New Horizons in Ulcerative Colitis

Introduction:

Achieving and maintaining clinical remission in ulcerative colitis (UC) remains a challenge for many patients. Novel therapies with new mechanisms of action are currently being investigated and offer the promise of overcoming factors that currently lead to primary and secondary nonresponse. New data are now available on the role that dual-action anti-integrins, newer Janus kinase inhibitors (JAK), interleukin-12 (IL-12)/interleukin-13 (IL-23) inhibitors, and sphingosine-1-phosphate (S1P) receptor modulators will play in achieving sustained remission in UC.

Primary Nonresponse in UC:

Primary nonresponse in UC is defined as the lack of improvement in endoscopic and clinical signs and symptoms following initial induction therapy. Some of the main factors leading to primary nonresponse include:

- Agent selection
- Disease severity
- Patient characteristics
- Adherence

The following are predictive factors for more aggressive therapy early in the course of treatment to prevent long-term sequelae in patients with moderate to severe UC[1-4]:

- Extensive colitis
- Deep colonic ulcers
- Age < 40 years
- Elevated C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR)
- Requirement for glucocorticoids to maintain remission
- Comorbid infections such as *Clostridioides difficile* or cytomegalovirus (CMV)

The main goal of treatment for patients with UC is clinical and endoscopic remission.[2] Primary response can be determined through symptom assessment, laboratory testing, and endoscopy with biopsies as needed. Selection of induction therapy should be individualized based on several factors such as patient preferences, patient characteristics, risk of adverse events (eg, infection), other medication use, and payer coverage.[5]

Induction regimens:

Anti-tumor necrosis factor (TNF) agents:

Studies have shown that the combination of an anti-TNF agents such as infliximab in combination with an immunomodulator such as azathioprine (or methotrexate in patients intolerant to azathioprine) is more effective than an anti-TNF agent alone.[6] In addition to infliximab, other anti-TNF agents include adalimumab, certolizumab, and golimumab, although

no direct head-to-head trials have been performed. Low serum albumin levels during the disease course have been shown to be associated with nonresponse or loss of response to anti-TNF therapy in patients with UC.[7]

Anti-integrin agents:
The 2 agents currently available in the class of anti-integrin antibodies are vedolizumab and natalizumab. Due to its gut selectivity, vedolizumab is typically the preferred agent in patients at higher risk for infection or malignancy over other forms of induction therapy. Vedolizumab efficacy has been demonstrated in clinical trials,[8] although its superiority over the anti-TNF adalimumab remains unclear as vedolizumab showed higher rates of clinical remission but lower rates of glucocorticoid-free clinical remission than adalimumab.[9]

IL-12 and IL-23 inhibitors:
Ustekinumab is an antibody that blocks the p-40 subunits of both IL-12 and IL-23; it can be used as initial therapy or in patients who have not responded to other therapies and has been shown to induce clinical and endoscopic remission in patients with moderate to severe UC.[10]

Secondary Nonresponse in UC:

Secondary nonresponse is when a patient initially responds to induction therapy but loses response during maintenance treatment. Factors that can influence secondary nonresponse include:

- Patient/disease changes over time
- Mechanistic escape
- Resistance to therapy
- Comorbid infections such as *C. difficile* or CMV
- Patient adherence

After ruling out infection as the source of symptoms, the decision to determine if current therapy is still effective should be based on both clinical symptoms as well as surrogate markers of inflammation, specifically CRP or fecal calprotectin levels.[11] Once continued inflammation has been confirmed, clinicians should assess drug levels and determine if antibodies to the drug are present.

- If there are low drug levels and no antibodies to the drug, the clinician should adjust the dose of the current drug
- If there are low drug levels and high levels of antibodies, the clinicians should switch to another drug in the class
- If there are high drug levels and no antibodies, the clinician should switch to a drug with a different mechanism of action

Novel Mechanisms of Action of Biologics and Small Molecules in UC:

Second-generation anti-integrins:
Unlike other anti-integrins, etrolizumab is a novel, gut-selective, anti-integrin antibody that has a dual mechanism of action specifically targeting the β7 subunit of both the α4β7 and αEβ7 integrins (see Figure 1). Similar to vedolizumab, etrolizumab binding to β7 prevents the interaction between α4β7 and its endothelial ligand, mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1), thus blocking T-cells from entering the gut lamina propia.[12] Unlike either vedolizumab or natalizumab, etrolizumab also blocks the interaction between TGF-β-induced αEβ7+ T cells on their ligand E-cadherin located on the intestinal epithelium, thus disengaging the T-cell from the endothelial cell to prevent further epithelial damage due to inflammation.[12,13] Etrolizumab is currently being studied in multiple ongoing clinical trials (see Figure 2). Phase 2 data have shown improvements in clinical and endoscopic response, as well as in patient-reported outcomes (see Figure 3).

Figure 1: Mechanism of Action of Etrolizumab – A Dual-Action Anti-Integrin

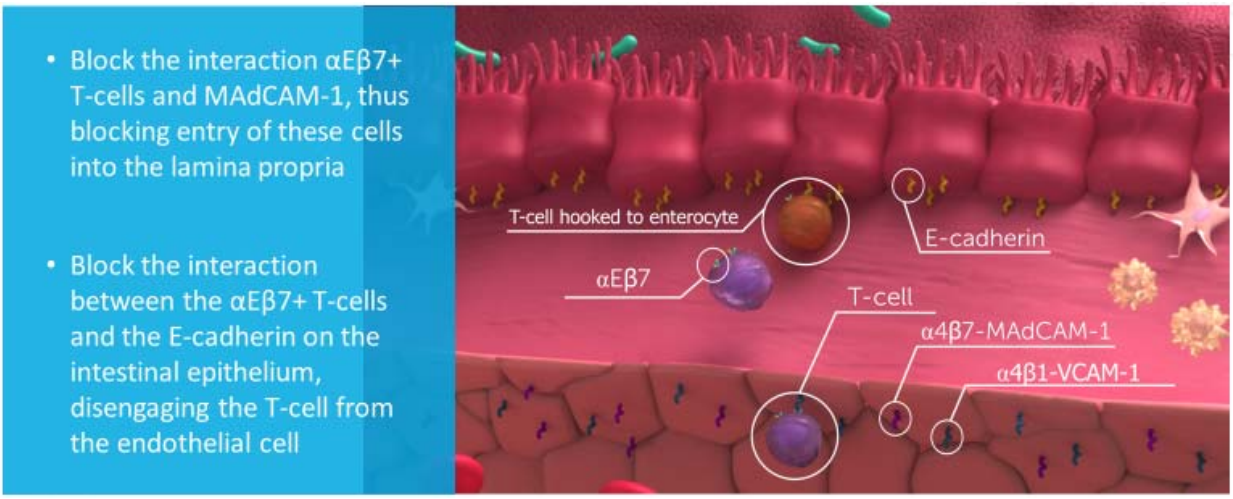
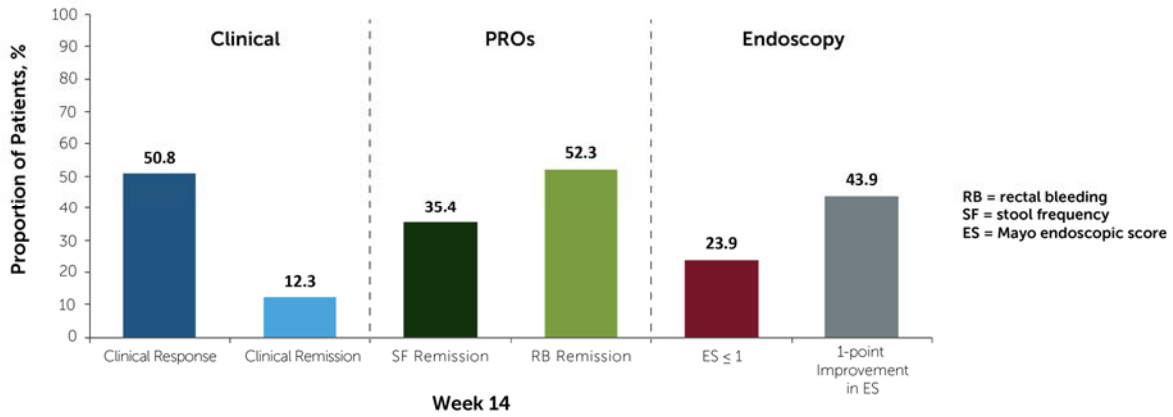


Figure 2: Ongoing Clinical Trials for Etrolizumab

ADA, adalimumab; ETRO, etrolizumab; EXP, experienced; IFX, infliximab; OL, open-label; OLI, open-label induction; PBO, placebo; TNF, tumor necrosis factor; H2H, head-to-head.

*TNF-EXP patients have been previously exposed to an anti-TNF agent and may have had an inadequate response, loss of response, or intolerance to treatment

Figure 3: Improvements With Etrolizumab: Phase 2 Study Results



Clinical response: ≥ 3-point decrease and 30% reduction of MCS and ≥ 1-point decrease in RB or RB ≤ 1; clinical remission: MCS ≤ 2, with individual subscores ≤ 1 and RB = 0.

RB remission: RB = 0; SF remission: SF ≤ 1 with ≥ 1-point reduction.

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Interleukin antibodies:

Heterodimeric pro-inflammatory cytokines IL-12 and IL-23 induce T-helper (T_H) lymphocytes such as T_H1 and T_H17, respectively, thus activating the JAK/signal transducers and activators of transcription (STAT) pathway.[14] While agents such as ustekinumab inhibit both IL-12 and IL-23, novel therapies look to target IL-23 in patients with UC as the IL-12 pathway is also involved in immune response and anti-tumor activity. Novel interleukin antibodies such as risankizumab,[15,16]

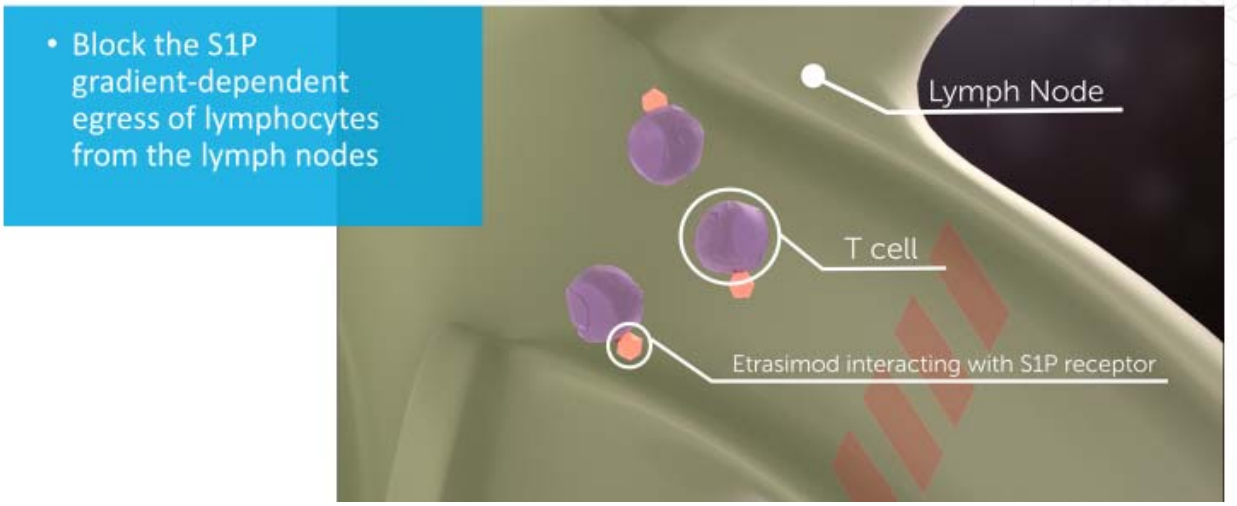
brazikumab,[17] mirikizumab,[18] and guselkumab[19] that target IL-23 by specifically inhibiting the p19 protein are currently being investigated.

JAK inhibitors:
JAK inhibitors are tyrosine kinases that play a significant role in signaling transduction for cytokines and growth factors; they are comprised of JAK1, JAK2, JAK3, and TYK2. The activation of specific cell membrane receptors by circulating cytokines results in the phosphorylation of STATs leading to cell proliferation, growth, differentiation, and migration. Blocking the JAK/STAT pathway inhibits the role of pro-inflammatory cytokines.[20] Because of the role that the JAK enzymes play across many biological processes, selectivity is important when attempting to minimize the risk of adverse events.[21]

Tofacitinib is a nonspecific small molecule JAK inhibitor, with preferential inhibition of JAK1 and JAK3, whose efficacy in ulcerative colitis was demonstrated in the OCTAVE trials, although with higher risks of infection.[22] To reduce serious side effects, selectivity for JAK1 is now being investigated with filgotinib,[23] upadacitinib,[24,25] and peficitinib.[26]

S1P Receptor Modulators:
An important factor in immune surveillance is the role of naïve T lymphocytes, whose activation occurs in secondary lymphoid organs such as lymph nodes or Peyer's patches guided by S1P.[27] S1P receptor subtypes are being investigated as a target for treatment in UC. Ozanimod and etrasimod are S1P agonists that prevent the release of lymphocytes from the lymph node (see Figure 4). Ozanimod is an S1P1 and S1P5 agonist currently being investigated in phase 3 trials after showing efficacy in a phase 2 clinical trial.[28] Etrasimod is an S1P1, S1P4, and S1P5 modulator that was also shown to be efficacious in achieving clinical remission in a phase 2 trial, and phase 3 studies are underway.[29]

Figure 4– Mechanism of Action of S1P Receptor Modulators



Conclusion:

With the advent of newer mechanisms of action in drugs that may potentially be used to treat UC, there are promising therapies in the near-term clinical pipeline. To treat patients effectively with either current or newer agents will require monitoring patients closely for signs of nonresponse; dosing therapy according to the severity of the disease; and, when facing nonresponse, selecting the appropriate approach of either adjusting the dosage or switching therapy based on mechanism of action.

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