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Janus kinase antagonists and other novel small molecules for the treatment of Crohn's disease

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Synopsis

There is an ongoing unmet need for effective therapies for Crohn's disease (CD). Treatments for Crohn's disease continue to evolve from the traditional biologics to novel small molecules with targeted mechanisms directed towards pathways that are dysregulated in Crohn's disease. There are multiple emerging mechanisms of action including JAK inhibition, Smad7 inhibition, and Sphingosine-1-phosphate (S1P) receptor modulators that are administered as oral medications, and small molecules represent the next generation of therapies for Crohn's disease.

Keywords

Crohn's disease; small molecule; Jak inhibitor; filgotinib; TGF-β; SMAD7; mongersen; sphingosine-1-phosphate receptor; ozanimod

INTRODUCTION

Current management of moderate to severe Crohn's disease typically includes thiopurines (azathioprine, 6-mercaptopurine), methotrexate, TNF inhibitors (infliximab, adalimumab, and certolizumab pegol), integrin inhibitors (natalizumab and vedolizumab), and most recently IL-12/23 inhibitors (ustekinumab). While these therapies are effective for a proportion of patients with Crohn's disease, approximately 2/3 of patients are primary or secondary failures to TNF inhibitors.[1,2] These patients who fail TNF inhibitors are less likely to respond to vedolizumab as well as to ustekinumab.[3,4] Therefore, there is a great need for therapies that are easier to tolerate and work through novel mechanisms of action. More specifically, small molecules that act on different pathways have emerged as an

appealing alternative to biologics based on their oral route of administration, minimal risk of immunogenicity, and less interpatient pharmacokinetic variability. Small molecule therapies are emerging as future therapies for Crohn's disease.

SMALL MOLECULE THERAPIES: ADVANTAGE OVER BIOLOGICS

Oral Administration

Many of the current effective therapies for induction and maintenance of moderate to severely active Crohn's disease are biologics which are complex proteins made by living cells, weighing up to 150 kilodaltons.[5] The complex structure of biologics necessitates an intravenous or subcutaneous route of administration and contributes to variability in pharmacokinetics and immunogenicity. In contrast, small molecules are defined by a molecular weight <900 daltons which allows diffusion across cell membranes.[6] The most clear benefit of small molecules is the ability to be administered as oral medications which is appealing to patients as a convenient route of administration, and small molecules importantly have less pharmacokinetic variability. Ultimately, oral medications increase patient satisfaction and treatment adherence which leads to improved efficacy.[7]

Shorter Half-Life

In contrast to the longer half-life of biologics, small molecules typically have much shorter half-lives with once or twice daily dosing of medications. While the more frequent dosing may be inconvenient in some instances, the shorter half-life enables faster withdrawal of medication, particularly in cases of infection, pregnancy, or surgery where one would like to stop an immune suppressing medication.

Less Immunogenicity

One of the major limitations in the practical use of biologics is immunogenicity which leads to the development of antibodies that may lead to loss of response to a medication as well as potentially adverse reactions. Immune modulators are frequently used in combination with biologics to reduce risk of antibody formation but are associated with potential side effects. Antibodies are the consequence of immunologic antigenic responses to large molecules; however, small molecules have significantly less antigenic potential based on their size. In effect, the minimal risk of immunogenicity may improve the durability of response to small molecules as compared to biologics.

While small molecules may have different side effects, such as more drug-drug interactions, as compared to biologics, they offer unique benefits including the oral route of administration and minimal immunogenicity.

PATHOPHYSIOLOGY OF JAK INHIBITION

The Janus Kinase Family

The JAK family are non-receptor tyrosine kinases with a conserved kinase which is enzymatically active and consists of JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). The JAK family plays a central role in signaling transduction for multiple growth factors as well

as cytokines, including ones that have been implicated in the pathogenesis of autoimmune diseases based on genome wide association studies as well as mouse models of inflammation[8,9].

Type I and II Cytokines—JAK proteins mediate intracellular signaling from type I and type II transmembrane receptors upon binding of the associated cytokine. Type I cytokines play a role in many bodily processes including inflammation as well as normal growth and maturation of myeloid cells. Receptors for Type I cytokines contain a common subunit, such as γ-chain (γc, or IL-2 receptor γ subunit), β-chain (CD131), glycoprotein 130 (gp130 or CD130). The γc-receptors include interleukin (IL)-2, IL-4, IL-7, IL-9, and IL-15 with intracellular signaling mediated by JAK1 and JAK3. Common β-chain receptors include IL-3, IL-5, and granulocyte macrophage colony stimulating factor (GM-CSF) with signaling dependent on JAK2. IL-6, IL-11, and IL-27 are part of the common gp130 chain receptors and signal via JAK1, JAK2, and TYK2.[9,10] The dimeric receptor family includes IL-12 and IL-23 which signal through JAK2 and TYK2 as well as IL-35 which utilizes JAK1 and JAK2. The hormone-like family consists of erythropoietin, thrombopoietin, growth hormone, granulocyte-CSF, and leptin which utilize JAK2 for intracellular signaling.[8,9](Table 2) Type II cytokines include the interferon (IFN) and IL-10 family. IFNα and IFNβ signal via JAK1 and TYK2, whereas IFNγ utilizes JAK1 and JAK2. The IL-10-related cytokines are associated with regulatory T cell activity and include IL-10, IL-19, IL-20, and IL-22 which signal through JAK1, JAK2, and TYK2.[8,9]

Mechanisms of JAK signaling

JAK proteins associate with the intracellular portion of cytokine and hormone receptors that lack intrinsic catalytic activity and propagate intracellular signaling that eventually leads to transcriptional changes (Figure 1). Upon binding of a cytokine or hormone to its receptor, the subunits of receptors form multimers, enabling JAK proteins to phosphorylate the associated cytokine receptor. The phosphorylated intracellular cytokine receptor facilitates recruitment of signaling transducers and activators of transcription (STATs). JAK proteins phosphorylate STAT proteins, leading to STAT homo-dimerization. The STAT homodimer localizes to the nucleus and activates downstream transcription with a critical role in inflammation and many other cellular processes.[10,11] Unique combinations of JAKs and STAT proteins lead to unique transcriptional changes associated with different cytokines or hormones.

JAK Signaling and IBD Pathogenesis

The pathophysiology of IBD is a complex process related to dysbiotic microbiota and environmental factors in a genetically susceptible individual that leads to an abnormal innate and adaptive immune response. The inflammatory response in IBD is related to activation of the innate and adaptive immune response that is characterized by an excess in inflammatory T cells, typically type 1 helper T cells (Th1) and type 17 helper T cells (Th17) in CD with insufficient activity of regulatory T cells, and JAK proteins are known to play a critical role in inflammation signaling.[12] Key pathways involved in the pathogenesis of IBD include IL-12 and IL-23 which drive differentiation of CD4 T cells into Th1 and Th17 cell, respectively, via JAK2 and TYK2,[13] and common γc cytokines, including IL-2, IL-4, IL-7,

IL-9, IL-14, and IL-21, utilize JAK1 and JAK3 to regulate the adaptive immune response.[14] Genome-wide association studies have underscored the importance of the JAK signaling pathway, identifying polymorphisms in JAK2, TYK2, STAT3, IL-23 receptor, and IL-12 that increase the risk of IBD.[15] Based on the role of JAK signaling in inflammation, JAK inhibition is an appealing target for the treatment of IBD; however, JAK signaling is complex and plays a critical role in multiple cellular pathways, regulating normal cellular growth and development which may lead to dose-limiting side effects.

TOFACITINIB: A PAN JAK INHIBITOR

Tofacitinib (CP-690550) was the first oral, small molecule JAK inhibitor used in clinical trials and approved for rheumatoid arthritis. Tofacitinib has a short half-life of 3 hours and specifically inhibits JAK1, JAK2, and JAK3; however, *in vitro* studies show preferential inhibition of JAK1 and JAK3 over JAK2.[16] As a consequence of JAK1 inhibition, tofacitinib blocks gp130 family cytokines, such as IL-6 and IL-11, as well as type II cytokines including IFN-α, IFN-β, and IL-10. In addition, tofacitinib inhibits IL-2, IL-4, IL-6, IL-7, IL-9, IL-15, and IL-21, that signal through JAK3. Tofacitinib has less effect on JAK2 signaling, but there is mild inhibition of β-chain signaling, including IL-3, IL-5, GM-CSF, EPO, and IFNγ signaling.[17] Through these effects, tofacitinib interferes with the development of pathogenic Th1 and Th17 cells as well as B cell function.[18,19] Pre-clinical studies confirmed that tofacitinib had a potential dampening effect on both adaptive and innate immunity that contribute to the pathogenesis of IBD as well as other autoimmune diseases, such as rheumatoid arthritis or psoriasis.[16]

Tofacitinib in Ulcerative Colitis

In an 8-week dose-finding phase 2 randomized, placebo controlled trial, tofacitinib showed a robust dose-dependent effect in patients with moderate to severely active UC (NCT00787202). There was a significant improvement in terms of the clinical response (32%, 48%, 61%, 78% in the 0.5-, 3-, 10-, and 15-mg tofacitinib arm versus 42% on placebo), clinical remission (13%, 33%, 48%, 41% in the 0.5-, 3-, 10-, and 15-mg tofacitinib arm versus 10% on placebo), and endoscopic remission (10%, 18%, 30%, 27% in the 0.5-, 3-, 10-, and 15-mg tofacitinib arm versus 2% on placebo) on tofacitinib as compared to placebo. Furthermore, reductions in objective markers of inflammation, including CRP and fecal calprotectin provided additional support for the clinical efficacy of tofacitinib.[20] As a consequence, two phase 3 studies of tofacitinib 10 mg twice daily were conducted in over 1000 patients with UC, OCTAVE 1 (NCT01465763) and OCTAVE 2 (NCT01458951). Clinical remission rates after an 8 week induction were higher in tofacitinib as compared to placebo (18.5% versus 8.2% in OCTAVE 1, p=0.007; 16.6% and 3.6% in OCTAVE 2, p=0.005), and rates of mucosal healing were greater in the tofacinib groups as compared to placebo.[21] Results on long-term maintenance of response and remission will be available in the coming weeks which will likely lead to its approval for UC.

Tofacitinib in Crohn's Disease

While tofacitinib showed early promise in phase 2 trials for UC, the Crohn's disease trial failed to meet its primary endpoint of clinical response defined as a reduction in the Crohn's

disease activity index (CDAI) by 70 points from baseline at week 4. The phase 2 placebo-controlled clinical trial (NCT00615199) enrolled a total of 138 patients who were randomized to 4 weeks of tofacitinib 1 mg, 5 mg, 15mg, or placebo twice daily. At week 4, the clinical response rates were 36%, 58% and 46% in the 1 mg, 5, mg, and 15 mg tofacitinib arms, respectively, but were not significantly different from the high placebo response rate of 47%. Clinical remission rates were not significantly different (31%, 24%, and 14% in the 1-, 5-, and 15- mg tofacitinib arms, respectively, versus 21% in the placebo arm). Though the primary and secondary endpoints were not met in the setting of high placebo response rates, there were modest dose-related reductions in week 4 CRP and fecal calprotectin concentrations with the higher doses, suggesting a reduction in objective inflammation and probable biologic effect. The phase 2 study included patients with active Crohn's disease defined based on (CDAI) scores between 250–450, but endoscopic confirmation of disease activity was not mandatory.[22] There were high placebo rates based on reduction in CDAI which may have potentially obscured the ability to detect clinically meaningful differences in a short study.

A second phase 2B study of tofacitinib in moderate to severely active Crohn's disease was conducted that aimed to address some of the weaknesses from the first phase 2 study. The study was an 8-week treatment study where baseline disease activity was confirmed with endoscopy. While the clinical remission rates of 43.5% and 43% on tofacinitib 5 mg and 10 mg, respectively, were higher than the placebo rate of 36.7%, there were notable improvements in objective markers of inflammation with reduction in mean CRP concentrations in the tofacintinib 5 mg and 10 mg dose (−2.2 and −7 mg/L, respectively) as compared to placebo (−0.4 mg/L). In stark contrast to results from most clinical trials in Crohn's disease, the response and remission rates were not lower in anti-TNF experienced as compared to anti-TNF naïve patients which, if clinically relevant, would make tofacitinib an ideal second line therapy.[23] To date, tofacitinib has not been shown to be an effective therapy for Crohn's disease though there are some objective markers to suggest potential efficacy.

Safety and Tolerability of Tofacitinib

Tofacinitib has been well tolerated in the clinical trials that have been conducted in UC and CD; however, the safety profile has primarily been derived from the phase 3 clinical trials in patients with rheumatoid arthritis (RA) where doses of 5 mg or 10 mg twice daily were initially studied leading to its approval and frequent use. In a meta-analysis of 8 randomized controlled induction trials with tofacitinib in RA, there were no significant differences in adverse events, including infections, or study withdrawal as a consequence of side effects in the tofacitinib groups as compared to the placebo.[24] In a pooled analysis of the phase 2, phase 3, and long term extension studies of tofacitinib in RA, the rate of serious infections was 3.09 per 100 patient years (95% confidence interval 2.73–3.95). The most common infections were bronchitis, herpes zoster (HZ), influenza, upper respiratory infections, and urinary tract infections, and age, corticosteroid dose, and tofacitinib dose were independent risk factors for infection. Overall, the risk of infection and mortality on tofacitinib was comparable to that of patients with RA being treated with biologics; however, there was an increase in the relative risk of herpes zoster that was specific to tofacitinib.[25]

As a consequence of JAK2 inhibition, tofacitinib has the potential to cause bone marrow suppression. In the phase 3 RA clinical trials, neutrophil counts decreased modestly with low rates of neutropenia (1.2% from months 0–3; 0.8% from month 3–6) but without an increase in associated infections. Interestingly, hemoglobin concentrations did not change significantly.[26] In addition, there have been consistent dose-related increases in high-density lipoprotein (HDL) and low-density lipoprotein (LDL) by an average of 10% to 20% which reverses after cessation of therapy.[20,22,26,27] The lipid changes, however, have not translated into a significant increase in cardiovascular events though larger studies are needed to assess the magnitude and significance of any cardiovascular signal.[27]

Herpes Zoster Risk with JAK Inhibitors

Reactivation of varicella zoster virus (VZV), called HZ, appears to be an infectious risk that may be relevant to JAK inhibitors.[25] The risk appears to be related to the suppressive effect on NK cells through JAK1 and JAK3 inhibition. Based on the phase 2, phase 3, and extension studies with tofacitinib in RA, 239 out of 4,789 participants were diagnosed with HZ with an incidence rate of 4.4 per 100 patient years (95% confidence interval of 3.8–4.9). Age, but not tofacitinib dose, was independently associated with risk of zoster. Overall, there were no cases of disseminated or visceral zoster, nor mortality-associated with HZ.[28] Based on the evolving experience in RA, VZV vaccination prior to initiation of JAK inhibitors may become a routine practice, particularly with the introduction of a non-live, highly effective vaccine.[29]

Risk of Malignancy with JAK Inhibitors

NK cells and interferon play critical roles in immune surveillance, and there is concern that disrupting these pathways though inhibition of JAK1 and/or JAK3 may lead to an increase risk of malignancy. Understanding the risk of malignancy with medications will require long term extension trials and extensive clinical experience, and to date the longest experience and greatest number of patients have been treated with tofacitinib in RA. In a pooled analysis of 14 phase II, III, and long term extension studies in RA, the incidence rate for all malignancies (excluding non-melanoma skin cancers) was 0.85 per 100 patient years and was not significantly different from the age-adjusted rates from the US National Cancer Institute Surveillance and Epidemiology and End Results (SEER) database. Specifically, the incidence rate for lymphoma was 0.08 events per 100 patient years without a time or dose-dependent association with therapy, and the rates were not significantly different than rates in RA patients though ongoing surveillance will further define the potential malignancy risk.[30] The early clinical data does not show a signal for malignancy, but long term extension studies will be critical in defining this risk with tofacinitib and other JAK inhibitors.

Filgotinib: Novel Selective JAK1 Inhibitor

Selective JAK1 inhibitors have been developed in an effort to improve both efficacy and minimize side effects from JAK2 and JAK3 inhibition. Filgotinib (formerly called GLPG0634, GS-6034) is an oral selective JAK1 inhibitor with a 6-hour half-life with maximal pharmacodynamics effects achieved with once daily dosing. Filgotinib shows 50-fold selectivity for JAK1 over JAK3 inhibition and 30-fold selectivity for JAK1 over JAK2 inhibition in human blood. The small molecule inhibited differentiation of Th1 and Th2 cells

with less of an effect on Th17 cells and showed a dose-dependent effect against a rodent model of collagen-induced arthritis.[31] In a phase 2B clinical trial in rheumatoid arthritis, filgotinib showed a dose-dependent response in combination with methotrexate.[32]

FITZROY: Phase 2 Filgotinib Study in Crohn's Disease

The first phase 2 clinical trial showed early but robust evidence supporting the efficacy and safety of filgotinib for moderate to severely active Crohn's disease. The FITZROY study (NCT02048618) was a randomized, placebo-controlled phase 2 clinical trial of filgotinib 200 mg daily for 10 weeks with an exploratory extension phase in 174 CD patients. The study was carefully designed to include patients with not only active symptoms (CDAI 220–450 inclusive) but also endoscopically active Crohn's disease as defined by the Simple Endoscopic Score for Crohn's disease (SES-CD) of 7 or 4 *in case of* isolated ileitis and confirmed by central endoscopic reading, leading to a high screening failure rate of 44%. The primary outcome, clinical remission with CDAI <150, was achieved in 47% of patients on filgotinib 200 mg daily as compared to 23% of patients on placebo (p=0.0077). The clinical remission rates increased throughout the duration of the study and may continue to increase with ongoing therapy. In addition, there were significantly higher rates of CDAI-100 response, biological remission defined as normalization of CRP, and improvement in quality of life scores in the treatment arm, supporting the clinical efficacy of filgotinib.[33]

With the use of centralized reading, the overall endoscopic response and remission rates in the FITZROY study were low at week 10; however, 25% of patients on filgotinib as compared to 14% on placebo had a 50% reduction the SES-CD score with similar but less robust trends in endoscopic remission.[33] While the phase 2 study was not powered for endoscopic outcomes, the endoscopic results confirm a meaningful effect from JAK1 inhibition beyond clinical response and remission; however, the low absolute endoscopic response at week 10 may raise mechanistic questions about the timing and potential for JAK inhibitors to completely heal the transmural inflammatory process in Crohn's disease. Alternatively, our endoscopic scoring systems have been developed for assessing active disease and may not be the best tools for assessing healing.

Filgotinib in Anti-TNF Exposed Patients with Crohn's Disease

The next generation biologics have consistently had lower clinical response and remission rates in anti-TNF exposed as compared to anti-TNF naive patients, creating an increasing need for effective therapies for anti-TNF experienced patients.[3,34] Similarly, in the FITZROY study, the difference in remission rates between filgotinib and placebo were much greater in anti-TNF naive patients (60% versus 13% in filgotinib versus placebo) as compared to TNF-exposed patients (37% versus 29% in filgotinib versus placebo).[33] Consistent with other studies, anti-TNF exposure appears to be a surrogate for refractory Crohn's disease that may be associated with lower rates of response to filgotinib.

Safety and Tolerability of Filgotinib

Overall, filgotinib has been well tolerated in the small studies of Crohn's disease though larger phase 3 studies are necessary to detect safety signals. The safety analysis from the

phase 2B clinical trial pooled the different filgotinib dosing regimens over 20 weeks, and serious infections were reported in 3% (4 out of 152) of the filgotinib group whereas none were reported in the placebo arm. In contrast to tofacitinib, there were no significant changes in lymphocyte or neutrophil counts. The higher dose of filgotinib had an effect on lipids with a mean increase of 11% in HDL and 12% in LDL at week 20; however, there was a mean rise of 4% in HDL and 13% in LDL in the placebo arm, raising some questions about the presence and magnitude of an effect of filgotinib on lipids. Overall, the selectivity of filgotinib appears to have significantly improved the tolerability and potentially efficacy in Crohn's disease as compared to tofacitinib.[33]

JAK Inhibitors: An Evolving Pipeline

Other JAK inhibitors are undergoing development and clinical trials for Crohn's disease. ABT-494, a specific JAK1 inhibitor, is being evaluated in Crohn's disease in a phase 2 clinical trial (NCT0236549) that has completed enrollment.[35] With an increasing understanding of the benefits of selective JAK inhibition, additional JAK inhibitors are being developed with specificities designed to maximize clinical effect and minimize side effects.

TARGETTING NOVEL INFLAMMATORY PATHWAYS

Transforming Growth Factor-β1 and Inflammation

Transforming growth factor-β1 (TGFβ1) is cytokine with pleiotropic effects that is expressed in the gut and serves a critical role in regulating inflammatory pathways. Upon TGF-β1 binding to its receptor, a heterodimer consisting of type I (TGF-βRI) and type II (TGF-βRII) subunits, TGF-βRI is phosphorylated and activated which leads to phosphorylation of downstream signaling molecules, Smad2 and Smad3. Upon phosphorylation, Smad2 and Smad3 form a complex with Smad4, translocating to the nucleus to initiate transcriptional changes that suppress inflammatory gene expression.[36–38] A counter-regulatory member of the Smad family, Smad7 attenuates TGF-β1 signaling through binding to the ligand-bound TGFβ1-RI complex that leads to degradation of the receptor and effectively prevents Smad2 and Smad3 phosphorylation as well as its downstream effects (Figure 2).[37,39]

TGF-β1 and Smad7 in Crohn's Disease

TGF-β1 plays a critical role in suppressing inflammation, and dysregulation of TGF-β1 plays an important role in the pathophysiology of Crohn's disease. Though TGF-β1 RNA is overexpressed in inflamed as compared to non-inflamed intestinal tissue from patients with Crohn's disease, Smad7 is simultaneously overexpressed and inhibits TGF-β1-dependent Smad signaling and its anti-inflammatory effects.[40,41] Inhibition of Smad7 in lamina propria mononuclear cells from patients with UC and CD restored TGF-β1-dependent signaling with Smad3-phosphorylation and reduced inflammatory cytokine production.[41] Moreover, Smad7 inhibition with an antisense oligonucleotide restored TGF-β1-dependent signaling with reduction in inflammatory cytokine expression and ameliorated the oxazolone- and TNBS-induced mouse models of colitis, although this could not be confirmed in the T-cell transfer model of colitis.[42] Together, these findings provided a strong rationale for Smad7 as a therapeutic target in IBD.

Mongersen: Smad7 Antisense Oligonucleotide

Based on successful use in mouse colitis models and homology between human and mouse SMAD7, mongersen (formerly GED0301), a 21-based single-strand anti-sense oligonucleotide, was developed to inhibit Smad7. The oligonucleotide is complementary sequence that binds to Smad7 messenger RNA and causes RNase H-mediated degradation, decreasing Smad7 expression. The oligonucleotide is coated by methacrylic acid-ethyl acrylate copolymers that facilitate pH-dependent delivery of the anti-sense oligonucleotide directly to the terminal ileum and right colon.[43] Based on mouse colitis models, Smad7 antisense oligonucleotides appear to undergo endocytosis by epithelial and lamina propria mononuclear cells in the gastrointestinal tract with minimal systemic absorption.[42] Furthermore, in the phase 1 dose finding study of mongersen in 15 patients with Crohn's disease, the study drug was only detected at a low concentration in a single blood sample from one patient, providing significant support for its lack of systemic delivery and distribution.[43]

In a phase 2 randomized clinical trial, a 2-week course of mongersen had a dose-dependent effect on clinical remission in participants with terminal ileum and/or right sided colonic Crohn's disease. 166 participants with active CD based on CDAI scores were randomized to 10 mg, 40 mg, or 160 mg daily of mongersen or placebo for 2 weeks, and the primary outcome was clinical remission, defined as CDAI <150 for two weeks after completing treatment. Clinical remission rates were 65% in the 160 mg group and 55% in the 40 mg group which were significantly higher than rates of 12% in the 10 mg group and 10% in the placebo group. Clinical response, CDAI reduction by 100, was achieved in significantly more patients in the 160 mg group (72%), 40 mg group (58%), and 10 mg group (37%) as compared to placebo (17%), suggesting a dose dependent effect. Of the patients with elevated baseline CRP (>3 mg/liter), mongersen did not, however reduce CRP at multiple times points, but there was a reduction in serum concentrations of IL-8 and TNFα in the higher doses.[44]

While the response and remission rates were markedly high, particularly given the short study duration, there remain significant concerns about the reproducibility of the study given the reliance on clinical scores in the absence of endoscopy as part of both the inclusion criteria and secondary endpoints, and the disconnect between clinical response and CRP response. Based on the initial study, the results were not generalizable to all patients with CD since the study excluded a significant proportion of patients with Crohn's disease, including those with lesions in the upper gastrointestinal track or left colon as well as those with fistulas or perianal disease. While the short duration of the study treatment raises some additional questions about the optimal duration of treatment and duration of effect, a local delivery system and a lasting clinical benefit beyond its use would be ideal characteristics of a new therapy.

In an effort to address the limitations of the phase 2 study, an exploratory open label trial randomized 163 participants with active Crohn's disease confirmed by endoscopy with central reading to mongersen 160 mg daily for 4 weeks, 8 weeks, or 12 weeks. Results show evidence that mongersen has an effect on endoscopic disease activity. At week 12, 37% of all participants had 25% reduction, and 15% had 50% reduction in SES-CD scores.

Specifically, in patients with baseline SES-CD over 12, 63% and 31% had 25% and 50% reduction in SES-CD, respectively. There was a decrease in mean concentrations of CRP and fecal calprotectin in participants with elevated concentrations at baseline, but it is unclear what proportion of patients normalized their CRP.[45] Phase 3 clinical trials of mongersen are ongoing and will provide a better understanding about its efficacy in Crohn's disease.

Effect of Smad7 Inhibition on Fibrosis

Based on its counter regulatory effects on inflammation, TGF-β1 has been identified as a potential therapeutic target in Crohn's disease; however, TGF-β1 is a pleiotropic cytokine with pro-fibrotic effects, stimulating fibroblasts to produce collagen.[46] Given the potential complications associated with fibrosis in Crohn's disease, there is concern about potential pro-fibrotic effects of SMAD7 inhibition. While limited data is available to address this concern, a phase 1 extension study of CD patients who were treated with mongersen for 1 week monitored for stricture development over 6 months using small intestine contrast ultrasound as well as serum biomarkers for intestinal fibrosis (basic fibroblast growth factors, human chitinase 3-like1, matrix metalloproteinases[MMP], and tissue inhibitor 1 of MMP). In this study with a short treatment duration with mongersen, there was no increase in development of bowel obstructions, strictures, nor changes in biomarkers for fibrosis in 14 participants.[47] While there was no evidence of fibrosis in this phase 1 extension study, further assessments for strictures with a longer duration of treatment with mongersen will be needed.

Safety and Tolerability of Mongersen

Mongersen was well tolerated in the phase 1 and phase 2 studies in CD. The majority of the serious adverse events were CD-related symptoms or complications, occurring in the placebo and mongersen arms with similar frequencies, and the majority of other adverse events were mild. There was no signal suggesting an increase in infections or opportunistic infections. While anti-sense toxicity has been reported to cause complement activation, complement concentrations were monitored and were unchanged during therapy.[44]

TARGETTING LYMPHOCYTE TRAFFICKING: OTHER SMALL MOLECULES FOR CROHN'S DISEASE

Lymphocyte trafficking plays a central role in the innate and adaptive immune response, and inhibition of lymphocyte trafficking using monoclonal antibodies to α4, such as natalizumab, and α4β7, such as vedolizumab, is an effective mechanism of action for treatment of CD.[4] Sphinosine-1-phosphate (S1P) receptor 1 agonists are an alternative mechanism to interfere with lymphocyte trafficking.

Sphinosine-1-Phosphate Receptors

There are five receptors in the S1P G-coupled receptor family ($S1P_{1-5}$) that upon binding of S1P help regulate a variety of cellular functions, including lymphocyte trafficking, vascular tone, heart rate, and many others. While the five receptors play roles in multiple cellular processes, $S1P_1$ receptors are expressed in unique anatomic locations and regulate

lymphocyte egress from the lymph nodes with S1P concentration gradients.[48](Figure 3) S1P expression is typically low in the lymph nodes and drives $S1P_1$ receptor expression on lymphocytes to facilitate migration to areas of higher S1P concentrations. S1P modulators bind to $S1P_1$ receptors, initiate internalization, and lead to reversible degradation of the $S1P_1R$. As a consequence, lymphocytes lacking $S1P_1R$ expression cannot migrate out of the lymph nodes and into the blood to perform effector functions. Successful modulation of this pathway leads to reduction in the number of effector T cells circulating in the peripheral blood and in the target organs, such as the gastrointestinal track.[49]

Fingolimod: S1P Modulator for Multiple Sclerosis

The first non-selective S1P receptor modulator used in clinical trials and approved for use in multiple sclerosis (MS) was fingolimod (FTY720). Fingolimod, a prodrug, undergoes phosphorylation and activation as an agonist of $S1P_{1, 2, 3, 4, 5}$ receptors.[50] In patients with MS treated with FTY720, there was an 80% and 60% reduction in peripheral CD4+ and CD8+ T cells, respectively, with a selective reduction in naïve T cell and central memory T cells while effector memory T cells that maintain immune surveillance were preserved.[51] The half-life of fingolimod was relatively long, translating into prolonged periods of lymphopenia. While modulation of the $S1P_1$ pathway drove the immune suppression, the $S1P_3$-mediated effects led to limiting cardiac side effects, including bradycardia, QT prolongation, and AV blockade.[52]

Ozanimod: S1P1 Receptor Modulator

Ozanimod (RPC-1063) is a small molecule developed with $S1P_1$ and $S1P_5$ receptor specificity and has greater than 10,000-fold selectivity for $S1P_1$ over $S1P_{2-4}$ which minimizes potential cardiac side effects. Like fingolimod, ozanimod induces sustained $S1P_1$ receptor internalization and degradation with a dose-dependent reduction in peripheral lymphocytes, specifically CCR7+ T and B lymphocytes. The half-life of ozanimod is shorter ($t_{1/2}$ of 5 hours in mice) than fingolimod in animal models, leading to shorter periods of lymphopenia. In the TNBS-induced and naïve T cell adoptive transfer colitis mouse model, ozanimod was associated with a dose-dependent reduction in weight loss and other indices of inflammation, providing rationale for use in humans with IBD.[53]

Ozanimod in UC: Phase 2 Study Results

A phase 2 double-blind, placebo-controlled phase 2 study of ozanimod (NCT01647516) examining the safety and efficacy in patients with moderate to severely active ulcerative colitis showed a positive clinical effect. 197 adults with moderate to severely active UC with a Mayo Clinic Score of 6 to 12 were randomized to ozanimod 0.5 mg, 1 mg, or placebo for 32 weeks. The primary outcome, clinical remission with a Mayo Clinic score of 2 at week 8 with centralized endoscopy reading, was achieved in 14% and 16% in the ozanimod 0.5 mg and 1 mg groups, respectively, as compared to 6% in placebo; however, the differences were only statistically significant between the ozanimod 1 mg group and placebo (p-value 0.0048). Clinical response rates at week 8 were higher at 54% and 57% in the 0.5 mg and 1 mg ozanimod arms, respectively, as compared to 37% in the placebo arm. Furthermore, the rates of mucosal healing rates were higher at 28% and 34% in the 0.5 mg and 1 mg ozanimod groups, respectively, as compared to 12% in the placebo arm (p-values of 0.06 and

0.02, respectively). Though the primary outcome was measured at week 8, the rates of clinical remission at week 32 were higher with larger differences between the treatment group and placebo: 26% and 21% in the 0.5 mg group and 1 mg group, respectively, as compared to 6% in the placebo group.[54] The increasing rates of remission from week 8 to week 32 suggest that longer duration of treatment improves the efficacy of ozanimod, mirroring the evolving experience with leukocyte trafficking inhibitors with a relatively slow onset of action with response rates that increase with duration of therapy.[54,34] Furthermore, the low placebo response rates were likely related to the use of blinded central reading of endoscopy at baseline, week 8, and week 32 with strict criteria for clinical remission.[54] Overall, the study suggests that ozanimod is likely to be effective in ulcerative colitis; however, the phase 3 study is ongoing.

Safety and Tolerability of Ozanimod in UC

While the phase 2 ozanimod study in UC was not powered for safety, the study drug was well tolerated. There was a single patient with pre-existing bradycardia who experienced a transient, asymptomatic episode of first-degree atrioventricular block; however, there were no additional cardiovascular side effects in contrast to fingolimod. Four patients on ozanimod developed elevated alanine aminotransferase blood concentrations that were more than 3 times the upper limit of normal without additional sequelae; however, the mechanism underlying this abnormality is not understood.[54]

Ozanimod: Effect on Lymphocyte Count

In the phase 2 study of ozanimod in UC, the mean absolute lymphocytes count from blood decreased by 32% and 49% in patients in the 0.5 mg and 1 mg ozanimod arms, respectively, at week 8. In the ozanimod 1 mg group, approximately 50% of patients had absolute lymphocyte counts below the normal range with a dose dependent effect; however, there were no incidences of grade 4 lymphopenia (absolute lymphocyte count of less than 0.2×10^9/L), nor infectious complications.[55]

Ozanimod in Crohn's Disease

While there are no data currently available to assess the efficacy of ozanimod in Crohn's disease, a phase 2 open label study of ozanimod in moderate to severely active Crohn's disease is being conducted to assess the efficacy.[35] Based on the efficacy of lymphocyte trafficking inhibitors in Crohn's disease, ozanimod has a high likelihood of being an effective therapy for Crohn's disease though may have a slow onset of action. While it is difficult to predict in the absence of any clinical trials in Crohn's disease, ozanimod may be an appealing alternative to leukocyte trafficking inhibitors, particularly if rapid drug clearance in biologics were a concern. In comparison to vedolizumab, ozanimod may have additional immune suppressing effects that may be provide some additional clinical benefit in Crohn's disease. Further studies will help elucidate the potential role of ozanimod in Crohn's disease.

Summary

There are a number of innovative small molecule, oral medications for Crohn's disease that act through unique mechanisms of action, including JAK-cytokine signaling inhibition, Smad7 inhibition on the TGF-β pathway, and S1P receptor modulation that interferes with lymphocyte trafficking (Table 3). The phase 2 study of filgotinib (FITZROY) in Crohn's disease showed a promising signal suggesting clinical efficacy with significantly less side effects as compared to non-specific JAK inhibitors. JAK inhibitors may, therefore, become the medication of choice in patients who developed antibodies to other biologics. While mongersen has limited clinical data at this time, its mode of local delivery to the areas of inflammation without systemic absorption may represent the next generation of treatments for Crohn's disease. Similarly, ozanimod is a potential therapy for Crohn's disease based on its efficacy in an early trial in UC and may become an oral alternative to lymphocyte trafficking agents. Small molecules offer unique benefits as compared to biologics in terms of the oral route of administration, minimal risk of immunogenicity, and shorter half-lives and represent the next era of therapies for CD.

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Key points

1. Small molecule therapies for Crohn's disease offer potential benefits over biologics, including shorter half-lives, lack of immunogenicity, and oral route of administration.

2. Janus kinase (JAK) inhibitors block multiple cytokine pathways simultaneously and will likely be an effective oral therapy for Crohn's disease and ulcerative colitis, and a JAK1-specific inhibitor filgotinib was recently shown to be effective in inducing clinical remission in Crohn's disease.

3. Mongersen, an antisense oligonucleotide, inhibits Smad7 and restores hereby tumor growth factor-β signaling and may be an effective oral targeted therapy for ileal and/or right colonic Crohn's disease with an appealing delivery mechanism and safety profile.

4. Sphingosine-1 Phosphate receptor modulators, such as ozanimod, impair B and T cell lymphocyte trafficking by downregulating receptors that facilitate egress from lymph nodes and may be effective in treating inflammatory bowel diseases.
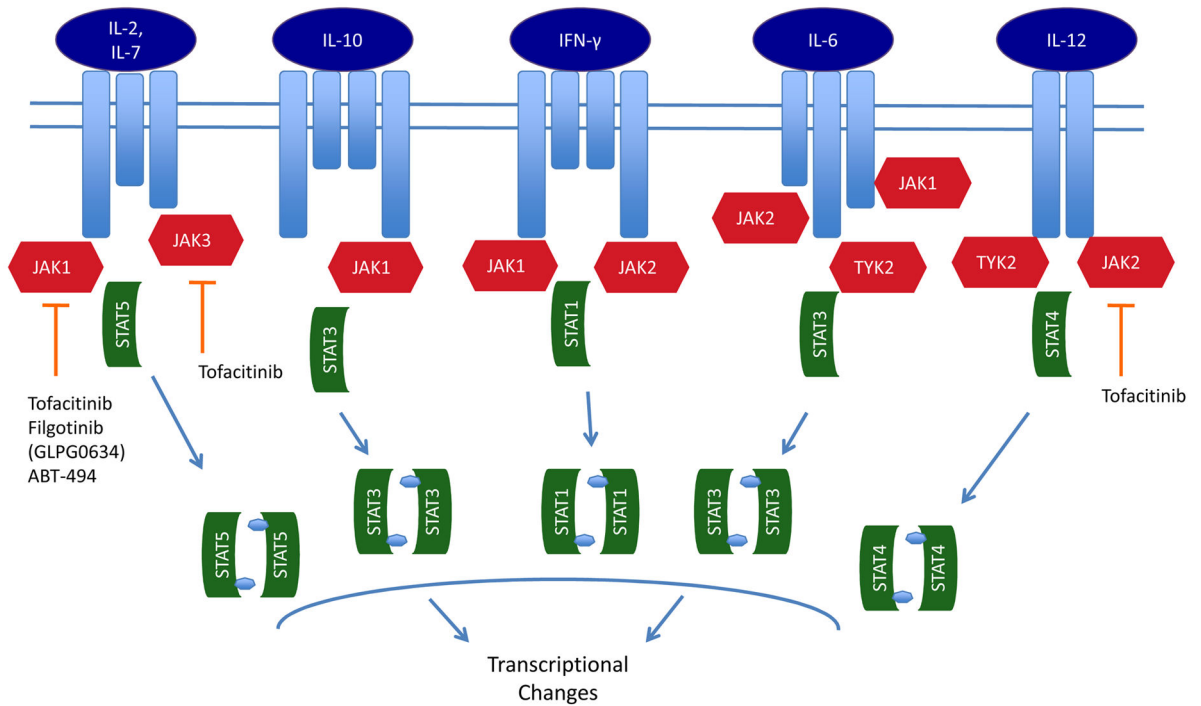
Figure 1. JAK signaling pathways related to inflammatory bowel disease and therapeutic targets of JAKINIBs

Upon cytokine binding to its receptor, JAKs phosphorylate its associated cytokine receptor and creates a docking site for STAT signaling molecules. JAKs then phosphorylate STAT proteins to facilitate STAT dimerization, followed by translocation to the nucleus and transcriptional activation of downstream target genes.

Note: For simplicity, some non-essential JAK family members have been omitted.

Adapted from Boland BS, Sandborn WJ, Chang JT. Update on Janus kinase antagonists in inflammatory bowel disease. Gastroenterol Clin North Am 2014;43(3):603–17; with permission.
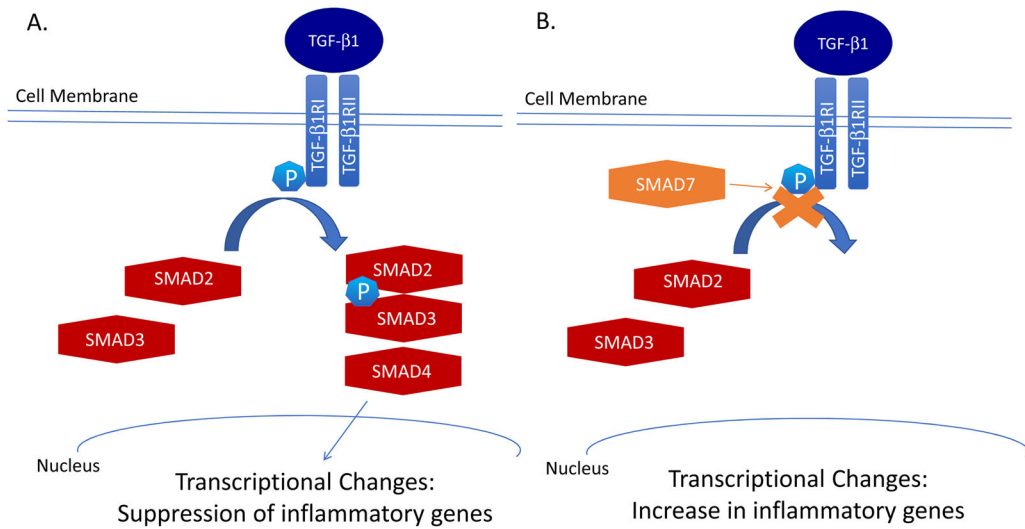
Figure 2. TGF-β1 Signaling Pathway and Smad7

A) TGF-β1 binds to the TGF-β1 Receptor that leads to phosphorylation of the intracellular portion of the TGF-β1 RI. TGF-β1 RI in turn phosphorylates Smad2 and Smad3, which then complex with Smad4. The complex of Smad2, Smad3, and Smad4 translocate to the nucleus of the cell and suppress inflammatory gene expression.

B) Overexpression Smad7 interferes with this pathway whereby Smad7 binds to TGF-β1 R1 and inhibits Smad2 and Smad3 phosphorylation. Smad7 interferes with the anti-inflammatory effects of TGF-β1, leading to an increase in inflammatory gene expression.
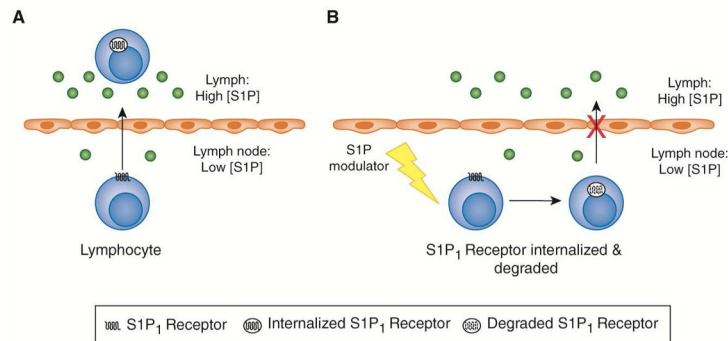
Figure 3. Lymphocyte Trafficking and S1P$_1$ Receptor Modulation
(A) In areas of low S1P concentration, S1P$_1$ receptors are expressed on lymphocytes which facilitate egress from areas of low to high S1P concentration. After egress out of the lymph node, S1P$_1$ receptor expression is downregulated.
(B) In the setting of an S1P modulator, the S1P$_1$ receptor is internalized and degraded, preventing lymphocyte egress from the lymph node.

Table 1

Comparison of Biologics and Small Molecules

	Biologics	*Small Molecules*
Weight (Daltons)	Large (>1000)	Small (<1000)
Route of Administration	Parenteral	Oral
Half-Life	Short	Long
Immunogenicity	Potential Risk	Low Risk
Drug-Drug Interactions	Rare	Potential

Table 2

Summary of Type I and Type II Cytokine Signaling

TYPE I CYTOKINE RECEPTORS	Cytokine	Associated JAK	Associated STAT
Common γ-chain			
	IL-2	JAK1, JAK3	3, 5
	IL-4	JAK1, JAK3	6
	IL-7	JAK1, JAK3	3, 5
	IL-9	JAK1, JAK3	1, 3, 5
	IL-13	JAK1, JAK3, TYK2	1, 3, 5
	IL-15	JAK1, JAK3	3, 5
	IL-21	JAK1, JAK3	1, 3, 5
Common β-chain			
	GM-CSF	JAK2	3, 5
	IL-3	JAK2	3, 5, 6
	IL-5	JAK2	3, 5, 6
gp130 chain			
	IL-6	JAK1, JAK2, TYK2	1, 3
	IL-11	JAK1, JAK2, TYK2	3
	IL-27	JAK1, JAK2, TYK2	1, 2, 3, 4, 5
Dimers			
	IL-12	JAK2, TYK2	4
	IL-23	JAK2, TYK2	3, 4
	IL-27	JAK1, JAK2	1, 3
	IL-35	JAK1, JAK2	1, 4
Hormone			
	EPO	JAK2	5
	TPO	JAK2	1, 3, 5
	G-CSF	JAK2	5
	Growth hormone	JAK2	3, 5
	Leptin	JAK2	3, 5
TYPE II CYTOKINE RECEPTORS			
IFN family			
	IFN α/β	JAK1, TYK2	1, 2, 3, 4, 5
	IFN γ	JAK1, JAK2	1
	IL-28	JAK1, TYK2	1, 2, 3, 4, 5
	IL-29	JAK1, TYK2	1, 2, 3, 4, 5
IL-10 family			
	IL-10	JAK1, JAK2, TYK2	1, 3, 5
	IL-19	JAK1, JAK2, TYK2	3
	IL-20	JAK1, JAK2, TYK2	3

TYPE I CYTOKINE RECEPTORS	Cytokine	Associated JAK	Associated STAT
	IL-22	JAK1, JAK2, TYK2	1, 3, 5

Adapted from Boland BS, Sandborn WJ, Chang JT. Update on Janus kinase antagonists in inflammatory bowel disease. Gastroenterol Clin North Am 2014;43(3):603–17; with permission.

Table 3

Summary of Small Molecules for Crohn's disease

Medication	Mechanism of Action	Clinical Trial Status	Safety Concerns	Approved Conditions
Tofacitinib	Pan JAK inhibitor	Phase 2 –completed	Effects of JAK2 inhibition	Rheumatoid Arthritis
Filgotinib (GLPG0634)	JAK1 inhibitor	Phase 2 – completed Phase 3 –recruiting	VZV reactivation	None
ABT-494	JAK1 inhibitor	Phase 2 –ongoing	VZV reactivation	None
Mongersen (GED0301)	Smad7 inhibitor	Phase 2 – completed Phase 3 –recruiting	Complement activation	None
Ozanimod	S1P$_1$R modulator	Phase 2 –recruiting	Lymphopenia	None