Biologic Therapy in PIBD

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TUMS

Pharmacologic Management of Monogenic and Very Early Onset Inflammatory Bowel Diseases

Recent studies suggest that a monogenic immunodeficiency may be identified in 20–30% of patients with VEO-IBD

The armamentarium of biologic and small molecule therapies continues to grow, which allows for more narrowly targeted treatments even in undifferentiated VEO-IBD.

Targeted Therapies for Monogenic IBD

Infliximab has been trialled to target TNF-driven IBD-like inflammation seen in **X-linked ectodermal dysplasia and immunodeficiency**, an epithelial cell **defect secondary to mutations in IKBKG/NEMO**, in which defective NF-κB activation impairs immune response to circulating TNF, as well as **Hermansky-Pudlak syndrome**, a hyperinflammatory disorder involving defective cellular trafficking of lysosome-related organelles

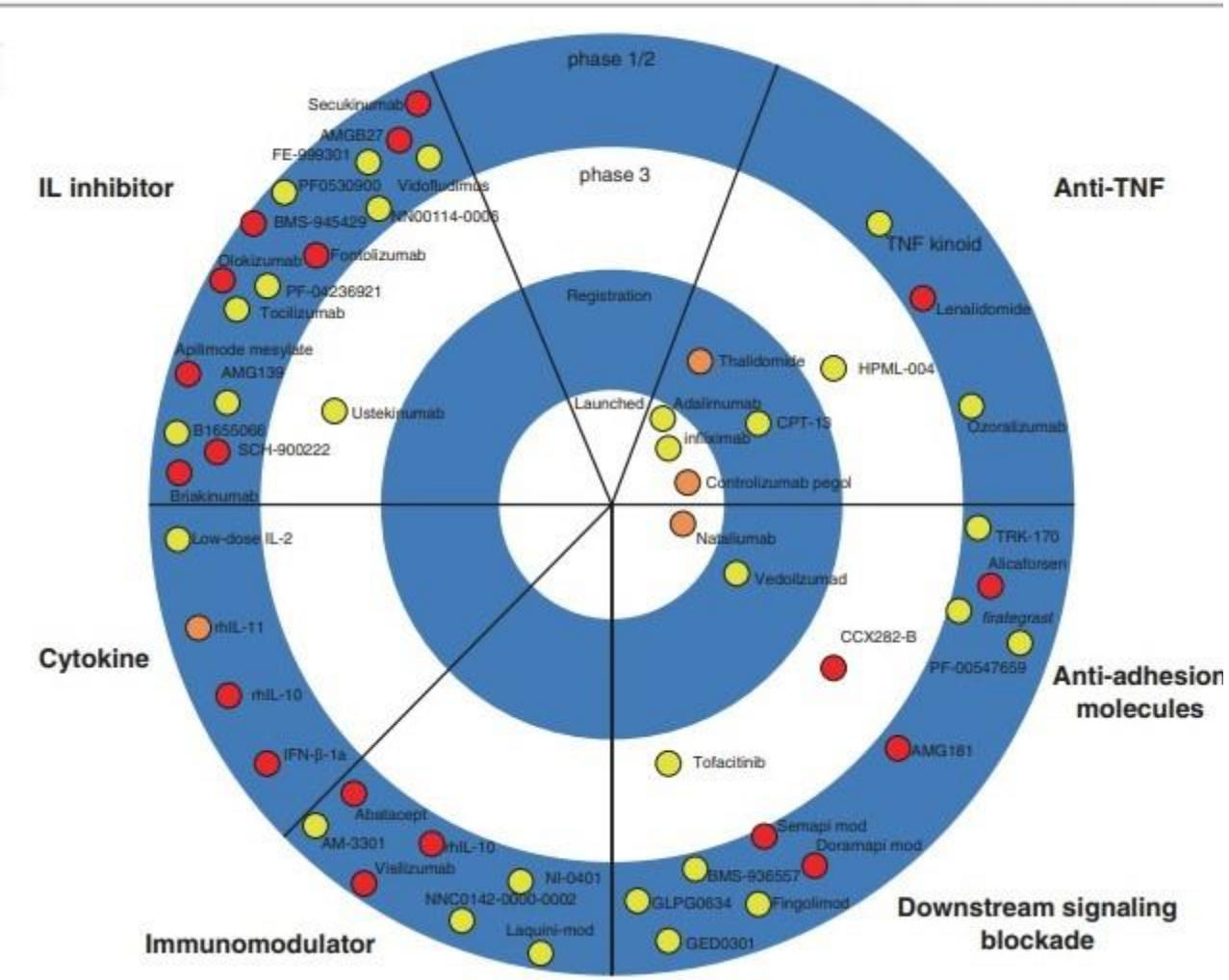
Pediatric General (Maintenance): >5 mcg/mL
Pediatric Perianal Fistulizing Disease (Maintenance): >12.7 mcg/mL [58] **Pediatric Luminal Crohn's Disease (Induction):** Infusion two and Infusion three: trough level of ≥29 mcg/mL at the 2nd infusion and ≥18 mcg/mL at 3rd infusion were strongly associated with improve outcomes early on in therapy and higher levels during maintenance phase
Pediatric Luminal Crohn's Disease (Induction/Maintenance): ≥25 mcg/mL at infusion two (week 2) and ≥15 mcg/mL at infusion three (week six) were associated with better outcomes
Pediatric Ulcerative Colitis (Induction): trough level of ≥33 mcg/mL prior to the second dose was associated with clinical remission at eight weeks of therapy. PK analysis showed that a trough level of ≥41.1 mcg/mL at week eight was associated with higher clinical remission, mucosal healing, and clinical response based on Mayo scoring

However, infliximab should not be used in patients with chronic granulomatous disease, as it has been linked with severe infections and death

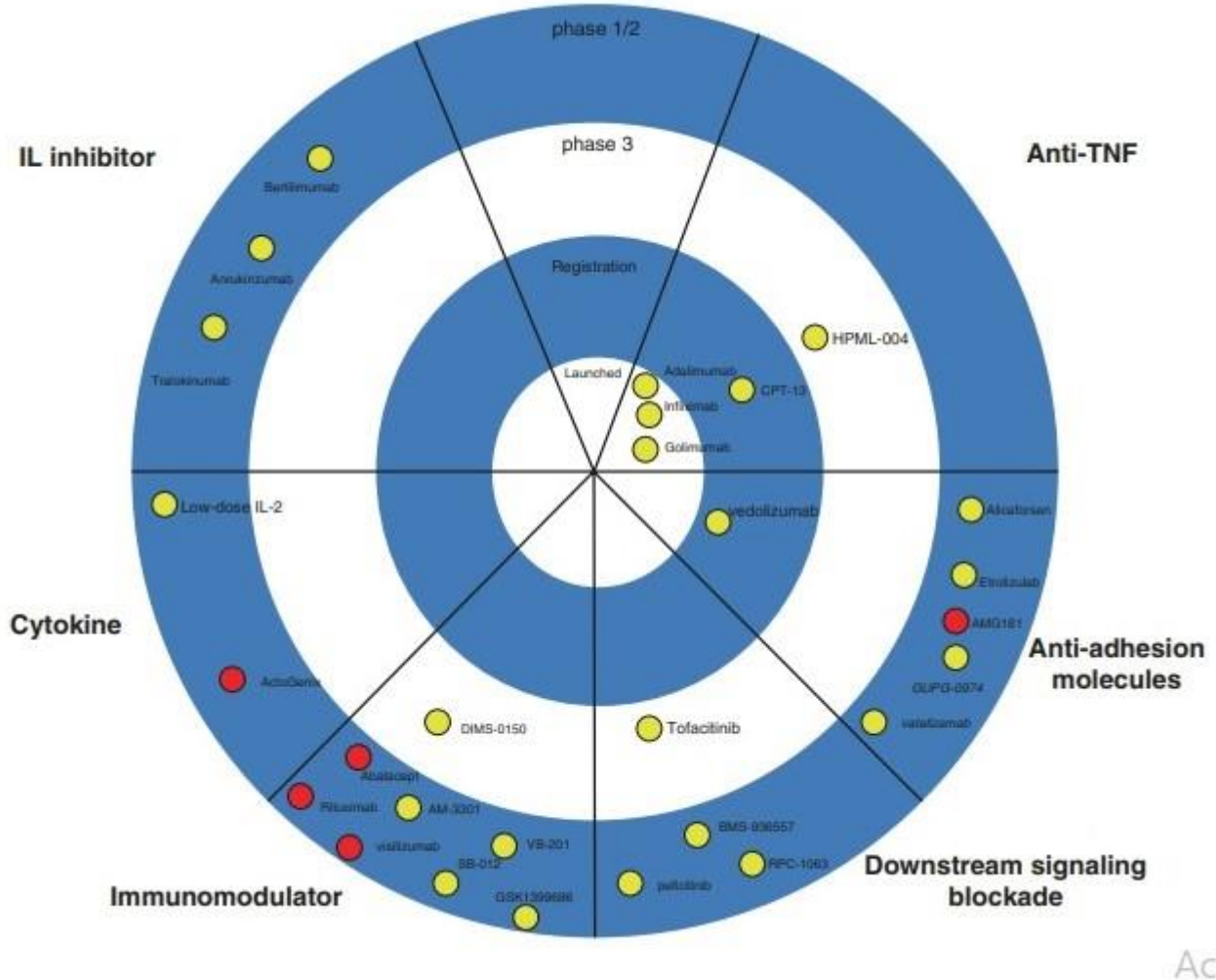
Recommendations regarding the use of adalimumab in undifferentiated pediatric IBD suggest that it can also be considered as a first line-agent. It remains an effective option in both biologic naïve patients, as well as those who have had previous biologic exposure. Trough levels are checked typically during the maintenance of treatment, with a goal level of at least 7.5 mcg/mL recommended for endoscopic healing by week eight of therapy

Pediatric General (Maintenance): >7.5 mcg/mL for endoscopic healing at week 8 **Pediatric Crohn's Disease (Maintenance):** levels of >22.5 mcg/mL at week four and trough levels > 12.5 mcg at week eight were associated with prediction of clinical remission at week 24

Drugs in pipeline for CD

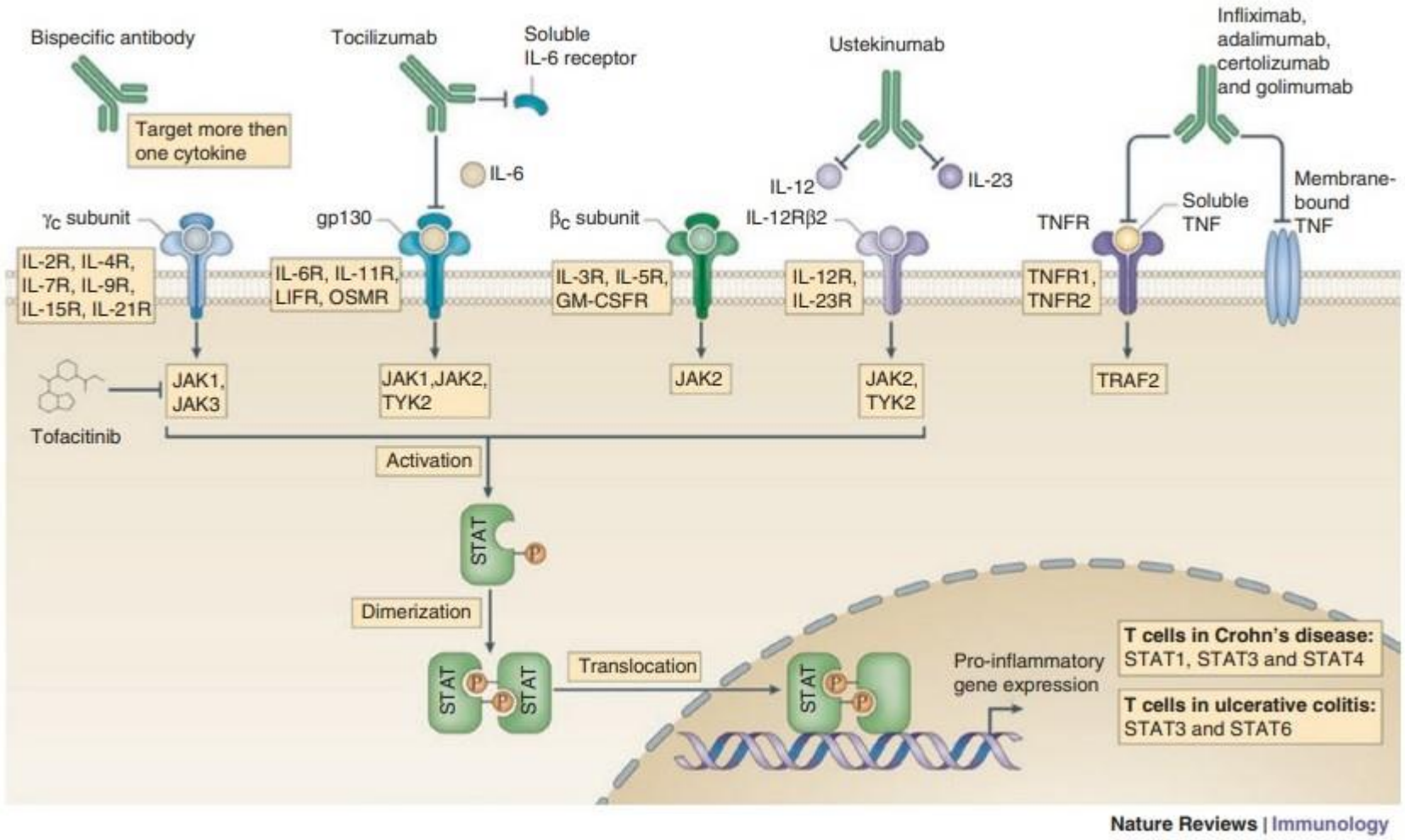


Drugs in pipeline for UC



New Non-anti-TNF-α Biological Therapies

Anti-TNF Biologic Therapies

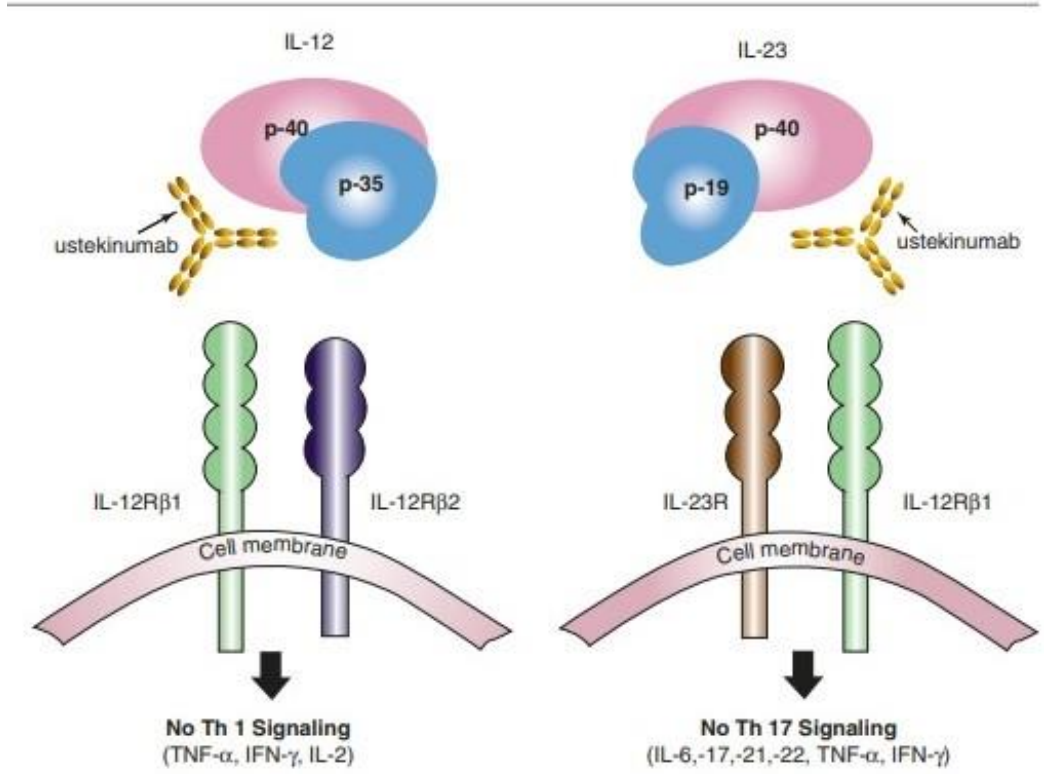


Ustekinumab

Ustekinumab, a monoclonal antibody targeting interleukin 12 and 23, has demonstrated efficacy for induction and maintenance of clinical remission in randomised placebo-controlled trials

Data on ustekinumab efficacy in paediatric CD are still limited. Dayan et al. retrospectively reviewed outcomes with ustekinumab therapy administered similarly to the UNITI trials in 52 patients with median age 16.8 years , 42 of whom had CD. Steroid-free clinical remission was achieved in 40% at Week 52

The first dose of ustekinumab is usually administered intravenously and is 6 mg/kg rounded to 130 mg [maximum 520 mg]. SC dosing starts at Week 8; adult patients receive a 90-mg injection. **Children should receive a body surface area [BSA]-adjusted dose [considering a standard adult of 1.73 m2] every 8 weeks.** Clinical benefit can be observed from 8 weeks following intravenous induction.



Vedolizumab

Vedolizumab is a gut-selective humanized monoclonal antibody targeting the α4β7 integrin that is effective in patients with IBD who are refractory or intolerant to systemic steroids, immunomodulators, or anti-TNF agents.

Vedolizumab downregulates intestinal inflammation by specifically inhibiting intestinal T-lymphocyte migration into the tissue

Vedolizumab is effective in both CD and ulcerative colitis [UC], but is likely more effective in UC

Higher rates of clinical response are observed when vedolizumab is given as a first-line biologic treatment [ie, no previous anti-TNF therapy]

Vedolizumab use is not associated with increased risk of opportunistic infections or malignancy

Standard vedolizumab dosing in adults has been adapted in pediatric studies (5 mg/kg up to 300 mg per dose at weeks 0, 2, 6 followed by every 8 weeks thereafter).

The effect of vedolizumab in UC has been described to occur by week 6 of treatment, but complete response may not be apparent until week 14. Shortening of interval between infusions to 4 weekly may be required during maintenance in partial responders

Tofacitinib

G-O068 Topic: AS01 GASTROENTEROLOGY / AS01i Inflammatory bowel disease

TOFACITINIB IN PEDIATRIC ULCERATIVE COLITIS: A RETROSPECTIVE MULTI-CENTER EXPERIENCE FROM THE PAEDIATRIC IBD PORTO GROUP OF ESPGHAN

Oren Ledder, Michael Dolinger, Marla Dubinsky, Ronen Stein, Siddhi Savla, Ayesha Fatima, David Suskind, Jarrad Scarlett, Dennis Roeser, Dror Shouval, Gabriele Meyer, Zarela Molle Rios8, Gemma Pujol, Ana Lozano Ruf, Kaija-Leena Kolho, Pejman Rohani, Seamus Hussey, Tim De Meij, Travis Ayers, Víctor Manuel Navas López, Dan Turner, Christos Tzivinikos

Objectives and Study: Tofacitinib, a Janus kinase (JAK) inhibitor, has recently been approved for treatment of moderate to severe active ulcerative colitis (UC) in adults. Data on efficacy and safety in pediatrics are limited. In this multicenter study from the Paediatric IBD Porto group of ESPGHAN, we describe the short-term effectiveness and safety of tofacitinib in an international pediatric IBD cohort.

Methods: Retrospective review of children (2-18 years) diagnosed with UC treated with tofacitinib from 15 pediatric centers internationally. Primary outcome was corticosteroid-free clinical remission (PUCAI <10) at week 8, with secondary outcomes including clinical response (≥20 point decrease in PUCAI), colectomy rate and safety. Primary outcome was calculated utilizing non-response imputation (NRI), whereby drug cessation for any reason was considered treatment failure

Results: 78 patients (43 (55%) female, mean age at diagnosis 12.5 (±2.7) years, median disease duration 20 months (IQR 10.3-38.8)), all with previous biologic failure, including 20/78 (26%) with previous failure of three biologic classes. 15/78 (19%) patients achieved corticosteroid-free clinical remission at week 8 with a further 18/78 (23%) demonstrating clinical response. 9/78 (12%) underwent colectomy by week 8, and 21/78 (27%) by week 24. Twelve adverse events were reported including five infective (three of which deemed possibly related to treatment – zoster, HSV-2 cheilitis and septic arthritis), one case of pancreatitis, and abnormal blood test results in 5 children (anemia, lymphopenia, elevated hepatic transaminases and hypercholesterolemia)

Conclusions: In this largest real-life cohort of tofacitinib in pediatric UC to date, tofacitinib seemed effective in at least 19% of highly refractory patients by week 8. Adverse reactions and safety were largely consistent with adult data.

Upatacitinib

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Upadacitinib Induction and Maintenance Therapy for Crohn's Disease

Loftus EV Jr. et al. DOI: 10.1056/NEJMoa2212728

CLINICAL PROBLEM

Treatment options with new mechanisms of action are needed for patients with moderate-to-severe Crohn's disease. Upadacitinib — an oral, reversible Janus kinase (JAK) inhibitor — showed promise for treatment of Crohn's disease in a phase 2 trial.

CLINICAL TRIALS

Design: Two multinational, phase 3, double-blind, randomized, placebo-controlled induction trials (U-EXCEL and U-EXCEED) and one maintenance trial (U-ENDURE) evaluated the efficacy and safety of upadacitinib in adults with moderate-to-severe Crohn's disease.

Intervention: 1021 patients were assigned to receive induction therapy with upadacitinib (45 mg) or placebo (2:1 ratio) once daily for 12 weeks; 502 who had a clinical response at week 12 were then assigned to receive maintenance therapy with upadacitinib (15 mg or 30 mg) or placebo (1:1:1 ratio) once daily for 52 weeks. The primary end points — clinical remission and endoscopic response — were evaluated at week 12 of induction treatment and week 52 of maintenance treatment.

RESULTS

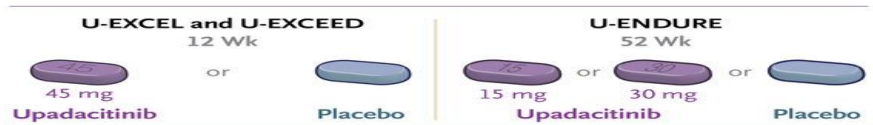
Efficacy: Upadacitinib was superior to placebo with respect to clinical remission and endoscopic response in both induction trials and in the maintenance trial.

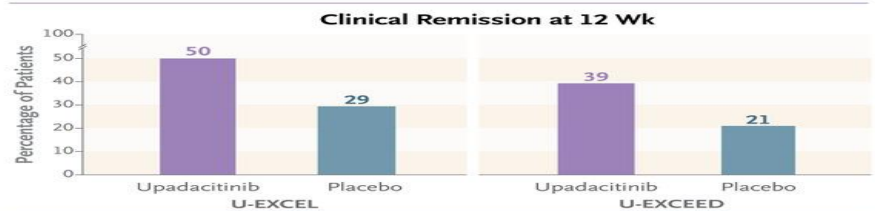
Safety: The frequencies of any, serious, and severe adverse events were similar across the groups at week 12 of induction and week 52 of maintenance. Herpes zoster, hepatic disorders, and neutropenia were more common with some doses of upadacitinib than with placebo.

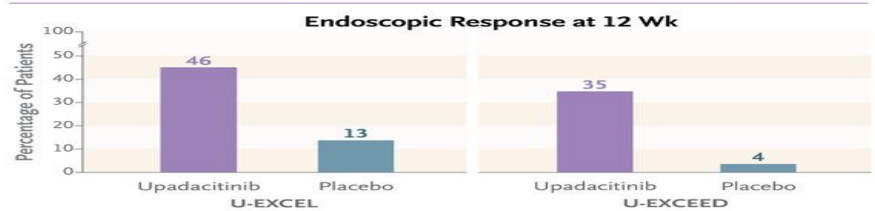
LIMITATIONS AND REMAINING QUESTIONS

- The trials could not identify adverse events that were rare or had a long latency. The ongoing extension study of U-ENDURE will continue to evaluate safety for up to 5 years.

Links: Full Article | NEJM Quick Take | Science behind the Study







CONCLUSIONS

In patients with moderate-to-severe Crohn's disease, induction and maintenance treatment with the JAK inhibitor upadacitinib was associated with higher percentages of patients with clinical remission and endoscopic response than receipt of placebo.

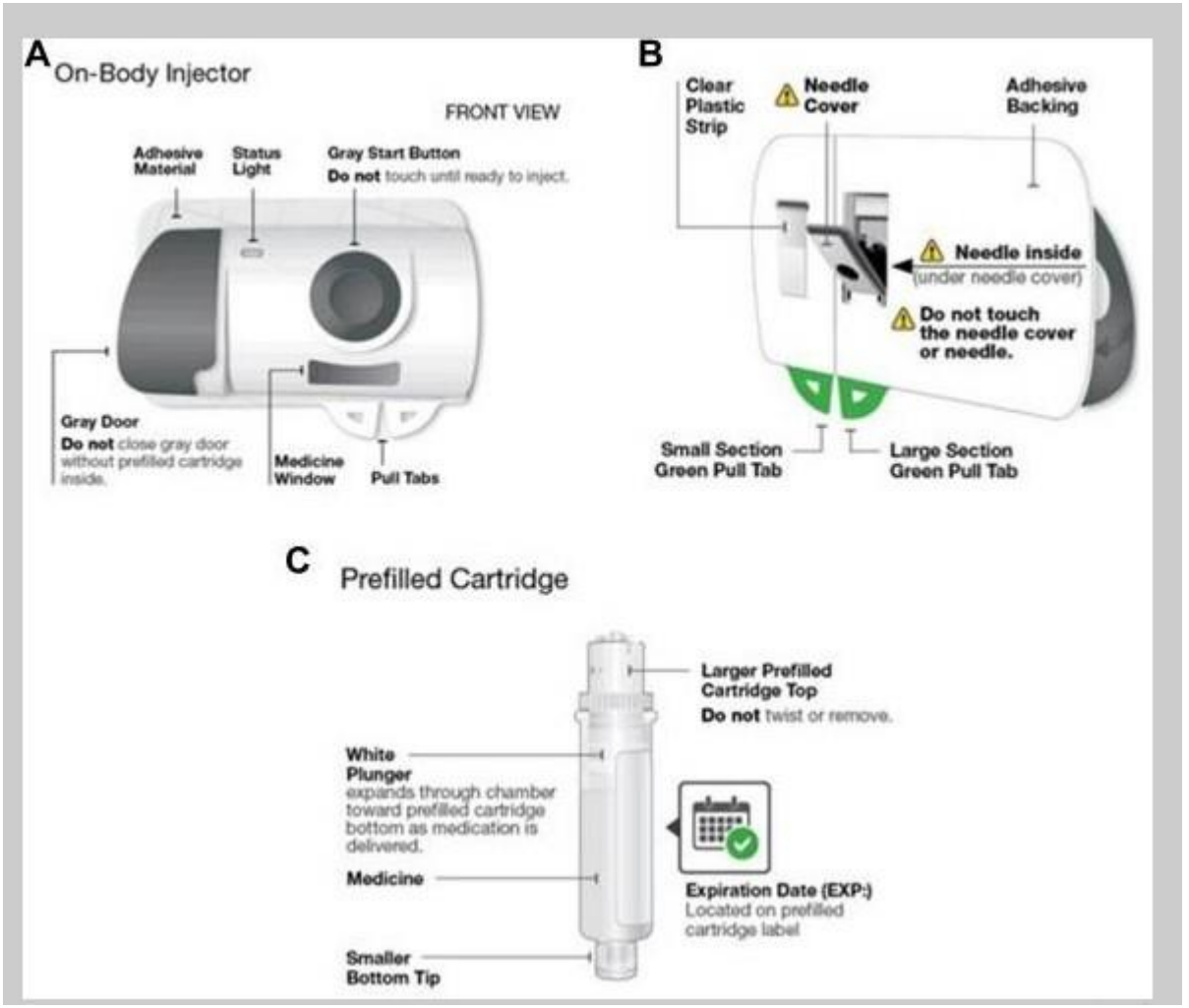
Risankizumab

FDA grants orphan drug designation to risankizumab for pediatric Crohn's disease

The FDA has issued orphan drug designation to AbbVie's investigational interleukin-23 inhibitor risankizumab for children with Crohn's disease, the company announced.

Risankizumab (ABBV-066; formerly BI 655066) selectively blocks IL-23, and is currently being evaluated in Crohn's disease, psoriasis, psoriatic arthritis and asthma, according to a press release.

Risankizumab is approved for treatment of moderately to severely active Crohn's disease in adults. Patients receive three intravenous induction doses of 600 mg over at least one hour at weeks 0, 4, and 8. They then start 180 mg/1.2 mL or 360 mg/2.4 mL injections at week 12 and continue every 8 weeks with an on-body injector device.



Ozanimod

Sphingosine-1-phosphate (S1P) is a membrane-derived phospholipid molecule.

Sphingomyelin, a major component in the mammalian cell membrane, is first broken down to ceramide and phosphorylcholine via acid sphingomyelinase. Ceramide is then converted to sphingosine and a fatty acid residue chain via ceramidase and sphingosine is then phosphorylated by sphingosine kinase to yield S1P

The current model of understanding lymphocyte and other leukocyte migration throughout their life cycle includes this S1P gradient and the ability for S1P to bind S1P1

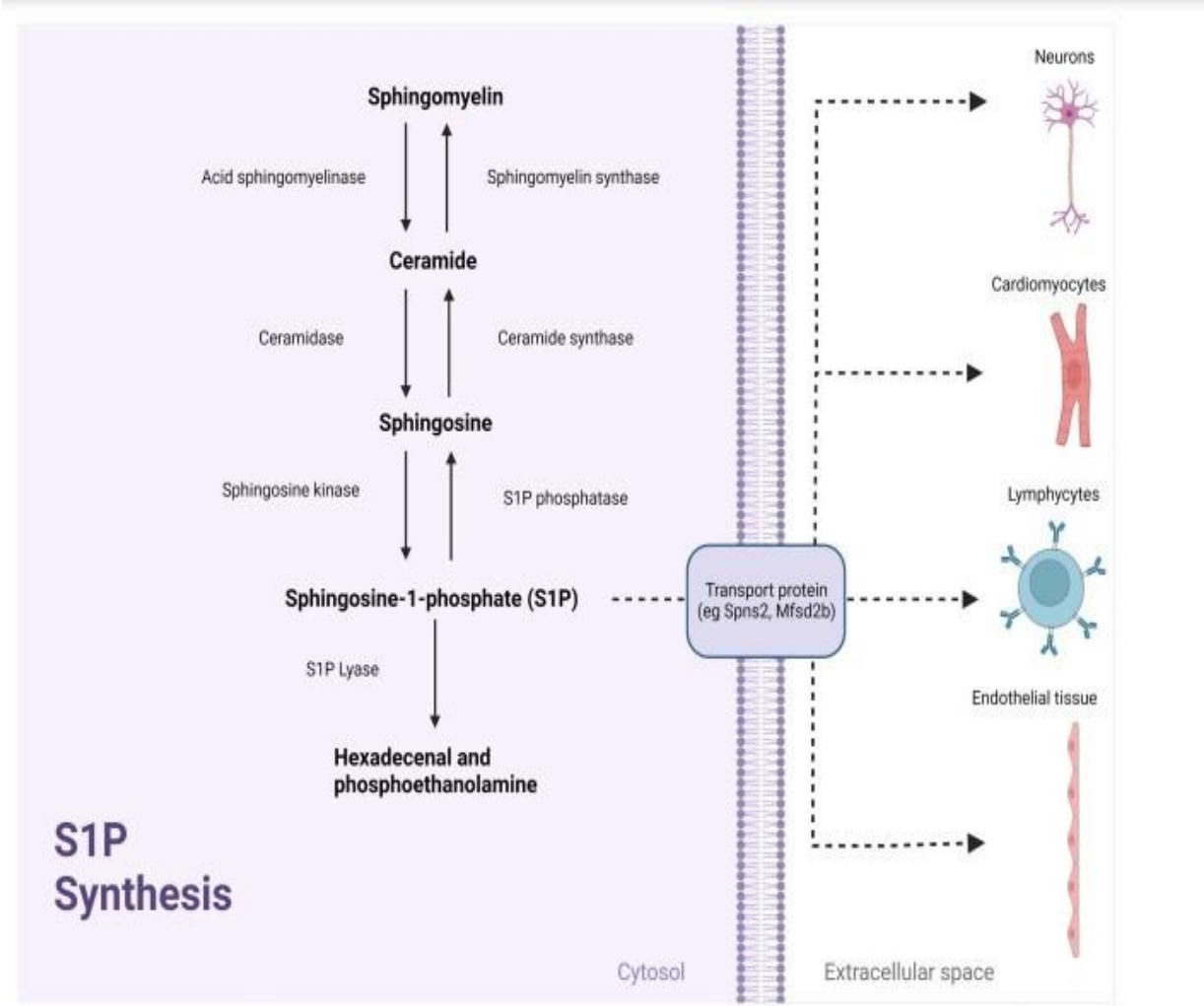
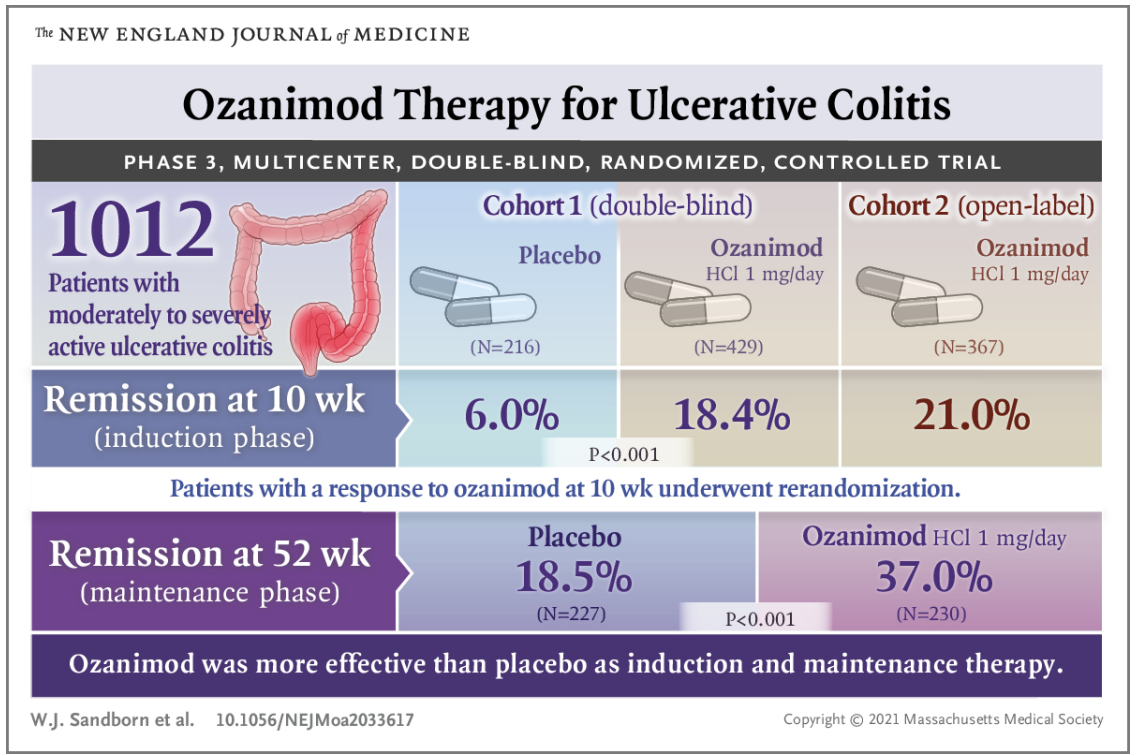


Figure 1 S1P Synthesis. Adapted from Nitric Oxide Synthesis 1, by BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates.

Small molecule therapy with ozanimod, a first in class S1P modulator for IBD, offers an oral treatment option for the treatment of UC. Ozanimod demonstrated efficacy and a favorable side effect profile, providing a unique option among the currently available therapies. **Though there are no restrictions to ozanimod as a first-line therapy, its correct positioning in the therapeutic algorithm for the treatment of UC remains to be defined**



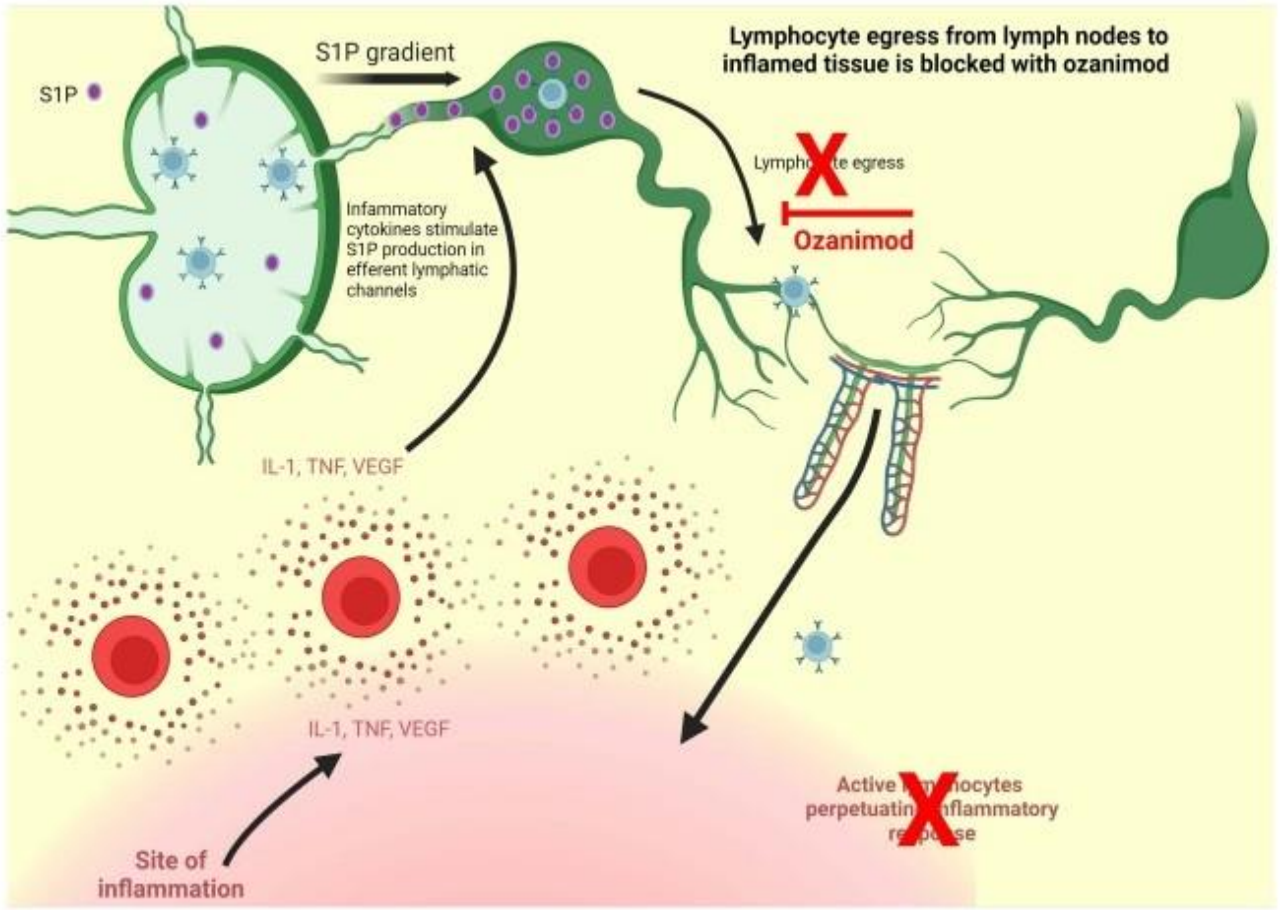


Figure 3 Ozanimod mechanism of action. Adapted from Stimulated T Cells Migrate Out of Lymph Nodes and Enter Inflamed Tissue, by BioRender.com; 2022. Retrieved from: https://app.biorender.com/biorender-templates.[32]