1. Etrolizumab for induction therapy in Ulcerative Colitis

Immune-cell trafficking blockade (preventing the migration of pro-inflammatory T-cells from blood into tissue) is an effective therapeutic option for both ulcerative colitis and Crohn’s disease. Two members of this family, natalizumab (Tysabri) and vedolizumab (Entyvio) are approved for clinical use in the US. A group of investigators are now reporting the results of a phase 2, randomized clinical trial utilizing a novel humanized monoclonal antibody, etrolizumab (ETZ) which blocks the β7 subunit of two integrins present on the surface of lymphocytes and prevents the migration and retention of T-cells into the bowel wall. Two different doses of ETZ were compared with placebo in patients with moderately-severe UC who failed conventional therapy for non-US patients and both immunomodulators and anti-TNF therapy for patients recruited in the US. The study design is rather complicated given that different protocols were used within and outside the US. The primary endpoint was clinical remission at week 10. Significantly more patients achieved clinical remission in the low-dose ETZ group compared with placebo and high-dose ETZ groups (21% vs. 0 vs. 10%). No significant differences were seen in the rate of clinical response or mucosal healing and no consistent association was found with concomitant use of steroids or IMM. Both doses of ETZ maximally saturated the β7 receptors on circulating lymphocytes and colonic tissue based on pharmacokinetic assays. In general, both doses were well tolerated with no serious opportunistic infections reported.

Comments: Lymphocyte trafficking inhibition is a rapidly growing field in the therapeutic management of IBD. The advantage of the newer agents such as ETZ, is that they are gut-specific in contrast with natalizumab which also blocks the migration of lymphocytes in the brain and thus predisposes patients to progressive multifocal leukoencephalopathy (PML). Although the efficacy of ETZ for induction therapy for UC in this trial appears quite modest, the study population was rather refractory with more than 60% of patients having failed anti-TNF drugs. The bad news is that patients who were anti-TNF non-responders also failed to respond to ETZ for reasons that are not entirely clear. A phase 3 program for this drug is likely to follow as are clinical trials in patients with Crohn’s disease. The question remaining for this class of biologics is their comparative efficacy with TNF-alpha blockers which have been traditionally considered as first line biologic therapy.
2. Does measuring biologic drug levels by different assays make a difference?

Recent studies have shown that therapeutic interventions based on the measurement of biologic drug trough and antibody levels may be more cost-effective than empirically increasing the dose or switching drugs (Velayos et al. – Clin Gastroent Hepatol ’13). Several lab assays using different analytic techniques have been in clinical use for a few years. It has been suggested that the newer, more sensitive assays that can detect anti-drug antibodies even in the presence of drug in the serum (i.e. mobility shift assay and RIA) provide an advantage over the more traditional ELISA-based assays. The authors of this study aimed to compare the performance of four different assays (ELISA, radio-immunoassay RIA, mobility shift MSA, and reporter gene assay RGA) and determine whether the use of different techniques can influence interventions and outcomes of drug optimization algorithms. To this end, they performed a post-hoc analysis of data from a prospective study in patients with Crohn’s disease and secondary IFX failure. IFX detection was comparable between all 4 assays and correlated significantly. The agreement was superior for lower than higher trough levels of IFX. As expected, there were notable differences in the anti-IFX antibody (ATI) results with MSA reporting a significantly higher proportion of ATI-positive sera compared with ELISA. However, when analyzed by reporter gene assay, the authors found that two thirds of ATI found with MSA were non-neutralizing or non-functional. In fact, the agreement on the classification of IFX failure was very high among all methods (>80%) and there were no differences in clinical outcomes of interventions based on results obtained using the four different methods. The authors conclude the newer and more sensitive (and costly) drug assays may not be superior for therapeutic guidance.

Comments: Although the study has a number of limitations including the retrospective design and small sample size, the findings are quite interesting and relevant for clinical practice. It has been previously shown that in some patients, the presence of low level anti-drug antibodies (ADA) can be overcome by increasing the biologic dose and frequently, these antibodies may disappear over time. The results of this study suggest that these “transient” ADAs may not be functional after all which is the reason why they have limited impact on clinical outcomes. The study also seems to support the fact that all pharmacokinetic assays have similar impact on patient management and therefore practitioners and reference labs may decide to choose the assay that is more cost-effective from their perspective.

3. Have we changed the natural history of inflammatory bowel disease?

Population and referral center-based studies published 2 decades ago primarily from Europe presented a relatively grim picture of the natural history of Crohn’s disease and ulcerative colitis with more than 80% of the former and 30% of the latter undergoing surgery for their disease in their lifetime. However, our treatment strategies have changed and it would be interesting to know if this has had an impact on the natural history of these disorders. Investigators from Denmark report the outcomes of an inception cohort of patients with IBD (n=513) diagnosed after 2003 and followed up for a median of 7 years. Treatment strategies utilized in these patients were based on guidelines published in the European and US literature. Overall, 24% of patients with CD and 29% of patients with UC had a change in disease location (or extension in the case of UC) and 16% of patients with CD had a change in disease behavior (towards stricturing or penetrating). 23% of CD patients and 6% of UC patients were treated with anti-TNF therapy. The rate of surgery at 7 years in CD was 29% and in UC 12%; 10% of CD patients also underwent perianal surgery. Four deaths were recorded and, interestingly, all but one was related to surgery. The non-surgical death was in an 88 year old patient with severe UC.

Comments: This study shows that changes in diagnosis and disease extent are common in both CD and UC. While in the case of UC this is likely due to natural disease progression, in the case of CD this may be due in part to the impact of newer diagnostic technologies; for instance, in the CD cohort, 18% of patients had upper GI involvement at follow-up which is far larger than any previously published data. The study also suggests that the rates of surgery in IBD have decreased which may be due to superior drugs and improved treatment strategies (earlier use of immunomodulators and biologics). It is unclear, however, if this inception cohort is actually representative of the general IBD population as a referral bias is likely to persist. Also, the significance of some of the findings (including the “proximal extension” in patients with CD) is unclear as the association with changes in therapy or outcomes is not reported. Finally whether a specific therapeutic strategy or rather lead-time bias are attributable to the improvement in outcomes is unclear.
4. How effective are biologic agents for ulcerative colitis?

Several biologic agents from two different classes (anti-TNF-alpha and anti-integrin) have shown efficacy for UC. Investigators now report the results of a systematic review and network meta-analysis to assess the comparative efficacy and harm of biologic agents in patients with moderate to severely active UC. They identified 8 randomized placebo-controlled trials utilizing 4 biologic drugs (3 anti-TNF and 1 anti-integrin) in patients with UC who were otherwise bio-naïve (bio-experienced patients were excluded to decrease bias). There were, of course, no head to head trials comparing biologics against each other. The summary results showed that all biologic drugs (infliximab IFX, adalimumab ADA, golimumab GLM and vedolizumab VDZ) are superior to placebo in every outcome (response, remission and mucosal healing) for induction therapy. The results of the network meta-analysis suggested that IFX was superior to ADA for induction of response and mucosal healing but no other comparisons reached statistical significance. All maintenance trials showed that biologics are superior to placebo but had high risk of bias (due to inclusion of responders only). There was no increased risk of side-effects with biologics in these studies.

Comments: while the results of this meta-analysis are informative and intriguing, the data has to be interpreted with a huge grain of salt. The lack of head-to-head comparisons precludes any definitive conclusions regardless of the fanciness of the artificial neural network utilized. The authors compared the odds ratios of response and remission among trials which is not more reliable than comparing percentages. Normalizing the response rates based on placebo is another technique that has been proposed and suggests that all biologic drugs are comparable. There are a number of other potential confounders that may affect the results of this meta-analysis including differences in treatment history, baseline steroid and IMM use (which was continued in the placebo groups), study design, geographic location (patients from Eastern Europe tend to respond better to placebo thus artificially decreasing the OR), enrollment ratio (patients are less likely to enroll in a clinical trial when a similar drug is already approved and available for use) and the central interpretation of the Mayo score (the disease activity measure used in all studies). Without head-to-head trials no meaningful conclusions can be drawn from studies such as this one. To their credit, the authors suggest that further placebo-controlled trials are unethical and also that comparative effectiveness trials among biologics should be a top priority for research.