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Review Article

Inflammatory Bowel Disease: An Updated Review of Diagnosis, Management, and Emerging Therapies

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Abstract

Context: Inflammatory bowel disease (IBD), comprising Crohn's disease and ulcerative colitis, is a chronic, relapsing inflammatory disorder of the gastrointestinal tract with a rising global burden. Despite an expanding therapeutic armamentarium, many patients fail to respond or lose response, and endoscopic remission remains elusive. Therefore, clinicians need a clear understanding of how the newest agents are positioned and what treatments are in development.

Evidence Acquisition: This narrative review, prepared in accordance with the SANRA recommendations, is based on literature available through October 2026. PubMed/MEDLINE, Scopus, Web of Science, and ClinicalTrials.gov were searched using combinations of disease terms with development and mechanism terms; reference lists were screened, and congress abstract books were hand-searched. Randomised trials at phase 2 or later, their extensions, prospective cohorts, guidelines, and mechanistic studies were eligible; case reports, editorials, non-English publications, and abstracts without data were excluded. The search returned 3111 records. Target, phase, endpoint, safety, and stated limitations were extracted; no quantitative synthesis was performed.

Results: Diagnosis still relies on endoscopy with biopsy, although faecal calprotectin and other biomarkers increasingly inform treatment targets and drug selection. Beyond conventional agents, the development pipeline is organized by pathway: TL1A/DR3 blockade is closest to approval and may also address fibrosis; oral IL-23 receptor antagonism yields induction rates comparable with those of subcutaneous p19 antibodies; selective JAK1 inhibition aims to reduce class toxicity; TNFR1-sparing TNF blockade, oral α4-integrin antagonists, and RIPK1 inhibitors offer more selective approaches; and strategies targeting cAMP/PKA, PD-1, PSGL-1, NLRX1, IL-7R, and miR-124 remain at an early stage. Dual-target combinations produced the largest induction effects reported to date. The evidence is limited by uneven development, non-interchangeable endpoints, and scarce head-to-head data.

Conclusions: IBD therapy is moving from broad immunosuppression toward pathway-specific, biomarker-guided treatment. Clinicians should systematically position and sequence agents, treat to objective targets, and remain vigilant for infection when advanced therapies are combined; the most promising agents remain investigational.

Keywords: Inflammatory Bowel Diseases, Crohn Disease, Colitis, Ulcerative, Tumor Necrosis Factor Ligand Superfamily Member 15, Interleukin-23, Janus Kinase Inhibitors

1. Context

Inflammatory bowel disease (IBD) comprises two chronic, relapsing inflammatory conditions of the digestive tract, Crohn's disease (CD) and ulcerative colitis (UC) (1). UC causes continuous colorectal inflammation with bloody diarrhoea and urgency, whereas CD is transmural, may involve any segment and typically shows

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skip lesions and complications such as strictures, fistulas and perianal disease (2-4). IBD has stabilised in industrialised countries while rising steeply elsewhere, a pattern attributed to environmental factors acting on a genetic background of susceptibility (5); genetic evidence now also links specific gut microbial taxa and circulating metabolites to disease risk (6). Because it affects young adults, the relapsing course, long-term treatment and risk of surgery burden patients and health-care systems (7).

Treatment has evolved substantially over the past two decades. Biologics targeting TNF-α, integrins, and interleukins, as well as oral small molecules such as JAK inhibitors and sphingosine-1-phosphate receptor modulators, have supplemented and, in many patients, superseded corticosteroids, aminosalicylates, and immunomodulators (8-10). Yet about one third of patients do not respond to a given agent, many lose response over time, and endoscopic remission remains elusive (11, 12). This therapeutic ceiling sustains an active treatment pipeline and underscores the need for clinicians to understand the pathways targeted by the newest agents (5, 13).

2. Evidence Acquisition

This narrative review follows the SANRA recommendations (14) and does not generate primary data. PubMed/MEDLINE, Scopus, Web of Science, and ClinicalTrials.gov were searched through October 2026, with priority given to the most recent evidence for each agent; reference lists of retrieved reviews were also screened. Disease terms were combined with development and mechanism terms (TL1A, IL-23, JAK, TNF, integrin, α4β7, MAdCAM-1, RIPK1, cAMP, PD-1, PSGL-1, NLRX1, IL-7R, miR-124, extracellular vesicles, drug repurposing), and major congress abstract books were hand-searched. Randomised trials at phase 2 or later, their extensions, prospective cohorts, guidelines, and mechanistic studies were eligible; case reports, editorials, non-English publications, and abstracts without data were excluded. Target, phase, endpoint, safety, and stated limitations were recorded for each agent; no quantitative synthesis was performed. The core search returned 3111 records, from which the sources cited here were selected.

3. Results

3.1. Diagnosis

Diagnosis combines symptoms, laboratory findings, endoscopy with biopsy and imaging (Figure 1). Endoscopy with histology remains the reference standard (3, 15): it shows continuous rectal inflammation in UC or patchy, transmural disease with aphthous ulcers in CD (16) and distinguishes IBD from other colitides, while cross-sectional imaging adds information on the small bowel and penetrating disease (17). Faecal calprotectin (FC) is the most used stool marker, with serum C-reactive protein (CRP) as a complement (18); an FC > 150 µg/g indicates endoscopic inflammation, whereas a value < 150 µg/g in an asymptomatic patient makes active inflammation unlikely (15). Normalising CRP and reducing FC are intermediate targets in treat-to-target paradigms (19-21), and serial monitoring is associated with sustained remission (22). Biomarkers are also entering drug selection: ARTEMIS-UC used a genetic companion diagnostic (23), and in CoTikiS a baseline FC > 250 µg/g identified the patients who benefited most (13).

3.2. Management and Standard of Care

Treatment goals have shifted from symptom control to objective endpoints—clinical, endoscopic, and increasingly histological remission—to avoid corticosteroids and prevent disability and surgery (19, 20). ECCO, AGA, and ACG guidelines offer a stepwise framework (Figure 2), but the growing number of advanced therapies has made their positioning and sequencing more personalized (2-4, 23). Oral and topical 5-aminosalicylates remain first-line treatments for mild-to-moderate UC (3), whereas budesonide, corticosteroids, enteral nutrition, and, for perianal disease, antibiotics are used in CD (2, 4); thiopurines and methotrexate are used less often because of their delayed onset and safety concerns (24). In moderate-to-severe disease, anti-TNF agents first demonstrated that endoscopic healing was achievable, vedolizumab added a gut-selective option (8), and ustekinumab further expanded the treatment choices (11, 12, 25). Anti-IL-23p19 antibodies (risankizumab, guselkumab, mirikizumab) (26-28), JAK inhibitors (tofacitinib, upadacitinib, filgotinib) (7, 9, 29), and sphingosine-1-phosphate receptor modulators (ozanimod, etrasimod) (10, 30) followed.

Treatment also reaches beyond the bowel wall: in a cross-sectional analysis, anti-TNF-α therapy was independently associated with lower bone mineral density, with osteoporosis observed in 65.5% of patients versus 20.7% of those receiving azathioprine-based regimens (31). In children, disease severity fell markedly after infliximab induction (32).

3.3. Emerging Therapies by Molecular Pathway

3.3.1. The TL1A/DR3 Axis

Table 1. Comparative Evidence Map of the Agents Reviewed (Selected Agents) [a]

Agent	Target	Phase	Key Efficacy Signal	Main Limitation
Tulisokibart	TL1A	Phase 3	Remission 25% vs 1.5% placebo	Companion-diagnostic design
Duvakitug	TL1A (DR3-sparing)	Phase 2b	Remission 36 – 48% vs 20%	Phase 2b only
Afimkibart	TL1A	Phase 2	50% endoscopic improvement at week 56	82% anti-drug antibodies
Icotrokinra	IL-23 receptor (oral)	Phase 2b	Response 63.5% vs 27%	Phase 2b in IBD
Ivarmacitinib	JAK1	Phase 3	Response 43.9 – 46.3% vs 26.8%	No head-to-head data
Carotegrast methyl	α4-integrin	Approved (Japan)	Response 45% vs 21%	Less gut-selective
Ontamalimab	MAdCAM-1	Phase 3 (stopped)	Positive phase 2 (TURANDOT)	Terminated for commercial reasons
ABBV-668 / eclitasertib	RIPK1	Phase 2	Epithelial necroptosis blockade	Results awaited
Orismilast	PDE4 (cAMP)	Phase 2a	Remission in one third	Gastrointestinal intolerance
Omilancor	LANCL2 (cAMP/PKA)	Phase 2	Remission 30.4% vs 3.7%	Subgroup analysis
Lusvertikimab	IL-7R (CD127)	Phase 2	Remission 22% vs 4%	Abstract data; lymphopenia
Obefazimod	miR-124	Phase 3	Durable maintenance	Modest phase 2b induction
Guselkumab + golimumab	IL-23p19 + TNF	Phase 2b	Response 83.1% vs 74.6% / 61%	Infection risk unclear
Vedolizumab + upadacitinib	α4β7 + JAK	Phase 2	Endoscopic remission 37.5% vs 15.1%	Open-label design

[a] Agents are grouped by the pathway they target; efficacy signals are the figures reported by the cited studies and are not comparable across trials. Abbreviations: DR3, death receptor 3; FC, faecal calprotectin; IL, interleukin; JAK, Janus kinase; MAdCAM-1, mucosal addressin cell adhesion molecule 1; PDE4, phosphodiesterase 4; RIPK1, receptor-interacting protein kinase 1; TL1A, TNF-like ligand 1A; TNF, tumour necrosis factor; UC, ulcerative colitis.

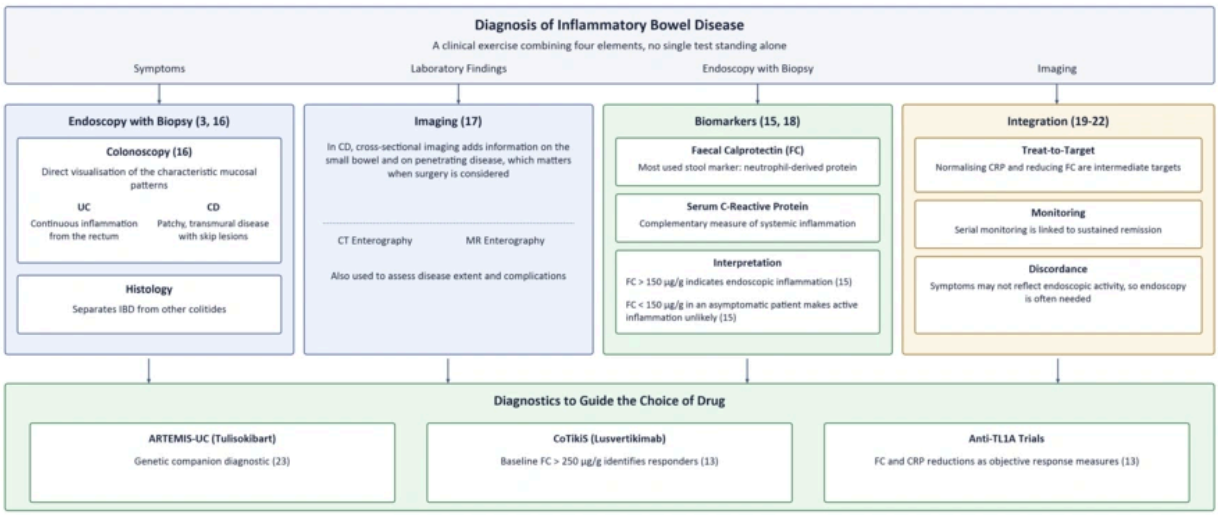


Figure 1. Integrated diagnostic framework and disease activity assessment in inflammatory bowel disease.

TL1A, a TNF superfamily member encoded by TNFSF15, is the most advanced of the new targets, and TNFSF15 variants have long been linked to IBD (33). Expressed mainly by antigen-presenting cells after Toll-like receptor stimulation, TL1A binds death receptor 3 on lymphocytes, recruits TRADD, TRAF2, and RIP1, and drives NF-κB, MAPK,

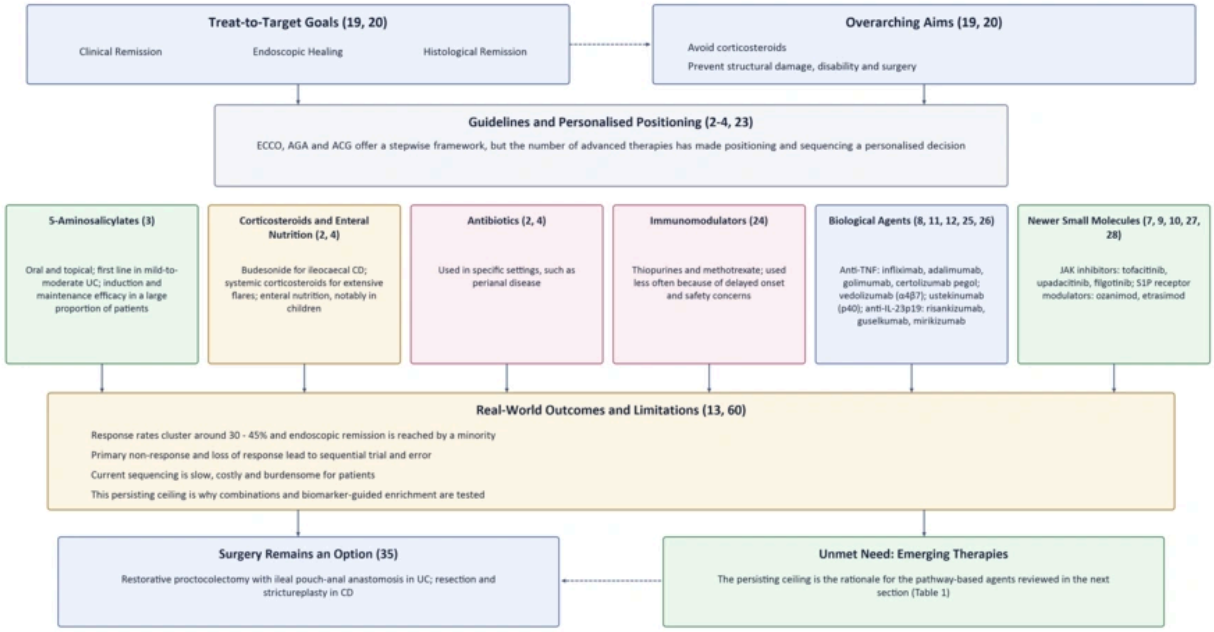


Figure 2. Management and standard of care in inflammatory bowel disease, and the unmet need that drives the emerging therapies.

Th1, Th17, and innate lymphoid responses (34). Through TGF-β1/Smad3 signaling in myofibroblasts, it also promotes collagen deposition and fibrosis, which no approved biologic addresses (35). Both ligand and receptor are upregulated in inflamed gut, suggesting a relatively gut-specific target (13).

Tulisokibart reached phase 3: in ARTEMIS-UC, clinical remission was about 25% versus just over 1.5% with placebo (23). Duvakitug, which spares the TL1A–DcR3 pathway, produced remission in 36% and 48% of patients at 450 and 900 mg, respectively, versus 20% with placebo (33). Afimkibart showed 50% endoscopic improvement and 36% remission at week 56 in TUSCANY-2, but the anti-drug antibody rate was 82% in phase 2a (13). Extended half-life constructs (XmAb942, SPY002) and the p40×TL1A bispecific RO7837195 are earlier in development (34). No head-to-head data are available, and long-term safety is unknown.

3.3.2. The IL-23/Th17 Pathway

The IL-23/Th17 axis has been validated by p19 antibodies (26-28, 36), and IL23R variants were among the first strong associations with IBD (37). IL-23 signals through JAK2/TYK2 and STAT3/STAT4 to stabilize pathogenic Th17 responses (38). Icotrokinra (JNJ-2113), a first-in-class oral macrocyclic peptide that antagonizes the IL-23 receptor without affecting IL-12, achieved a clinical response in 63.5% of patients versus 27% with placebo at week 12 in the phase 2b ANTHEM-UC trial (39, 40); it is approved for plaque psoriasis but remains investigational in IBD. Picankibart (IBI112) met the phase 2 primary endpoint in Chinese patients with UC (13). Oral blockade thus matches the induction rates of subcutaneous p19 antibodies; phase 3 data are awaited.

3.3.3. JAK/STAT Signalling

Tofacitinib and upadacitinib established JAK inhibition as the foundation of oral IBD therapy (9, 29), and development now targets selectivity because IL-6, IFN-γ, IL-13, and the γc cytokines converge on JAK1 (41). Ivarmacitinib (SHR0302), a selective JAK1 inhibitor, achieved a week-8 response in 43.9 - 46.3% of patients versus 26.8% with placebo in phase 2 UC, with a reassuring short-term safety profile; a phase 3 programme is under way (13). Whether selectivity improves the class risk–benefit ratio, as assessed by herpes zoster, venous thromboembolism, and cardiovascular events, remains unproven.

3.3.4. TNF/TNFR Signalling

Anti-TNF antibodies neutralize both soluble and membrane TNF, and this broad activity has a cost (42). TNFR1 drives NF-κB, MAPK, apoptosis, and necroptosis, whereas TNFR2 mediates Treg survival and tissue repair. Balinatunfib (SAR441566), an oral molecule that stabilizes the asymmetric form of soluble TNF, blocks TNFR1 while sparing TNFR2 and is being studied in a phase 2 trial in UC that is recruiting about 204 patients; no efficacy data are yet available (13).

3.3.5. Gut Homing and Integrins

Vedolizumab showed that blocking lymphocyte traffic to the gut is effective and safe (8); the challenge is to reproduce this effect orally. Migration depends on α4β7 binding to MAdCAM-1 and α4β1 binding to VCAM-1. Carotegrast methyl (AJM300), an oral α4-integrin antagonist that blocks both integrins, produced a 45% week-8 response versus 21% with placebo in phase 3 and became the first orally available α4-integrin antagonist to be approved (43, 44). MORF-057 and emvistegrast are more α4β7-selective; MORF-057 lowered the histopathology score by 6.4 points, with 31.4% remission at week 52 (13). Targeting the ligand instead, ontamalimab was positive in the phase 2 TURANDOT trial, although the phase 3 programme was terminated for commercial reasons (45). Safety, rather than efficacy, remains an unresolved issue for the class.

3.3.6. RIPK1 and Necroptosis

Attention is also shifting from immune cells to the epithelium (46). RIPK1 is central to epithelial cell death: TNFR1 and NOD1/NOD2 signals drive the RIPK1/RIPK3 complex to phosphorylate MLKL and trigger necroptosis, a lytic form of cell death that releases damage-associated molecular patterns and amplifies inflammation (47). Excessive mucosal necroptosis has been implicated in refractory IBD (5). The oral RIPK1 inhibitors ABBV-668 and eclitasertib are undergoing or have completed phase 2 trials in UC, with results pending, whereas the earlier inhibitor GSK2982772 did not separate from placebo (13).

3.3.7. Activating Endogenous Anti-Inflammatory Pathways

A parallel strategy engages endogenous anti-inflammatory machinery rather than blocking mediators, and much of this strategy converges on cAMP/PKA (48). Orismilast, a PDE4 inhibitor that raises cAMP, produced remission in one third of patients in phase 2a, with notable gastrointestinal intolerance (13); PL-8177, an oral melanocortin-1 receptor agonist that induces IL-10 and suppresses NF-κB, produced remission in 33% of patients versus none receiving placebo (49); and omilancor, a gut-restricted LANCL2 agonist that couples cAMP/PKA to IL-2/STAT5, stabilizes mucosal FOXP3+ regulatory T cells (50) and produced remission in 30.4% of patients versus 3.7% with placebo in the active-disease subgroup (13).

Rosnilimab, a PD-1 agonist antibody, depletes PD-1-high pathogenic helper T cells, and enrollment in the phase 2 ROSETTA trial in UC has been completed (51); leiolizumab engages PSGL-1 to induce exhaustion of activated effector T cells, and a phase 2a study is ongoing in biologic-refractory UC (52); and the NLRX1 agonist amelenodor produced a response in 8 of 11 patients versus none receiving placebo, although the program was stopped (13). Lusvertikimab, an anti-CD127 antibody that blocks the IL-7 survival signal, produced remission in 22% (450 mg) and 16% (pooled arms) of patients versus 4% with placebo at week 10 in CoTikiS, with the greatest benefit among patients with a baseline FC > 250 µg/g (53, 54). Obefazimod (ABX464) increases miR-124, which suppresses STAT3 and boosts IL-22, and its durable maintenance makes it one of the most advanced oral agents (53, 54).

3.3.8. Dual-Target Combinations

Combining two targets may raise the ceiling. In VEGA, guselkumab plus golimumab achieved a clinical response at week 12 in 83.1% of patients with UC, compared with 74.6% with guselkumab and 61% with golimumab (55), and the DUET programmes are extending evaluation of the combination. When trafficking blockade was combined with intracellular inhibition, vedolizumab plus upadacitinib achieved endoscopic remission in 37.5% versus 15.1% with vedolizumab alone and clinical remission in 65% versus 35.6% (56). Two biologics used together in refractory CD had already shown a favorable benefit–risk balance (57), and co-formulated antibodies are being developed for quarterly dosing (34). These are proof-of-principle studies, none of which was powered to assess infection.

3.3.9. Drug Repurposing and Cell-Free Therapy

A FAERS pharmacovigilance analysis found lower-than-expected reporting of IBD with dulaglutide (ROR 0.181), liraglutide (0.419), empagliflozin (0.400), metformin (0.446), and sitagliptin (0.460) (58). Metformin acts through AMPK and NF-κB, GLP-1 receptor agonists through cAMP/PKA, and SGLT2 inhibitors through AMPK and Nrf2 (59). These signals are hypothesis-generating and may be most relevant in the presence of coexisting metabolic disease. In preclinical studies, orally administered lyophilised mesenchymal stromal cell-derived extracellular vesicles reduced disease activity and restored

barrier integrity in DSS colitis (55, 56), but clinical translation remains years away.

3.4. Synthesis of the Evidence and Its Limitations

Taken together, agents in late development are no longer variations on TNF blockade but engage distinct nodes, from TL1A/DR3 and the IL-23 receptor to epithelial cell death and endogenous circuits such as cAMP/PKA, PD-1, PSGL-1, NLRX1, IL-7R, and miR-124 (13, 48). The ceiling persists: response rates cluster around 30 - 45%, endoscopic remission is achieved by a minority, and differences from placebo are modest (13, 60), which is why combinations and biomarker-guided enrichment are being tested. Compared with recent pipeline reviews and guidelines (2-5, 13, 24), this review is organized by pathway, places inhibitory strategies alongside activating strategies, and links diagnostics to drug choice.

Several gaps limit the conclusions. Development is uneven; several compounds are known mainly from congress abstracts; endpoints range from clinical to histological, are assessed at weeks 8 to 52, and are not interchangeable; multi-drug-refractory patients, older patients, pregnant women, and children are under-represented; head-to-head trials are almost absent; immunogenicity remains an obstacle; and programs have been stopped for futility or commercial reasons. Literature selection was author-driven and restricted to English-language publications, and no formal quality appraisal was undertaken. Therefore, the evidence is best read as a map of mechanisms and development status rather than as a ranking of efficacy.

4. Conclusions

The therapeutic landscape of IBD is increasingly shaped by two complementary strategies: blocking key pro-inflammatory pathways—TL1A/DR3, IL-23/Th17, JAK/STAT, TNF/TNFR1, RIPK1, and $\alpha4\beta7$-mediated gut homing—and enhancing endogenous regulatory pathways, such as cAMP/PKA, PD-1, PSGL-1, NLRX1, IL-7R, and miR-124. Together, these strategies are moving treatment toward a pathway-specific and personalized approach.

The contribution of this review lies in its presentation: agents in development through 2026 are assembled into a pathway-based map showing their stage, key efficacy signal, and main limitation (Table 1), and diagnostics are linked to drug choice. Positioning and sequencing now determine outcomes more than the number of available drugs, and choices should be guided by objective targets (20, 22, 60). Biomarker-guided selection is becoming feasible, as demonstrated by the ARTEMIS-UC companion diagnostic and the benefit of lusvertikimab at a baseline FC > 250 µg/g (12, 60, 61). The combinations that produced the largest induction effects also make infection risk a practical concern, supporting screening for tuberculosis and hepatitis B, vaccination before treatment, and surveillance when two advanced agents are used (23, 62, 63).

For internists, the value lies in the framework of available and imminent mechanisms, bearing in mind that decisions reach beyond the intestine (29); for infectious disease specialists, it lies in the immunogenicity of the antibody classes, the infection signal of dual-target therapy, and the lymphopenia seen with IL-7 receptor blockade; for patients, it lies in oral options that avoid injections, longer remission with treatments that also address fibrosis, and less corticosteroid exposure, hospitalization, and surgery; and for the health sector, it lies in the services that position and sequence advanced therapies, in pharmacy and health-technology assessment, and in trial design. These agents remain largely investigational and do not replace guideline-based care.

Footnotes

AI Use Disclosure: Claude was used for minor text editing in the abstract section.

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