs include infections (such as upper respiratory tract infections, rhinopharyngitis, sinusitis and dental infections), headaches, dizziness, rash, nausea, muscle pain as well as arthralgia[164]. Anti-IL-23 drugs can result in elevated liver enzymes and bilirubin levels[36,165]. Liver function tests should be conducted at the beginning of treatment, during the induction phase and up to at least 12 weeks of risankizumab and at least 24 weeks for mirikizumab[166,167]. Further monitoring for liver function should be done according to standard patient management protocols[166,167]. Although not formally studied in clinical trials, post-marketing data from cohort studies suggests that this class of therapy can be safely continued during pregnancy and breastfeeding[62,95,168].

JAK inhibitors

JAK, including JAK1, JAK2, JAK3 and TYK2, are enzymes linked to the intracellular domains of cytokine receptors[169]. When an extracellular ligand (usually cytokines, such as interferons and interleukins) binds to these receptors, JAKs are activated and autophosphorylated[170]. This leads to JAK-mediated phosphorylation of the receptor, which facilitates the binding and JAK-mediated phosphorylation of a C-terminal tyrosine residue in STAT family members, leading to their homodimerization or heterodimerization. This process results in a subsequent translocation to the cell nucleus and the binding of dimerized STATs to DNA-regulatory elements controls the transcription of associated genes[170]. JAK inhibition, therefore, has the potential to affect multiple pro-inflammatory cytokine-dependent pathways.

Tofacitinib (oral pan-JAK inhibitor, acting mainly on JAK1 and JAK3 enzymes), filgotinib (oral selective JAK1 inhibitor) and upadacitinib (oral selective JAK1 inhibitor) have been approved by the FDA and EMA for the management of patients with moderate-to-severe ulcerative colitis (following the OCTAVE I, II and sustain studies for tofacitinib[171,172], the SELECTION study for filgotinib[173] and the U-ACHIEVE and U-ACCOMPLISH studies for upadacitinib[174]). For Crohn's disease, two phase IIb randomized placebo-controlled clinical trials showed no superiority of tofacitinib over placebo[175] and, therefore, there is no evidence to support the use of tofacitinib for this indication. However, upadacitinib (following the two induction U-EXCEL and U-EXCEED phase III trials and the U-ENDURE phase III maintenance trial) has been approved for Crohn's disease[176]. For these JAK inhibitors approved in ulcerative colitis and Crohn's disease, efficacy has been observed for all JAK inhibitors, regardless of the

number of lines of treatment or mode of action that have been received and failed previously[171–174]. JAK inhibitors are administered orally, in tablet form.

Common adverse effects include headaches, nausea, arthralgia and increased infection risks (especially of the upper respiratory tract and herpes zoster infections). Patients >50 years of age with additional risk factors that increase the likelihood of herpes zoster infection might benefit from receiving a herpes zoster vaccination, preferably a recombinant vaccine, before initiating JAK inhibitor therapy[177–179]. These risk factors, in patients receiving JAK inhibitors, include age, glucocorticoid use, concurrent therapies and underlying immunological dysregulation[180]. If infection occurs, antiviral treatment is typically effective and adjusting or temporarily discontinuing JAK inhibitors might be necessary depending on the severity of the infection[180]. A decrease in the absolute count of lymphocytes and neutrophils, and a decrease in haemoglobin levels, could also occur following treatment with JAK inhibitors[181]. Additionally, alteration of the liver enzymes (cytolysis), increased low-density lipoprotein and high density lipoprotein cholesterol, as well as transient and mild elevations in creatine phosphokinase levels, have been reported[181]. Treatment with JAK inhibitors requires regular blood monitoring, including a complete blood count and a liver work-up 1–2 months after initiation and then every 3 months, as well as a lipid work-up at 8–12 weeks[182]. In patients aged 65 years and over, those with risk factors for major cardiovascular events, for thromboembolic events or cancer and with current or past smoking habits, it is recommended to use JAK inhibitors only when no alternatives exists and at a reduced dose[182,183]. The Oral Rheumatoid Arthritis Trial (ORAL) Surveillance, a randomized study involving patients with rheumatoid arthritis over 50 years old with at least one cardiovascular risk factor, found that tofacitinib was associated with a higher incidence of major adverse cardiovascular events and cancer when compared with adalimumab or etanercept[184,185]. However, these risks were not observed in patients with IBD[186], probably owing to differences in the pathogenesis of rheumatoid arthritis and IBD, but also that the prevalence of certain specific risk factors (such as older age and smoking status) are not the same for individual patients who have ulcerative colitis or rheumatoid arthritis[187–189]. Patients with IBD are generally younger, have fewer comorbidities (such as diabetes and hypertension) and therefore a lower baseline cardiovascular risk than those with rheumatoid arthritis. Treatment decisions should, therefore, be individualized, considering patient profiles, benefit–risk balance and specific risk factors such as age, smoking status and baseline cardiovascular, venous thromboembolism or cancer risks. An annual dermatological exam is recommended but should be part of health maintenance of any patient with IBD[190]. Specific dosing adjustments are needed for users of CYP3A4 inhibitors treated with tofacitinib or upadacitinib[191]. In the absence of sufficient data, JAK inhibitor use during pregnancy or lactation is not recommended at present[62,95].

Sphingosine-1-phosphate receptor modulators

Sphingosine-1-phosphate (S1P) is a membrane-derived phospholipid that acts as an extracellular signalling molecule and influences inflammation by affecting lymphocyte trafficking through activation of five G protein-coupled receptor isoforms (S1PR1 to S1PR5), expressed in T and B cells, as well as other immune cells[192,193]. During inflammation, pro-inflammatory cytokines promote S1P production in lymphatic vessels, creating an S1P gradient between the lymph nodes (where the concentration is low) and the efferent lymphatic vessels (where concentration is higher). This gradient causes lymphocytes, particularly autoreactive T and B cells, to exit the lymph nodes, re-enter the bloodstream and move to the inflammation site, perpetuating the inflammatory response[194–196]. S1P receptor (S1PR) modulators cause receptor internalization inside immune cells, subsequent ubiquitination and degradation by the proteasome, preventing the cells from following the S1P gradient and migrating and thus preventing their access to the inflammation site[197–199].

Ozanimod (which selectively binds S1PR1 and S1PR5)[200–202] and etrasimod (which binds S1PR1, S1PR4 and S1PR5)[203] are two S1PR modulators approved by the FDA and EMA in 2021, safe and effective for the induction and maintain of remission in ulcerative colitis (following the results of the TRUE NORTH study for ozanimod[200] and the ELEVATE study for etrasimod[203]). Ozanimod and etrasimod are both taken orally once daily. For ozanimod, a gradual dose increase (known as the titration period) is required during the first week to prevent bradycardia, whereas no titration is needed for etrasimod as per the label.

S1PR modulators induce reversible lymphopenia by sequestering lymphocytes in lymphoid tissues, correlating with therapeutic

Box 1 | Factors to consider when choosing a treatment

Disease characteristics

- Disease activity: mild, moderate, severe
- Disease phenotype: inflammatory, stricturing, penetrating
- Extent of the disease
- Presence or absence of perianal disease
- Presence or absence of extraintestinal manifestations
- Presence or absence of associated conditions on which treatments can act
- Impact on quality of life and nutritional status

Patient status

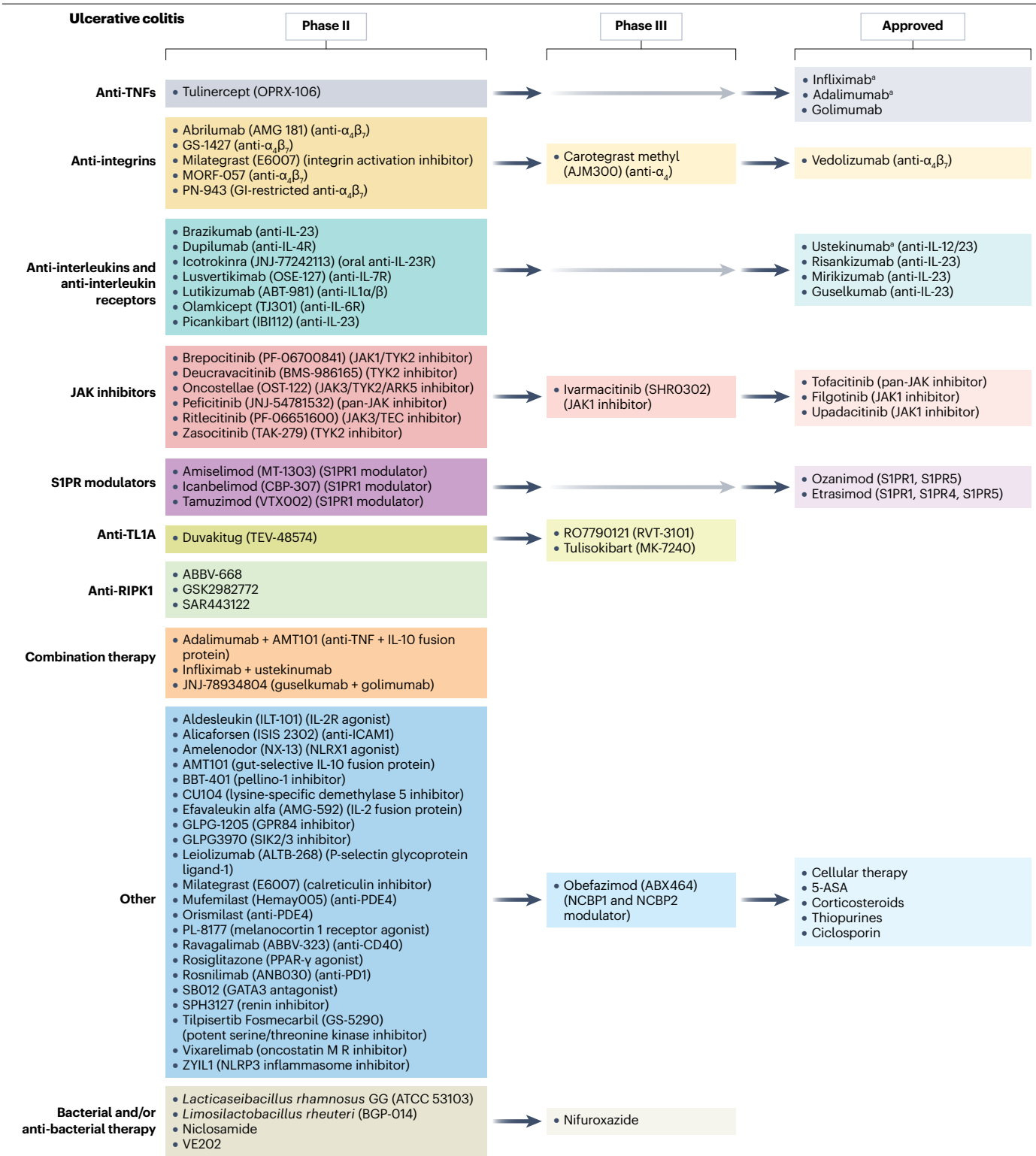
- Age
- Comorbidities (such as cardiac, neurological, oncological)
- Family planning
- Patient preferences (including considerations for the mechanism of action and mode of administration)
- Risk profile
- Adherence
- Relevant biomarkers

Treatment history

- Previous treatments
- Response and complication to previous treatment
- Potential for optimizing therapy
- Decision between monotherapy and combination therapy
- The speed of treatment action
- Current algorithms and guidelines

Other considerations

- Type of healthcare centre
- Level of education and expertise
- Familiarity with available treatments
- Insurance coverage
- Treatment costs



response in clinical trials. If lymphopenia drops below 200/mm^3, ozanimod should be paused until levels reach 500/mm^3. For less severe leukopenia or lymphopenia, treatment can continue with a possible dosage reduction. There are no specific guidelines for absolute lymphocyte counts with etrasimod, as treatment was not discontinued in clinical trials even when counts fell below 200/mm^3. The drop in lymphocytes is not associated with increased infection rates according to trial evidence[204,205], but as for all treatments patients should be instructed to report infection symptoms promptly and treatment should be paused if a serious infection develops[206]. There is also a risk

Fig. 2 | Current ulcerative colitis treatments approved and in clinical trials. Single agent or combination therapies approved or under evaluation in phase II or III trials in ulcerative colitis. The left column lists molecules currently under investigation in phase II clinical studies, the middle column represents those being evaluated in phase III studies and the right column includes molecules that have received regulatory approval. The treatments are organized and colour-coded into sections based on their mechanisms of action: anti-tumour necrosis factor (TNF) agents; anti-integrins; anti-interleukins or inhibition of their receptor; Janus kinase (JAK) inhibitors; sphingosine-1-phosphate receptor (S1PR) modulators; anti-tumour necrosis factor-like ligand 1A (TL1A); anti-receptor-interacting serine/threonine-protein kinase 1 (RIPK1); combination therapies; other mechanisms of action; and therapies targeting bacteria. Information correct as of 26 November 2024. 5-ASA, 5-aminosalicylic acid; CCR, chemokine receptor; GI, gastrointestinal; ICAM1, intercellular adhesion molecule 1; MAP, *Mycobacterium avium* subspecies paratuberculosis; PDE4, phosphodiesterase-4; TYK, tyrosine kinase. [a]Treatments for which biosimilars are now available.

of bradycardia (although the drop in heart rate was minimal in the RCTs) and heart block with this class of drugs, necessitating a titration period with ozanimod and making them contraindicated in patients with cardiac issues (myocardial infarction, symptoms of unstable angina, episode of cardiac decompensation requiring hospitalization, class III or IV heart failure, transient ischaemic attack in the past 6 months, presence of second-degree or third-degree atrioventricular block, sick sinus syndrome, except in patients with a functional pacemaker)[206]. Because of the risk of macular oedema, a fundoscopic examination is advised and required for patients with diabetes and ocular complications, uveitis or a history of retinal disease, before the ozanimod and etrasimod initiation, respectively. Finally, rare neurological disorders have been reported in patients with multiple sclerosis treated with S1PR modulators, including progressive multifocal leukoencephalopathy and posterior reversible encephalopathy syndrome[207]. Although these issues have not been reported in patients with ulcerative colitis, it is recommended to stop the S1PR modulators if neurological symptoms occur, until a neurologist excludes such conditions[207]. Owing to the risk of adverse effects, regular monitoring is required, including electrocardiograms, heart rate, blood pressure (hypertension was more frequently reported in clinical trials), blood count and liver function tests. This monitoring is recommended before starting and at regular intervals (at months 1, 3, 6, 9 and 12 on therapy and periodically thereafter, according label recommendations)[206,207]. Fundoscopic examinations should be repeated if any visual changes occur. Concomitant medications should also be regularly reviewed in patients treated with ozanimod to avoid interactions. It is not recommended to co-administer ozanimod with monoamine oxidase inhibitors, medications that can increase norepinephrine or serotonin, strong CYP2C8 inhibitors (for example, gemfibrozil), strong CYP2C8 inducers (for example, rifampin) or treatment that can affect cardiac conduction, such as QT prolongers, β-blockers and calcium-channel blockers[207]. As with JAK inhibitors, this class is contraindicated during pregnancy and breastfeeding owing to limited data[95,208].

Optimal use of therapeutic options

The choice of treatments is influenced by a variety of factors (outlined in Box 1). With the introduction of new compounds and emerging study results, therapeutic algorithms are continuously evolving. In this context, although not exhaustive, it might be more effective to focus on highlighting key studies that have had a major influence on treatment approaches.

For example, regarding the use of anti-TNF agents, the PROFILE trial demonstrated the benefits of early anti-TNF initiation, suggesting that early combined immunosuppression with infliximab and an immunomodulator (known as the top-down approach) should be considered the standard of care for patients with newly diagnosed active Crohn's disease, as it demonstrated markedly better 1-year outcomes than the accelerated step-up (conventional) treatment strategy[130]. Similarly, the CALM study showed that early escalation to anti-TNF therapy, based on a combination of clinical symptoms and biomarkers in patients with early Crohn's disease, led to improved clinical and endoscopic outcomes compared with symptom-based treatment decisions alone[209]. For patients with Crohn's disease in long-term corticosteroid-free remission on combination therapy with infliximab and an immunomodulator, the SPARE trial showed that discontinuing infliximab should be carefully evaluated on a case-by-case basis, weighing the risks and benefits[210]. By contrast, stopping the immunomodulator is generally a safer and more preferable approach when considering treatment de-escalation[210].

Head-to-head trials enable clinicians to directly compare the effectiveness of two treatments, rather than relying on placebo comparisons. This approach helps determine which therapy is superior in achieving key outcomes for specific patient populations and aids in treatment selection. For example, the VARSITY trial demonstrated that vedolizumab was more effective than adalimumab in achieving clinical remission and endoscopic improvement in patients with moderate-to-severely active ulcerative colitis, though it did not show superiority in achieving corticosteroid-free clinical remission[211]. The SEAVUE study found that both ustekinumab and adalimumab monotherapies were highly effective in biologic-naive patients, with no statistically significant difference in the primary outcome (clinical remission at week 52) between the two treatments[212]. Additionally, the SEQUENCE study showed that in patients with moderate-to-severe Crohn's disease who experienced unacceptable adverse effects or inadequate response to anti-TNF therapy, risankizumab was noninferior to ustekinumab in achieving clinical remission at week 24 and was superior in achieving endoscopic remission at week 48[213].

Landscape of new drugs

New drugs are currently being developed within the aforementioned classes, as well as through entirely different mechanisms of action. Mirikizumab, an IL-23p19 antagonist already approved by the FDA and EMA in 2023 for ulcerative colitis, demonstrated safety and efficacy as both induction and maintenance treatment in the phase III VIVID-1 study, showing clinical remission and endoscopic response over a 52-week period in patients with moderate-to-severely active Crohn's disease who had experienced intolerance, insufficient response or loss of response to standard treatments[214]. This successful phase III trial will serve as the foundation for global regulatory submissions for Crohn's disease[214]. A new class of treatment that is emerging are the anti-TNF-like ligand 1A (TL1A) therapies, having both anti-inflammatory and anti-fibrotic effect, with development of tulisokibart (MK-7240, formerly PRA-023) currently being evaluated in phase III trials both in ulcerative colitis[215] and Crohn's disease[216]. Finally, certain combinations of treatments are currently being assessed, with potentially promising

results, as shown by the VEGA study (guselkumab plus golimumab)[217]. Approved molecules, along with those under evaluation in phase II and III studies, are shown in Fig. 1 (mechanism of action), Fig. 2 (for ulcerative colitis) and Fig. 3 (for Crohn's disease). Supplementary Table 1 provides detailed information on the conditions being studied, the method of administration, the type of molecule, the mechanism of action and the clinical phase of each drug.

Physician therapeutic toolkit beyond inflammatory bowel disease drugs

In addition to medications for treating intestinal inflammation, IBD specialists have a variety of tools at their disposal to manage issues associated with IBD (such as malnutrition, extraintestinal manifestations or anaemia) and treat complications (including infectious complication or abscesses and stricture), which can include surgery. These tools also encompass strategies for preventing complications (such as prophylactic treatments) and therapeutic tools specific to particular clinical scenarios (Table 2).

Surgery and management of complications

It is recommended in guidelines that IBD surgeries be performed in high-volume IBD centres, with a laparoscopic approach as the preferred first-line treatment for abdominal surgery in Crohn's disease[218,219]. In Crohn's disease, biologic agents can be continued leading up to surgery, whereas corticosteroids should be tapered whenever possible to minimize the risk of complications[219]. For patients with limited terminal ileal or ileocecal Crohn's disease involvement, the LIR!C study showed that laparoscopic ileocecal resection is a viable alternative to anti-TNF therapy[220]. Long-term data from this randomized trial revealed that, although 48% of patients in the anti-TNF group required surgery within 5 years, there were no cases of surgical recurrence in the surgery group during the same period[221]. Additionally, findings from a meta-analysis

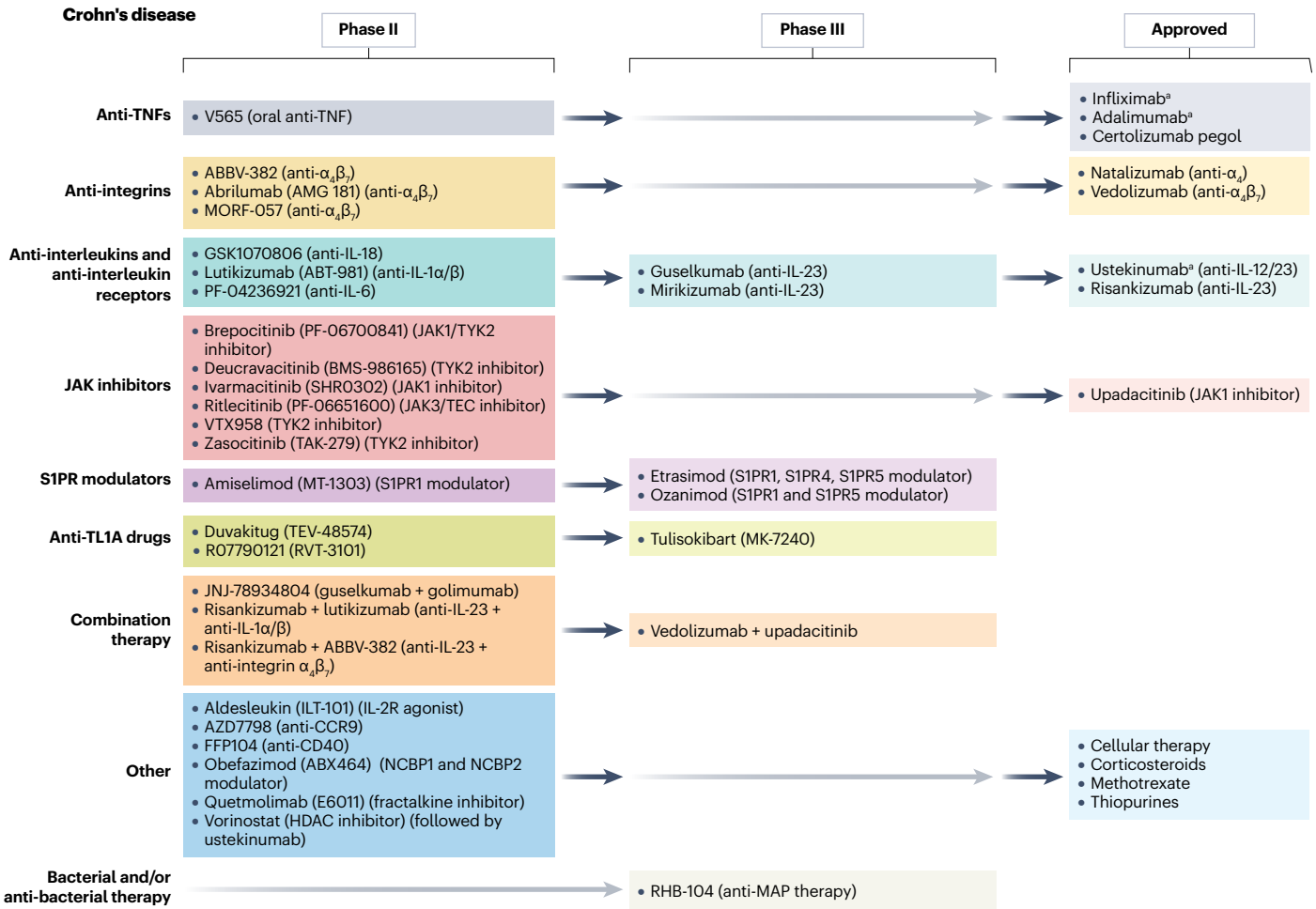


Fig. 3 | Current Crohn's disease treatments approved and in clinical trials. Single agent or combination therapies approved or under evaluation in phase II or III trials in Crohn's disease. The left column lists molecules currently under investigation in phase II clinical studies, the middle column represents those being evaluated in phase III studies and the right column includes molecules that have received regulatory approval. The treatments are organized and colour-coded into sections based on their mechanisms of action: anti-tumour necrosis factor (TNF) agents; anti-integrins; anti-interleukins or inhibition of their receptor; Janus kinase (JAK) inhibitors; sphingosine-1-phosphate receptor (S1PR) modulators; anti-tumour necrosis factor-like ligand 1A (TL1A); combination therapies; other mechanisms of action; and therapies targeting bacteria. Information correct as of 26 November 2024. CCR, chemokine receptor; HDAC, histone deacetylase; MAP, *Mycobacterium avium* subspecies paratuberculosis; TYK, tyrosine kinase. [a]Treatments for which biosimilars are now available.

Table 2 | Other management strategies that are used alongside inflammatory bowel disease drugs

Management strategy	Details
Symptomatic treatment and management of associated conditions	
Anti-diarrhoeal medications	Anti-motility: loperamide, diphenoxylate-atropine, eluxadoline Bile salt resins : colestyramine, colestipol, colesevelam Spasmolytics[a]: pinaverium, trimebutine Absorbants[a]: psyllium, methyl cellulose Probiotics[a]
Analgesics	Antispasmodics Antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors)[a] In case of small intestinal bacterial overgrowth: antibiotics (such as metronidazole, ciprofloxacin, rifaximin)[a] Probiotics[a] Diet intervention: low-FODMAP diet[a] Psychological approaches Chronic use of opioids should be avoided
Transfusion	Administered in case of anaemia
Nutritional supplementation	
Renutrition	Oral nutrition supplements, exclusive enteral nutrition, partial enteral nutrition, parenteral nutrition
Macronutrients and vitamins	Supplementation to correct deficiencies in iron, vitamins B_9, B_{12}, A, D, K, selenium, zinc, magnesium and calcium
Treatment of complications	
Antibiotics	Used for infectious complications or abscesses
Endoscopic treatments	Endoscopic balloon dilatation for Crohn's disease strictures
Radiological intervention	Percutaneous image-guided drainage
Surgical interventions	Includes surgical resection, stricturoplasty, total colectomy, anal abscess drainage, seton placement, ileostomy and colostomy
Prophylactic measures	
Vitamin D and calcium supplementation	Recommended during long-term corticosteroid therapy
Low-molecular-weight heparin	Used during relapses requiring hospitalization, sometimes even at home, to prevent thromboembolic complications
Tuberculosis prevention	Administer antituberculosis treatment following recommendations
Hepatitis B prevention	Prophylactic antiviral treatment with nucleotide or nucleoside analogues for hepatitis B virus carriers
Vaccinations	Before initiation of conventional or advanced therapies; important for varicella-zoster virus, pneumococcal and COVID-19 vaccinations
Pneumocystis jirovecii prevention	Prophylactic trimethoprim and/or sulfamethoxazole following local recommendations
Herpes simplex virus prevention	Daily oral therapy with aciclovir or valaciclovir for frequent and/or severe recurrences

These management strategies can be symptomatic treatments and taking these treatments can mask symptoms or be contraindicated in some individuals (detrimental or ineffective depending on scenario). [a]Low evidence.

published in 2020 have suggested that, in comparison with initial medical therapy, early bowel resection is associated with a lower risk of both overall and surgical recurrence, as well as a reduced need for postoperative biologic therapy[222]. Elective bowel resection in patients with Crohn's disease, is also linked to substantially lower mortality than emergency surgery, underscoring the importance of perioperative optimization (including preoperative nutritional assessment and renutrition, iron supplementation if needed) and the need to avoid emergency procedures whenever possible[223]. In selected cases of colonic Crohn's disease, segmental colectomy could also be considered[219]. After surgery, it is recommended to perform endoscopic surveillance within 6–12 months following surgical resection in Crohn's disease[219].

In cases of small bowel stricture, endoscopic balloon dilatation can be recommended for strictures less than 5 cm in length, provided that the necessary technical expertise is available[224]. Stricturoplasty is also considered a viable alternative to resection in case of stricture[219]. For intra-abdominal abscesses related to Crohn's disease, intravenous antibiotics and percutaneous, image-guided drainage are recommended as first-line treatments, with surgery reserved for cases that do not respond to medical management[219]. In cases of Crohn's disease-associated colorectal cancer or high-grade dysplasia, proctocolectomy is generally advised, although segmental colectomy followed by endoscopic surveillance might be suitable in selected cases[219,225,226].

For perianal disease, seton drainage is recommended as a preliminary step before initiating medical or surgical treatment for complex perianal Crohn's disease fistulas[219,227]. Combining anti-TNF therapy with seton removal can lead to better healing rates, quicker time to healing, longer remission periods and a reduced need for surgery than either treatment on its own[219]. Infliximab is the first-line treatment

for inducing and maintaining remission in complex perianal fistulas in Crohn's disease[219,228]. However, a post hoc analysis of the CHARM trial demonstrated the superiority of adalimumab over placebo for fistula healing after 56 weeks, indicating that adalimumab is also a viable option for this condition[111]. Additional data indicate that combining anti-TNF therapy with ciprofloxacin might enhance the short-term (12 weeks) effectiveness of anti-TNF treatment, with a favourable safety profile, although it does not affect longer-term (24 weeks) healing rates[229,230]. In cases of complex perianal fistula, advancement flap or ligation of the intersphincteric fistula tract can be considered and fistulotomy can be advised for carefully chosen patients with Crohn's disease who have a simple fistula and no signs of proctitis[219]. Combining medical treatment with surgical closure is recommended for suitable patients with complex perianal fistulas, as surgical closure leads to better long-term outcomes[219]. Autologous adipose-derived stem cells can be considered a treatment option for complex perianal Crohn's disease. Additionally, faecal diversion through a defunctioning ileostomy or colostomy can be used to manage refractory, complex perianal disease[219]. If the condition remains resistant to treatment despite a defunctioning stoma, proctectomy can be recommended[219].

In patients with ulcerative colitis who are medically refractory or corticosteroid-dependent, total proctocolectomy can be offered, followed by ileal pouch–anal anastomosis (IPAA; the procedure of choice) or permanent end-ileostomy (a reasonable option for some patients), according to European Crohn's and Colitis Organisation guidelines[231]. The choice of procedure should be personalized through a shared decision-making approach that aligns with patient preferences[231,232]. The modified two-stage IPAA, which involves an initial total colectomy with end-ileostomy whilst leaving the rectum in situ, followed by a proctectomy and ileal pouch–anal reconstruction with ileostomy take-down, could become a standard of care[231]. In ulcerative colitis, patients receiving biologic therapies can have an increased risk of early and late complications specific to the pouch. In such circumstances, a three-stage or modified two-stage approach with deferred pouch construction should be considered, whereas single-stage restorative proctocolectomy should be avoided in patients receiving biologic therapies[219].

Management of issues associated with inflammatory bowel disease

IBD is often associated with disorders of gut–brain interaction including irritable bowel syndrome (IBS), making it common for patients with IBD in remission to continue to experience pain and transit issues[233,234]. Consequently, IBD specialists can resort to symptomatic treatments, including anti-diarrhoeal medications such as loperamide and spasmolytic agents, to relieve symptoms related to IBS[234]. Another condition frequently linked with IBD is bile acid malabsorption, reported in up to 50% of adults with Crohn's disease, particularly those with ileal involvement or ileal resection[235,236]. Some patients with this IBD-associated condition can continue to have diarrhoea even in remission, and treatment with loperamide, colestyramine, colestipol or colesevelam, which are commercially available, can therefore be administered[237,238]. Future options could include liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, and tropifexor, a non-bile acid farnesoid X receptor agonist[237].

Patients with Crohn's disease can also require nutritional support. Exclusive enteral nutrition, using liquid formulations, is a well-established therapy for inducing clinical remission and endoscopic improvement in Crohn's disease, with stronger evidence supporting its effectiveness in children than in adults[239]. Additionally, this strategy can be beneficial for malnourished patients preparing for elective surgery for Crohn's disease[239]. Parenteral nutrition can be used in particular situations, such as when intra-abdominal abscesses or phlegmonous inflammation impede the ability to obtain adequate nutrition[239]. It is also indicated for patients with high-output gastrointestinal fistulas, prolonged ileus, short bowel syndrome, or those with severe malnutrition related to IBD, for which both oral and enteral nutrition have been unsuccessful or when enteral access is not possible or contraindicated[239]. Additionally, it is often necessary to supplement patients with IBD in macronutrients and vitamins, as deficiencies are common among patients with IBD owing to decreased intake, excessive losses or malabsorption, in particular in patients with Crohn's disease and active small bowel disease or those undergoing intestinal resection[240]. Identifying and correcting deficiencies in iron (particularly in cases of anaemia), vitamins B_9 (folic acid), B_{12} (cobalamin) and fat-soluble vitamins A, D, K, zinc, selenium, magnesium and calcium are essential[241]. In rare cases, blood transfusions might be necessary. Lastly, extraintestinal manifestations of IBD require specialized management, although the specifics fall outside the scope of this Review and have been reviewed elsewhere[242].

Prophylactic treatment

The IBD specialist toolkit also includes a series of prophylaxis, which can be primary or secondary, and can be used in a variety of circumstances. This approach can involve vitamin D and calcium supplementation in the case of long-term corticosteroid therapy, prophylaxis with low-molecular-weight heparin in the case of relapses requiring hospitalization (and sometimes even at home) and vaccination before initiation of IBD therapies (in particular varicella-zoster virus vaccine in seronegative patients, annual influenza vaccination, pneumococcal vaccination or coronavirus disease 2019 (COVID-19))[243]. If live attenuated vaccines are necessary, they should be administered at least 1 month before starting immunosuppressive therapy[243]. The use of live attenuated vaccines should indeed be avoided during immunosuppressive treatment and for a period of 1–4 months after discontinuation, depending on the elimination half-life of the drug[243]. In patients with suspected latent or active tuberculosis, initiation of advanced therapies should be postponed and antituberculosis treatment should be given according to national guidelines. A rare event of severe hepatitis B flare can occur during drug-induced immunosuppression[244,245]. For patients who are carriers of the hepatitis B virus (hepatitis B surface antigen positive), it is advised to initiate prophylactic antiviral treatment with nucleotide or nucleoside analogues. This treatment should ideally begin 2 weeks prior to starting advanced therapies and should continue for 1 year after discontinuing these medications[243]. Prophylaxis for *Pneumocystis jirovecii* infection should follow local recommendations[243]. Frequent and/or severe outbreaks of herpes simplex virus disease can be mitigated with the daily use of oral medications such as aciclovir or valaciclovir[243].

Multidisciplinary team and shared decision-making

Given the complexity of IBD, the best approach to ensure holistic management is through collaboration with a multidisciplinary team, which is particularly important for managing extraintestinal symptoms. This team could include an IBD nurse specialist, surgeon, rheumatologist, dermatologist, ophthalmologist, hepatologist, cardiologist, dietician, psychologist, obstetrician and gynaecologist, sexologist, radiologist,

pathologist, stomatotherapist, physiotherapists and the general practitioners. Finally, patients are increasingly involved in making decisions about their treatment and care. IBD specialists should, therefore, have access to decision aid tools (which should be updated continually) to invite patients actively to the decision-making process (particularly with regard to the choice of treatment), even though not all situations are suitable for shared decision-making[246].

These tools could include printed booklets that present treatment options, risks and benefits in an easily understandable format. Examples include the Crohn's & Colitis Foundation's Treatment Options decision aid and web-based platforms like IBD&Me, which help personalize treatment choices based on individual preferences and medical history. This approach could improve patient compliance and satisfaction and could lead to better results[247].

Tools for personalized care

Despite the numerous tools at our disposal, a plateau in drug effectiveness exits, with a substantial proportion of patients still experiencing suboptimal responses to medical treatment[6]. One reason for this limited therapeutic success is that, currently, our therapeutic decisions are largely based on factors related to the disease, comorbidities, safety considerations, drug characteristics and patient preferences[248]. However, these criteria have limited predictive accuracy, making reliance solely on these clinical factors inadequate for guiding effective clinical decision-making. Despite the proposal of potential biomarkers in various studies, precision medicine in IBD has made limited progress since the introduction of the first targeted therapy, the anti-TNF antibody infliximab, over two decades ago. Few tools are currently available in the therapeutic toolkit to personalize care. Tools that could aid the personalization of care include prognostic biomarkers to predict disease complications and bowel damage (to guide step-up or top-down strategies), biomarkers to predict the efficacy (or lack thereof) of therapies and biomarkers to assess the risk of adverse effects, whether in the first-line of treatment or after its failure (to optimize the treatment sequence for each patient)[249].

Regarding prognostic biomarkers, preliminary studies have shown that in patients newly diagnosed with Crohn's disease and treatment-naive, the gene-expression signature of $CD8^+$ T cells can be used as a prognostic blood test[250]. However, the PROFILE (Predicting Outcomes For Crohn's disease using a Molecular Biomarker) trial, a biomarker-stratified interventional trial published in 2024, showed that the use of the 17-gene blood-based biomarker had no clinical utility for guiding treatment strategies in Crohn's disease[130]. For predicting drug safety, thiopurine methyltransferase genotyping is the primary biomarker used by clinicians before initiating thiopurines, to identify patients with a high risk of thiopurine-induced myelosuppression[87]. Few markers are used in clinical practice to predict response (or lack of response) to IBD therapies. Dulai et al.[251] developed a clinical decision support tool for vedolizumab in patients with Crohn's disease, demonstrating that the absence of prior anti-TNF agents, bowel surgery, fistulizing disease, high serum albumin and low C-reactive protein levels, were associated with therapeutic response. Additionally, certain markers have been linked to non-response to anti-TNF therapy, including the *HLA-DQA1*05* allele (which increases the risk of immunogenicity)[252], high levels of oncostatin M (OSM) and its receptor (OSMR) in the inflamed gut of patients with IBD[253], downregulation of the triggering receptor expressed on myeloid cells 1 (TREM1)[254] and the GIMAT module (a cellular module consisting of five different cell populations)[255]. Although these tools show promise, they are not yet ready for widespread use owing to insufficient strong evidence, but they could become part of the therapeutic toolkit in the future.

Patient therapeutic toolkit

The patient is an essential active partner for treatment of IBD and should have their own set of resources (Box 2) alongside the IBD specialist and their therapeutic toolkit. This personal toolkit can assist patients in finding necessary information or tools, providing education and answering their questions.

Informing patients about inflammatory bowel disease

Empowerment, defined as an active process of acquiring knowledge, confidence and self-determination to self-manage health and make informed decisions about care, is known to enhance patient competencies, attitudes and behaviours and can lead to greater involvement and engagement[256]. It is therefore important that, in their therapeutic toolbox, patients have easy access to unbiased and accurate information, in a form they can understand, on basics of IBD: symptoms; differences between ulcerative colitis and Crohn's disease; causes of

Box 2 | Patient therapeutic toolkit

Information on inflammatory bowel disease

- Inflammatory bowel disease (IBD) symptoms
- Key differences between ulcerative colitis and Crohn's disease
- Current understanding of IBD causes
- Potential effects of IBD on social life, work life, sexual health and mental well-being
- Family planning considerations
- Risk of complications and potential for surgery
- Associated or concurrent conditions related to IBD, such as extraintestinal manifestations
- Information about particular situations: vaccination, travel with IBD, taking part in clinical trials
- Contact details for further queries
- Existing patient organizations

Actionable recommendations for patients

- Smoking cessation for patients with Crohn's disease
- Adoption of a mediterranean diet
- Reduce consumption of ultra-processed foods
- Regular low-to-moderate-intensity exercise
- Consider psychological support
- Sleep hygiene improvement

Advice on self-management and necessary equipment

- Individual care plan
- Education on the appropriate use of steroids
- Pain management and the risks of overusing narcotic analgesics
- Avoid long courses of NSAIDs
- When to ask a physician for stool analysis
- Medications that should not be discontinued without medical consultation
- Equipment: disinfectant swabs, fridge box, syringe disposal containers

Box 3 | Unmet needs and future directions

Breaking the therapeutic efficacy ceiling
Enhance understanding of pathogenesis and the mechanisms of action of available therapies, develop innovate drug formulations and develop more targeted therapies, including microbiome-targeted treatments, explore treatment combinations leveraging different mechanisms of action to address distinct pathways, and conduct more comparative effectiveness and safety studies to evaluate these combinations.

Better risk stratification and biomarkers for personalized treatment
Identify biomarkers to predict prognosis, therapy response or non-response, and the occurrence of complications; evaluate the effect of biomarkers on patient outcomes and cost-effectiveness; and develop tools for integrating and interpreting biomarker data.

Optimizing treatment sequencing and role of surgery
Conduct more head-to-head trials comparing the effectiveness and safety of pharmacological agents, determine the optimal positioning of therapies through comparative research, investigate the long-term use of anti-inflammatory treatments, initially used for induction as maintenance therapies, and define the role and optimal timing of surgery within the treatment algorithm.

Restoring immune system and intestinal homeostasis
Develop therapies aimed at resetting the immune system, restoring homeostasis and potentially repairing intestinal function, as current treatments are predominantly anti-inflammatory.

Treatment of specific situations
Develop therapies to prevent or reverse fibrosis and reduce the risk of strictures, advance treatments for perianal disease and refractory ulcerative colitis proctitis.

Safe de-escalation strategies
Investigate strategies for treatment de-escalation in patients achieving deep remission, including the role of biomarkers to guide these approaches.

Role of lifestyle and modifiable risk factors
Conduct well-designed studies evaluating the effect of lifestyle interventions on disease outcomes, explore and assess new dietary interventions, and expand research on the role of integrative and behavioural health strategies to complement medical treatment.

Improving care delivery
Enhance patient education and shared decision-making practices to empower patients, strengthen multidisciplinary care models for holistic management, and address inequities in care access and outcomes across diverse patient populations.

IBD; effect of IBD on social life; psychological effect; the risk of complications (including increased risk of colorectal cancer, stricture, fistula, perianal involvement); concurrent or associated conditions (IBS, extraintestinal manifestations, women's health, infection and so on); medication safety information and monitoring; and contact details for queries as well as existing patient organizations.

Tools required for treatment

There are several pillars on which patients can focus that form an integral part of the IBD therapeutic toolkit. These pillars enable a synergic effect on current therapies, by combining different approaches[257]. One key factor that patients can control is smoking. Although individuals who have never smoked and former smokers are at a higher risk of developing ulcerative colitis than current smokers[258], tobacco increases the risk of developing Crohn's disease (notably by modifying the microbiome), the likelihood of early surgery and postoperative recurrence[259,260]. Quitting smoking substantially improves the prognosis for these patients[261,262].

Regarding diet, ultra-processed foods (including emulsifier consumption) should be avoided[263–265]. The American Gastroenterological Association states that unless there is a contraindication, all patients with IBD should be advised to follow a mediterranean diet[239]. Although a low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (termed FODMAP) diet for 4–6 weeks could improve symptoms and quality of life in patients with quiescent or mildly active disease, the effect on biomarkers is more controversial[266,267]. Studies have demonstrated that low-to-moderate-intensity exercise improves disease activity and provides benefits in areas such as fatigue, muscular function, body composition, cardiorespiratory fitness, bone mineral density and psychological well-being[268]. Physical exercise not only modulates the gut microbiota and reduces visceral fat[269], which can be implicated in the inflammatory process, but also leads to the production of 'exerkines'. These molecules, produced in response to exercise, can reduce inflammation and enhance cellular repair and maintenance[270]. As the importance of the gut–brain axis and the effect of mental health on IBD management are increasingly acknowledged, psychological support (such as cognitive-behavioural therapy) can help the patient[271]. Sleep disturbances and circadian misalignment can adversely affect immune function and increase the risk of relapse, particularly in Crohn's disease[272,273]. These issues are also linked to more aggressive forms of Crohn's disease, such as stricturing and fistulizing behaviour, as well as an increased likelihood of Crohn's disease-related surgeries[271,272]. Finally, certain drugs can be associated with an increased risk of relapse[274], such as courses of NSAIDs, and patients should be advised to avoid these. Applying lifestyle modification tips is an important non-pharmacological intervention in managing IBD owing to its accessibility and cost-effectiveness.

The toolkit for patients should also include information on individual care plans, such as information for 5-ASA escalation, education on use of steroids, pain management strategies and the risks of overusing narcotic analgesics. It should advise patients on when to ask the physician for faecal calprotectin assessment or stool culture in case

of clinical worsening. Additionally, it should provide advice on medications that should not be discontinued without consulting the IBD team and outline safety expectations to keep patients well-informed. Then, on a more practical level, patients also need equipment to treat themselves, such as disinfectant swabs for patients undergoing subcutaneous biologic treatments and a fridge box to store injections that must be kept at 4°C for patients who travel.

Conclusions

This Review provides a comprehensive summary of the current treatments for IBD and introduces emerging therapies under development. Additionally, it explores the concept of a therapeutic toolkit for IBD, encompassing management strategies beyond pharmacological treatments and highlighting tools accessible to both specialists and patients. The management of IBD faces several critical unmet needs (Box 3) that hinder the achievement of optimal therapeutic outcomes. Despite the available tools, there is a ceiling of therapeutic efficacy and more methods are needed to select the most effective therapeutic strategies.

Future directions in IBD treatment should focus on a deeper understanding of the pathophysiological processes involved in IBD and inter-individual heterogeneity, the exploration of new therapeutic strategies (including new treatment, new combination and new formulation), the move towards personalized medicine and the development of biomarkers (or other tools) to ensure that these tools are appropriately chosen. It is important to put patients back at the centre of their care (giving them a better understanding of their condition, helping them to make decisions about their health and acting on modifiable risk factors), and therefore helping them to understand the therapeutic toolkit for IBD as well.

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Author contributions

S.V. researched data for and wrote the article and created figures and tables. S.V. and L.P.-B. made substantial contributions to discussion of content. All authors reviewed/edited the manuscript before submission.

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