Inflammatory Bowel Disease Seattle Journal Club
August 2013
Comments by Michael Chiorean, MD, Director IBD Center of Excellence, Virginia Mason Medical Center, Seattle, WA

1. Vedolizumab looks like a winner for UC, less so for Crohn’s disease.

Blockade of lymphocyte trafficking to the inflamed gut is a proven therapeutic strategy in Crohn’s disease (CD) but not ulcerative colitis (UC). The first agent in clinical use, natalizumab (Tysabri) – an α4 integrin blocker, was relatively non-specific and blocked the migration of lymphocytes to multiple tissues including the brain and has been associated with a severe brain infection (PML). In contrast, a newly developed drug, vedolizumab (Ved), which is a selective α4-β7 integrin blocker, works specifically in the gut and thus is postulated to be safer yet maintain efficacy against IBD. A very large program called GEMINI has been established to evaluate the efficacy of Ved in both UC and CD. In GEMINI 1 patients with moderate-severe UC were enrolled in separate induction and maintenance trials and evaluated at 6 and 52 weeks. Approximately 70% of patients were either on steroids or immunomodulators (or both), and 50% had been previously exposed to anti-TNF biologics. Patients with prior exposure to natalizumab were excluded. In the induction study, Ved was significantly more effective than placebo for both response (47% vs. 25%) and remission (17% vs. 5%). In the maintenance study, 521 patients received open label vedolizumab. Responders in this cohort were combined with responders from the induction cohort and were randomized to either 4 or 8 weekly active drug vs. placebo. At 52 weeks, significantly more Ved patients were in remission compared to placebo (42% vs. 16%) and there was no difference between the 4 week and 8 week infusion groups. Mucosal healing and steroid-free remission rates were also significantly and substantially higher (2.5 fold) in the Ved group vs. placebo. There was no difference in the rate of adverse events including infusion reactions between placebo and active drug. Importantly, no cases of PML occurred. In fact, the authors mention that, in the entire GEMINI program which includes approximately 3,000 patients followed for a median of 18 months, no cases of PML have been described. The GEMINI 2 trials had a similar design for patients with moderate-severe Crohn’s disease. Here, though, the differences between vedolizumab and placebo were much smaller (14% vs. 7% remission and 31% vs. 26% response at wk. 6 and 36% vs. 22% remission at wk. 52). The rate of serious adverse events was also higher in the Ved group compared to placebo but no cases of PML were reported.

Comments: Vedolizumab is a selective integrin blocker which seems to be effective for both Crohn’s disease and UC. The reason for the striking difference in response rates between the two diseases is unclear. In fact, if Ved was going to follow in the foot-steps of its more storied predecessor natalizumab, the rates in CD should be higher than UC. The authors suggest that the Crohn’s cohort contained sicker patients (more patients who were steroid-dependent or refractory) and substantially more patients who failed anti-TNF than other trials. Mechanistically, vedolizumab may also work slower compared to a-TNF biologics given its
pharmacokinetics and pharmacodynamics. Natalizumab also took more than 6 weeks to reach its peak benefit in clinical trials. However, this could not explain the difference between remission (positive) and response rates (no difference) in Crohn’s patients receiving vedolizumab as well as the major difference between patients with UC and Crohn’s disease. Another potential explanation is that the higher selectivity of Ved actually makes it less effective than natalizumab at least for CD. Since no patients previously exposed to natalizumab were allowed in these trials, the answer to this question remains elusive. The good news is that no cases of PML were reported in either trial as well as follow-up open label extension trials to date. The FDA will probably require additional safety data given the drug’s similarity to natalizumab but I suspect that the safety data will pan out long-term. This is certainly good news for UC patients with severe disease who will soon have another treatment option available. How this drug will compete with anti-TNF biologics for first line therapy at least in ulcerative colitis remains to be seen.


2. Does poor sleep cause IBD flares?

There is a correlation between quality of life and disease activity in IBD. Factors such as external environment, behavior and lifestyle may play a role in the pathogenesis of both Crohn’s disease and ulcerative colitis. Prior studies have shown that sleep disturbance can be associated with a number of psycho-somatic and organic diseases including obesity, migraines and GERD. Whether such association exists in IBD is unclear. Investigators used data from a self-reported IBD database maintained by the CCFA (the CCFA Partners IBD cohort) to analyze the relationship between sleep disturbance and disease activity in both CD and UC. The disease type, activity and degree of sleep disturbance was collected using self-administered questionnaires at 2 time points. Of the almost 3,200 patients eligible for the study, 1,800 were reportedly in symptomatic remission at baseline. Despite this, 2/3 of this cohort reported disordered sleep. Coexistent depression, smoking, use of narcotics, steroids and active disease were associated with poor sleep but use of anti-TNF agents was not. Half of CD patients in remission at baseline had disturbed sleep. Almost twice as many CD patients in remission but with poor sleep at baseline had active disease at 6 months follow-up compared to those with normal baseline sleep (22% vs. 12%). Depression at baseline was a strong predictor in this group. This difference was not seen in UC. The authors conclude that CD patients in remission who have poor sleep have a higher risk of disease flare compared to those with good sleep.

Comments: I think this is a provocative study with interesting but far from conclusive results. The baseline cohort is cross-sectional so information about recent disease activity is not
available. It is likely that patients who had a flare within 6 months of the baseline evaluation had a higher risk of flare in the subsequent 6 months. Both sleep and disease activity were self-reported and it is possible that disease activity or medications were the triggers for poor sleep and not vice-versa. In fact, patients in remission who had good sleep at baseline but poor sleep at follow-up were more likely to have a flare. The disease activity was self-reported and strictly based on symptoms. As it has been nicely demonstrated with GERD, patients who are intentionally sleep-deprived are more likely to report GERD symptoms compared to those with normal sleep despite no change in pH exposure (Shey et al. – Gastro ‘07). It is also difficult to explain the discrepancy between Crohn’s disease and UC as UC patients are typically first to flare under stress such as natural disasters. Depression is a common root for both insomnia and symptom reporting and patients with active disease either at baseline or follow-up in this study were far more likely to be depressed compared to those in remission. Finally, it is remarkable that no information about sedatives and pro-hypnotics (sleeping aids) is provided which is a major confounder for such study. Overall I believe this study supports association but not causality. In fact, I suspect that the alternative hypothesis is actually stronger, which is that patients with active disease are more likely to have disturbed sleep owing to their symptoms or medications and this further leads to anxiety and depression with further symptom awareness in a vicious cycle. In fact, a study reported recently in the IBD Journal (Ali et al. – Aug ‘13) reached a slightly different conclusion, showing that active endoscopic activity is associated with poor sleep in patients in “clinical” remission. That said, educating patients about good sleeping habits may have an impact in IBD patients just as it has in other patients with GI disorders.


3. Long-term outcome of peri-anal fistulas treated with infliximab.

Infliximab IFX is effective for Crohn’s disease patients with peri-anal fistulas (PAF) based on randomized clinical trials. The long-term effectiveness of IFX in these patients is not well known. Investigators from France report on an observational cohort of patients with PAF evaluated at 2 referral centers over a period of approximately 10 years. During the entire observation period, 70% of patients had at least one fistula closure and 46% had sustained fistula closure. Fistulas recurred in 33% of patients including 30% with an abscess. Ileo-colonic disease (L3), long-term IFX therapy, short duration of seton drainage and combination with immunomodulators were associated with fistula closure whereas additional surgical interventions including fistulotomy, flap advancement and fibrin plug were not. Ileal disease and discontinuation or short duration of IFX were associated with recurrence.
Comments: The major limitation of this retrospective study is the lack of a control group. Otherwise the data shown is consistent with that reported in clinical trials. The most important message here is that patients who close their fistulas quickly are likely to have good long-term results, whereas patients who discontinue biologic are likely to see a recurrence. The seton duration is probably only a surrogate marker for fistula severity and complexity. It also appears that combination therapy is beneficial although more than 40% of patients in this cohort received episodic therapy. It is interesting that information on smoking and long-term steroid use is lacking although both are important risk factors for fistula activity and recurrence.