1) Vedolizumab after failure of anti-TNF therapy for Crohn’s disease

Vedolizumab is a new trafficking inhibitor immunosuppressive with selective activity in the gut which has shown activity for both UC and CD (the GEMINI 1 and 2 studies). Given its different mechanism of action, it has been speculated that it can be particularly effective in patients who fail anti-TNF therapy, just like its predecessor, natalizumab. In the GEMINI 3 study, investigators sought to test this hypothesis in a randomized controlled 6 weeks induction study. Patients with moderate-severely active CD were randomized to receive 3 doses of VDZ at 0, 2 and 6 weeks. All patients evaluated for the primary endpoint of remission at 6 weeks had failed anti-TNF drugs (primary or secondary failure or intolerance) and the majority were receiving immunosuppressives at baseline. For the secondary analyses, a smaller group of anti-TNF naïve patients was added. In the intent to treat analysis, among patients previously exposed to anti-TNF, there was no significant difference in remission rates between VDZ and placebo treated group. However, the response rates at week 6 and remission rates at week 10 were both significantly higher with VDZ (39% vs. 22%, RR 1.8 and 27% vs. 12%, RR 2.2). The difference between VDZ and placebo persisted for a number of other exploratory analyses at week 10. There was no significant difference in the rate of side effects between the two groups.

Comments: As seen in a previous Crohn’s disease trial, VDZ has a slower onset of action compared to anti-TNF drugs so it’s clear that the primary endpoint was set too early. Thus, although this is, strictly speaking, a negative study, the results suggest a significant benefit at 10 weeks. Similar findings were seen with natalizumab, another trafficking inhibitor, so this is likely a class-effect. The present study did not include a maintenance arm. In the previous GEMINI 2 study, patients treated with VDZ maintained response and remission at 52 weeks at a significantly higher rate compared to placebo. Although the finding of a lower response rate among anti-TNF failures compared to anti-TNF naïve is somewhat counterintuitive, the former group had a longer disease history and likely more severe structural damage thus precluding a fair comparison. Therefore the answer to this question remains unclear. Overall, it appears that VDZ is effective for both anti-TNF naïve and experienced CD patients but with a slower onset of action compared to anti-TNF drugs.


2) Accelerated Infliximab induction therapy for patients with acute severe UC
Infliximab at standard dose is effective for patients with moderately active UC who are not hospitalized. However, the half-life of IFX is shorter in patients with acute, severe UC (ASUC) due to a higher drug “sink” (higher concentration of TNF alpha), more rapid drug catabolism and likely drug loss in the gut (immunoglobulin-losing enteropathy). Therefore standard IFX dose has a high failure rate in these patients. In this retrospective, observational study from the UK, investigators report the colectomy outcomes in a series of 50 hospitalized patients with ASUC who received either standard dosing (3 infusions over 42 days) or accelerated dosing (3 infusion in an average of 24 days) after failure of systemic steroids. The treatment regimen was chosen by the clinician based on clinical and laboratory data (CRP). There were no significant differences in baseline variables between the two groups. The rate of colectomy was significantly lower in the accelerated dosing group compared to the standard group at the end of induction (6.7% vs. 40%, p=0.039). Among patients who completed induction, the rate of colectomy during maintenance therapy remained stable. Predictors of successful induction were serum albumin, CRP level and the administration of accelerated therapy. Only 3.2% of patients who normalized their CRP required colectomy compared to 68% of those who didn’t.

**Comments:** Although this is a provocative study it has a number of major limitations. A careful look at the survival curve shows that the vast majority of patients in the standard group underwent colectomy before they received the second dose of drug (in the first 14 days) which suggests that the decision to operate was strongly biased by the response rate after a single dose in the “eyes of the clinical team”. Had the authors waited through the end of induction in both regimens the results may have been different. No information is provided on IFX trough levels or concomitant IMM. However, this study reinforces the idea that a one-size-fits-all approach with anti-TNF biologics in patients with acute severe UC may not be appropriate and should be re-evaluated. It also emphasizes the importance of using the CRP curve as an early predictor of response.


3) Have colectomy rates in UC decreased after the introduction of anti-TNF drugs?

Anti-TNF drugs are effective for induction and maintenance of remission in patients with UC. Post-hoc analyses of registration trials have also suggested they can decrease short-term colectomy rates in patients with moderate-severe UC. Whether this observation carries over in the community is unknown. In this paper, investigators from a Canadian province have analyzed the annual incidence of colectomy (colectomy cases divided by the prevalence of UC during the calendar year) for refractory UC in a single large city over a period of 13 years using several administrative databases. The period of study straddles the year when infliximab (IFX) was approved for the treatment of UC and therefore they compared the colectomy rates “before and after” IFX. Among a total of 481 patients who underwent colectomy for refractory disease,
there was negligible variance in the colectomy incidence rate before 2005 but a major and significant drop in the annual colectomy rate (16%/year) after 2005. During the period of the study, the use of IFX has increased from 0 to 60% among patients hospitalized with UC who underwent colectomy. Based on this data, they conclude that the drop in colectomy rates is due to an increase in IFX use.

Comments: Although the conclusion of the study seems rational, if the results seem too good to be true, it is because they probably are. First, the reported increased use of IFX was only among hospitalized patients who underwent colectomy (and therefore failed IFX) rather than in the general population. The authors could have collected data on the use of IFX in the population of the province quite easily using one of the administrative databases. Also, a careful look at the annual colectomy incidence suggests that the decreasing trend had started a few years before the introduction of IFX and may be due to improved care pathways in UC patients including the use of other medications likely immunomodulators. Lastly, based on this paper, the estimated prevalence of UC in Alberta, has increased by nearly 60% while the population increased only by 10% during this 13 year interval. This is likely due to improved access to diagnostic tests and specialized care particularly among patients with mild disease, aka a detection bias. Thus, by increasing the denominator (the pool of UC patients) in the equation, the authors have spuriously decreased the annual incidence of colectomy. Thus, the positive results of this study are likely due to an ecological fallacy rather than a true cause-effect relationship. The only conclusion that can be drawn from this study is that an increasing number of patients are treated with IFX prior to undergoing colectomy. While it’s very plausible that IFX decreases colectomy rates in UC, the drop rate is unlikely to be of such magnitude.