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DUAL TARGETED THERAPY IN CROHN'S DISEASE – CURRENT OPTIONS, CLINICAL EFFICACY, AND SAFETY PROFILE

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ABSTRACT

Background and Aim: Monotherapy with biologic agents in patients with severe Crohn's disease (CD) is frequently limited by secondary loss of response or failure of subsequent treatment lines. Dual targeted therapy (DTT), combining two agents with distinct mechanisms of action (biologics or Janus Kinase [JAK] inhibitors), represents an innovative strategy for medically refractory CD. This review aims to evaluate the clinical efficacy, mucosal healing, and safety profiles of various DTT regimens based on literature published between 2019 and 2026.
Methods: Data were synthesized from meta-analyses, cohort studies, and real-world evidence (RWE) registries.
Results: DTT achieves a pooled clinical response rate of approximately 68% and clinical remission in 51% of patients with refractory CD. Mucosal healing (endoscopic remission) is achieved in approximately 34% of patients, and histological remission in up to 29%. Combinations of anti-IL-12/23 agents (ustekinumab, risankizumab) with vedolizumab or anti-TNF-α agents, as well as combinations with JAK inhibitors (upadacitinib), show particularly high potential. Steroid-free remission and mucosal regeneration directly translate into reduced chronic fatigue, improved nutritional status, and enhanced quality of life (QoL). The overall rate of serious adverse events (SAEs) is approximately 8.3%, which is comparable to monotherapy in similarly advanced patient cohorts.
Conclusions: DTT represents a promising therapeutic strategy with an acceptable safety profile in medically refractory Crohn's disease. Clinical implementation requires standardized monitoring (TB/HBV/VZV screening, vaccination, therapeutic drug monitoring [TDM]) and further validation in randomized controlled trials.

KEYWORDS

Crohn's Disease, Dual Targeted Therapy, Biologic Therapy, JAK Inhibitors, Mucosal Healing, Safety Profiles, Quality of Life

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1. Introduction and Clinical Context

Crohn's disease (CD) is a chronic, transmural inflammatory bowel disease of complex immune-mediated etiology, characterized by alternating periods of relapse and remission. Due to its progressive nature, CD can lead to irreversible structural intestinal damage over time, including strictures, fistulas, and abscesses, requiring surgical intervention in a substantial proportion of patients [1, 2]. The introduction of biologic agents into clinical practice in the late 1990s, initially tumor necrosis factor-alpha (TNF-α) inhibitors, followed in subsequent decades by integrin receptor antagonists (vedolizumab) and interleukin 12/23 inhibitors (ustekinumab, risankizumab), fundamentally transformed the prognosis of patients with moderate-to-severe CD [1, 2]. Current clinical guidelines emphasize early and effective disease suppression to prevent structural bowel complications [1, 3].

Despite significant advances in pharmacotherapy, a subset of patients experiences primary non-response to biologic therapy, while approximately 30–50% of patients develop secondary loss of response within the first year of treatment [2, 4]. The traditional approach involving sequential switching from one biologic agent to another in monotherapy (so-called biologic swapping) is characterized by progressively declining efficacy. The probability of achieving remission with a subsequent line of biologic monotherapy rarely exceeds 15–20% [4, 5]. Clinical guidelines across inflammatory bowel disease management underscore the clinical challenge of managing refractory disease phenotypes [3, 6].

To address the growing population of patients with a complex, medically refractory phenotype (refractory CD), the concept of dual targeted therapy (DTT) has emerged in gastroenterology. DTT involves the simultaneous blockade of two independent inflammatory pathways using either two biologics or a combination of a biologic and a small-molecule drug (such as a JAK inhibitor) [3, 5]. The aim of this review article is to summarize current evidence regarding the clinical efficacy, tissue-level outcomes, safety profiles, and perspectives for implementing DTT in clinical practice.

2. Molecular Mechanisms and Synergism of Dual Blockade

2.1. Complementarity of Immunological Pathways

The pathogenesis of Crohn's disease is driven by redundant, interconnected cytokine networks and gut-specific leukocyte trafficking pathways, which allow chronic tissue inflammation to persist despite single-pathway inhibition [1]. Monotherapy targeting a single molecular axis (e.g., TNF-α inhibition) suppresses a dominant pathway, but alternative inflammatory cascades may remain active or become upregulated —a phenomenon known as pathway switching [5, 7]. Dual targeted therapy enables simultaneous neutralization of two key inflammatory pathways:

IL-12/23 and TNF-α blockade: Ustekinumab inhibits the shared p40 subunit of IL-12 and IL-23, preventing their binding to the IL-12Rβ1 receptor complex and suppressing Th1 and Th17 cell lineage differentiation and expansion. Concurrently, anti-TNF-α agents neutralize both soluble and membrane-bound TNF-α (mTNF-α), inducing reverse signaling-mediated apoptosis of activated lamina propria T lymphocytes and proinflammatory monocytes/macrophages. [5, 7].

Adhesion and cytokine blockade: Vedolizumab selectively binds to the α4β7 integrin expressed on gut-homing memory T lymphocytes, inhibiting their interaction with mucosal addressin cell adhesion molecule-1 (MAdCAM-1) on intestinal endothelial cells and preventing gut mucosal extravasation. Combining gut-selective cell trafficking inhibition with systemic cytokine blockade (anti-TNF-α or anti-IL-12/23) establishes a complementary two-compartment therapeutic strategy, suppressing localized tissue inflammation while minimizing cumulative systemic immunosuppression. [7, 8].

2.2. Gut Selectivity vs. Systemic Action

A critical consideration when designing DTT regimens is avoiding excessive systemic immunosuppression [5]. Agents with gut-selective mechanisms, such as vedolizumab, exert their therapeutic effect almost exclusively within the gastrointestinal tract [8, 9]. Pairing a gut-selective agent with a systemic agent mitigates the cumulative risk of opportunistic infections while maintaining potent anti-inflammatory efficacy within diseased tissue [5, 9].

2.3. Combination of Intracellular and Extracellular Blockade (JAK Inhibitors and Anti-IL-23 / Anti-Integrin Agents)

The introduction of small-molecule drugs (Janus kinase inhibitors, e.g., upadacitinib) into DTT enables simultaneous inhibition of inflammatory cascades at two distinct cellular levels [7, 9]. While biologic agents (e.g., selective anti-IL-23 p19 subunit inhibitors such as risankizumab, or anti-integrins) neutralize cytokines and adhesion molecules in the extracellular space, JAK inhibitors penetrate intracellularly to suppress the JAK-STAT signaling pathway across multiple inflammatory cytokines simultaneously [7, 9]. This dual-level mechanism facilitates rapid control of acute inflammatory flares by the small molecule alongside sustained, long-term tissue-level remission driven by the biologic agent.

3. Clinical and Mucosal Efficacy in Light of Current Studies

3.1. Pooled Clinical Response and Remission Rates

Real-world evidence (RWE) registries and cohort studies [10] as well as meta-analyses [11] and additional national cohort data [12] evaluating DTT focus primarily on patients with severe, refractory Crohn's disease who have experienced treatment failure with one or more classes of biologic agents [10, 11]. Evidence across IBD management demonstrates that combining targeted therapies can overcome treatment resistance in highly bio-experienced cohorts [6, 11].

Data from observational cohorts [10, 12] and meta-analyses [11] demonstrate the following overall efficacy rates for DTT in refractory IBD:

~68% pooled clinical response rate [10, 11],

~51% pooled clinical remission rate [10, 11].

In studies examining complex CD phenotypes, DTT achieves clinical response in over half of treated patients, with steroid-free remission reaching up to 80% among responders [12].

3.2. Detailed Characteristics and Efficacy of Selected Combination Regimens

Various combination regimens have been evaluated in clinical practice and clinical studies, differing in anti-inflammatory potency and organ-specificity. These include combinations of biologics from different therapeutic classes (e.g., UST + ADA [10], UST + VDZ [13]), combinations of biologic agents and JAK inhibitors co-therapies (RISA + UPA [14]), and triple combination protocols (EXPLORER trial: VDZ + ADA + MTX [8]).

Table 1. Overview of major dual targeted therapy (DTT) regimens in Crohn's disease.

Combination Regimen	Molecular Targets / Mechanism	Efficacy (Clinical & Endoscopic Remission)	Patient Profile & Clinical Considerations	Refs
Ustekinumab (UST) + Adalimumab (ADA)	IL-12/23 p40 subunit + systemic anti-TNF-α	Clinical remission: ~69% Endoscopic remission: up to 56% (at 27 mos.)	High durability of response; potent systemic immunomodulatory combination	[10]
Ustekinumab (UST) + Vedolizumab (VDZ)	IL-12/23 p40 subunit + gut-selective α4β7 integrin	Clinical remission: ~76% (at week 52)	High safety profile (no added systemic immunosuppression from VDZ); preferred in complex/elderly patients	[13]
Risankizumab (RISA) + Upadacitinib (UPA)	IL-23 p19 subunit + selective JAK1 inhibition	Clinical and tissue response in complex CD	Combines a selective anti-p19 biologic with an intracellular small-molecule drug in highly refractory disease	[14]
Triple Combination Therapy (VDZ + ADA + Methotrexate)	Triple blockade: α4β7 integrin + TNF-α + antimetabolite	Clinical remission: 54.5% Endoscopic remission: 34.5% (at week 26)	Evaluated in EXPLORER trial in newly diagnosed CD patients with high risk of severe progression	[8]

Abbreviations: ADA, adalimumab; DTT, dual targeted therapy; IBD, inflammatory bowel disease; JAK, Janus kinase; RISA, risankizumab; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.

3.3. Impact on Mucosal Healing and Histological Remission

Achieving deep remission, which encompasses mucosal healing (endoscopic remission and subsequent tissue regeneration) and histological remission, is a central endpoint in contemporary treat-to-target management, thereby preventing cumulative structural bowel damage [15, 16].

In meta-analyses evaluating DTT in refractory IBD, the pooled endoscopic remission rate is approximately 34.3% [11, 17], while histological remission has been reported in up to 29% of patients [17, 18]. These outcomes are markedly superior to sequential biologic monotherapy in bio-experienced cohorts, where endoscopic remission rarely exceeds 12–18% [17, 18]. Normalization of inflammatory biomarkers (C-reactive protein [CRP] and fecal calprotectin) combined with endoscopic healing serves as a strong predictor of long-term sustained remission without surgical resection [15–19].

3.4. Efficacy According to Phenotype and Disease Location

The therapeutic response to dual targeted therapy is not uniform across all anatomical segments and clinical phenotypes of Crohn's disease. Observational data and subgroup analyses demonstrate that patients with colonic involvement (colonic CD) achieve significantly higher rates of clinical and endoscopic remission during DTT compared to those with isolated, complex terminal ileal disease (ileal CD) [10, 11]. This differential responsiveness is driven by distinct regional microenvironments: colonic tissue exhibits higher

endothelial density of MAdCAM-1, which enhance the tissue-specific efficacy of α4β7 integrin blockade, and a predominantly inflammatory immunophenotype. Conversely, isolated ileal lesions frequently harbor underlying fibrostenotic components mediated by TGF-β pathways, which are less amenable to dual immunomodulatory suppression alone [5, 7].

In the setting of severe, medically refractory perianal fistulizing Crohn's disease, a phenotype historically associated with high surgical morbidity, DTT demonstrates remarkable clinical utility. Evidence from real-world cohorts combining systemic anti-TNF-α agents (infliximab) with IL-12/23 inhibitors (ustekinumab) or gut-selective biologics demonstrates complete fistula closure in 48.5% of bio-experienced patients and partial response in an additional 45.5%, yielding an overall clinical response rate of 94.0% [20]. The synergy between systemic TNF-α neutralization and IL-12/23 p40 pathway inhibition effectively suppresses local transmural inflammation and tissue destruction within fistulous tracts, providing a rationale for early DTT escalation alongside surgical drainage in refractory perianal disease [20].

4.1. Incidence of Adverse Events and Comparison of Complications

Combining two potent immunomodulatory agents inherently raises concerns regarding cumulative toxicity and infection risks [21]. Recent meta-analyses [22] and comparative safety evaluations [22] indicate that the safety profile of dual targeted therapy in refractory Crohn's disease remains acceptable and comparable to monotherapy used in patient cohorts with similar disease severity [10, 11, 21, 22].

Data from the meta-analysis by Xu et al. [11] report an overall adverse event rate of approximately 28.2% during DTT, with serious adverse events (SAEs) occurring in 8.3%. Safety outcomes vary by drug class [22]:

Regimens combining vedolizumab (gut-selective) with ustekinumab or risankizumab carry the lowest rate of infectious and systemic complications [11, 21].

Regimens containing TNF-α inhibitors (infliximab, adalimumab) or JAK inhibitors (upadacitinib) require closer monitoring due to their systemic immunosuppressive actions [11, 22].

4.2. Infection Risk and Patient Profiling

Patient-specific factors significantly influence infectious risk:

Age >65 years: Older patients exhibit increased susceptibility to infections due to immunosenescence and age-related comorbidities [23, 24].

Concomitant Corticosteroids: Systemic corticosteroid use is an independent risk factor for serious infections [25]. Sparing and tapering corticosteroids promptly upon achieving response to DTT is essential for risk mitigation [25].

Smoking and Polypharmacy: These factors impair tissue repair and complicate overall therapeutic monitoring [25].

Overall, most reported infections during DTT are mild to moderate (upper respiratory tract infections, urinary tract infections, herpes labialis) [20]. Serious opportunistic infections remain uncommon, though isolated cases of pulmonary fungal infections or herpesvirus reactivation have been reported, primarily in patients with baseline risk factors [11, 25].

4.3. Clinical Monitoring Procedures and Risk Mitigation

Implementing DTT requires a standardized clinical monitoring protocol [3]:

1. Baseline Screening: Screen for latent tuberculosis (IGRA, chest radiography) and verify viral status (HBV, HCV, HIV, VZV) prior to treatment initiation [3].

2. Vaccination: Update recommended non-live vaccinations (VZV recombinant, pneumococcal, annual influenza) prior to or during treatment initiation [3].

3. Laboratory Monitoring, Biomarkers, and TDM: Perform regular complete blood counts, hepatic and renal panels, monitor biomarker kinetics (fecal calprotectin, CRP), and utilize therapeutic drug monitoring (TDM) [26] to optimize trough levels and minimize anti-drug antibody formation (anti-drug antibodies – ADAs) [3, 26]. Systematic monitoring and disease control directly contribute to sustained remission, reduced chronic fatigue, and enhanced health-related quality of life (QoL) [27].

5. Summary and Conclusions

Dual targeted therapy (DTT) represents a significant advance in the management of severe, refractory Crohn's disease where biologic monotherapies have failed [10, 11]. Simultaneously blocking complementary immunological pathways enables clinicians to overcome therapeutic resistance and achieve clinical remission in patients with challenging disease phenotypes [10, 12].

Key conclusions from the available evidence include:

1. Clinical Efficacy: DTT induces clinical response in approximately 68% and clinical remission in 51 % of patients with refractory Crohn's disease, with pooled endoscopic remission reaching 34% [11, 17]. Mucosal and transmural healing translates into improved quality of life and reduced fatigue [27].

2. Regimen Selection: Combinations pairing IL-12/23 inhibitors with anti-TNF agents or vedolizumab, as well as biologic plus JAK inhibitor combinations (such as those under prospective evaluation in trials like VICTRIVA [28]), show high potential for durable steroid-free remission [10–14, 28].

3. Safety Profile and Biomarkers: The overall incidence of serious adverse events is approximately 8.3%, which is acceptable in this highly refractory population. Regimens utilizing the gut-selective agent vedolizumab demonstrate the most favorable safety profile [11, 20]. Biomarker-guided optimization and TDM are recommended to maintain long-term therapeutic response [3, 19, 26].

4. Clinical Implementation: Safe integration of DTT requires baseline infection screening, updated vaccinations, corticosteroid tapering, and routine monitoring [3, 26] within a multidisciplinary IBD care framework.

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