NEW THERAPEUTIC AGENTS IN IBD
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There are a variety of new therapeutic agents for the treatment of inflammatory bowel disease (IBD) which are either recently approved or in later stage clinical development. These include budesonide, the anti-tumor necrosis factor (TNF) agent golimumab, agents directed against lymphocyte trafficking, anti-cytokine therapy with anti-interleukin 12/23p40, and Janus kinase (JAK) inhibition with tofacitinib.

**Budesonide**
Oral controlled ileal release budesonide (Entocort) is in widespread clinical use as induction therapy for mild to moderate Crohn’s disease. It is targeted to the terminal ileum and right colon and has been shown to be ineffective in Crohn’s colitis involving the left colon. Oral MMX budesonide (Uceris) was recently approved for the treatment of mild to moderate ulcerative colitis. MMX budesonide is provides extended release throughout the colon. Oral budesonide MMX 9 mg was more effective than placebo for inducing remission at 8 weeks in patients with mild to moderate ulcerative colitis. In contrast, controlled ileal release budesonide was less effective as an active comparator. A rectal budesonide foam for ulcerative proctitis and distal ulcerative colitis is also in clinical development.

**Anti-TNF Therapy**
Golimumab is a subcutaneous fully human anti-tumor necrosis factor IgG1 monoclonal antibody to TNF. Golimumab was recently approved for moderate to severe ulcerative colitis. The approved dose for ulcerative colitis is 200 mg at week 0 and 100 mg at week 2 for induction and 100 mg every 4 weeks for maintenance. Golimumab comes in 50 mg and 100 mg auto-injectors or syringes. A Phase III induction trial demonstrated that golimumab administered at doses of 400 mg at week 0 and 200 mg at week 2 and 200 mg at week 0 and 100 mg at week 2 were more effective than placebo for the induction of clinical response, clinical remission, and mucosal healing. A Phase III maintenance trial demonstrated that golimumab 100 mg every 4 weeks was more effective than placebo for maintenance of clinical response, clinical remission, and mucosal healing. A 50 mg dose administered every 4 weeks failed to achieve the primary endpoint of maintenance of clinical remission, but was effective for the secondary endpoints of maintenance of clinical response and mucosal healing.

**Inhibition of Lymphocyte Trafficking**

**Inhibition of α4β7/MAdCAM1 binding**
There are a variety of ways to inhibit the binding of the α4β7 integrin on the surface of lymphocytes to the MAdCAM1 receptor on the vascular endothelium of the gut. This binding mediates selective trafficking of lymphocytes to the gut, and blocking it can gradually lead to lymphocyte depletion in the gut. Vedolizumab is a humanized, monoclonal antibody against α4β7 integrins that is administered intravenously over 30-60 minutes. A Phase III induction trial demonstrated that vedolizumab 300 mg at weeks 0 and 2 is effective for induction of clinical response, clinical remission and mucosal healing in patients with moderate to severe ulcerative colitis. A Phase III maintenance trial demonstrated that vedolizumab 300 mg every 4 or 8 weeks is effective for maintenance of clinical response, clinical remission, mucosal healing, and steroid sparing. Similarly, Phase III trials demonstrated that vedolizumab 300 mg at weeks 0 and 2 is effective for induction of clinical remission and that vedolizumab 300 mg every 4 or 8 weeks is effective for maintenance of clinical response, clinical remission, and steroid sparing in patients with moderate to severe Crohn’s disease. Vedolizumab is currently under regulatory review by the FDA for the indications of ulcerative colitis and Crohn’s disease.

There are currently three other gut selective anti-integrins under development for inflammatory bowel disease. Anti-MAdCAM1 antibody (PF-00547,659) showed evidence of clinical benefit in a Phase IIa trial in ulcerative colitis and is currently in Phase IIb trials in both ulcerative colitis and Crohn’s disease. Etrolizumab (anti-β7 antibody) recently demonstrated efficacy for inducing clinical remission at week 10 in patients with moderate to severe ulcerative colitis. AMG181 is another anti-β7 antibody that is currently in Phase IIb trials for both ulcerative colitis and Crohn’s disease.

**Inhibition chemokine receptor 9 (CCR9)**
Some activated T cells express CCR9 on the surface. CCR9 binds to TECK and leads to selective homing or trafficking to the gut. GSK1605786 is an oral CCR9 antagonist. Phase II induction and maintenance trials demonstrated some evidence of efficacy in patients with moderate to severe Crohn’s disease. Phase III induction and maintenance trials in Crohn’s disease are currently underway.

**Sphingosine 1-Phosphate Receptor 1 (S1P1) Modulation**
SIP1R agonism induces receptor internalization such that lymphocytes lose response to S1P gradient and become trapped in lymph nodes causing peripheral lymphopenia. SIP1 inhibition with fingolimod is effective for multiple sclerosis. SIP1 inhibition with RPC1063 is currently being evaluated in a Phase II trial in ulcerative colitis.
Andrographis Paniculata
HMPL-004 is an extract of andrographis paniculata. HMPL-004 is an herbal mixture that is anti-inflammatory and inhibits TNF-α, IL-1β and NF-kB. The marker compound, one of a series of closely related diterpene lactones, composes only 1-2% of the mixture. In pre-clinical models, no single component is as effective as the mixture indicating that the components are probably synergistic. In a Phase Ib trial HMPL-004 1,800 mg/day was more effective than placebo for induction of clinical response, clinical remission, and mucosal healing in patients with mild to moderate ulcerative colitis.11 Phase III induction and maintenance trials in ulcerative colitis are underway.

Anti-Interleukin 12/23p40
Ustekinumab is an IgG1 monoclonal antibody against the shared p40 subunit of interleukin 12 and interleukin 23. Ustekinumab can be administered subcutaneously or intravenously. Ustekinumab is approved for the treatment of psoriasis. A Phase IIa trial of subcutaneous and intravenous ustekinumab in moderate to severe Crohn’s disease demonstrated a reduction in CRP concentrations, and induction of clinical response, with the most pronounced effect in patients who had previously been treated with infliximab.12 Subsequently, a Phase IIb trial demonstrated that intravenous ustekinumab 6 mg/kg was effective in inducing clinical response and that subcutaneous ustekinumab 90 mg every 8 weeks was effective in maintaining clinical response and remission in patients with moderate to severe Crohn’s disease who had previously failed anti-TNF therapy.13 Phase III induction and maintenance trials are underway.

Janus Kinase (JAK) Inhibitors
Janus kinase inhibitors can be targeted with varying degrees of selectivity to JAK1, JAK2, and JAK3, and can directly or indirectly modulate signaling for various pro-inflammatory cytokines including interleukin-2, -4, -7, -9, -15, and -21. Tofacitinib inhibits JAK1, JAK2, and JAK3 in vitro with functional cellular specificity for JAK1 and JAK3 over JAK2. Tofacitinib 5 mg twice daily is currently approved for rheumatoid arthritis. A Phase II trial of tofacitinib in moderate to severe ulcerative colitis demonstrated efficacy at doses of 10 and 15 mg twice daily for induction of clinical response, clinical remission, and mucosal healing.14 A Phase II trial of tofacitinib in moderate to severe Crohn’s disease failed to demonstrate induction efficacy over 4 weeks at doses of 5 and 15 mg twice daily.15 However, the 15 mg dose did significantly reduce CRP and fecal calprotectin concentrations. Phase III induction and maintenance trials in ulcerative and a Phase IIb trial in Crohn’s disease are underway.

Conclusions
Budesonide and agents targeted against multiple targets including TNF, beta 7 integrin, MAαCAM-1, the p40 subunit of interleukin 12/23, chemokine receptor 9, and JAK3, hold great promise for the future.

REFERENCES