Inflammatory Bowel Disease Seattle Journal Club

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Comments by Michael Chiorean, MD, Director IBD Center of Excellence, Virginia Mason Medical Center, Seattle, WA

1) Incidence and Mortality from Colorectal Cancer in Patients with IBD.

IBD affecting the colon has been linked to the development of colorectal cancer. Studies published in the early ’90s showed a consistently elevated risk of colon cancer among patients with pancolitis, long disease duration or coexistent PSC. Investigators have now used a population database from a single large HMO in Northern California to determine the incidence and mortality from CRC in patients with IBD compared to the general membership (non-IBD patients) from 1998 to 2010. During this interval, the Kaiser Permanente group covered roughly 4.5 million persons. Among patients with IBD, the incidence of colon cancer was increased by 60% compared to the general population and remained stable over time. The ratios were similar for patients with Crohn’s and UC. In contrast, colonoscopy screening and consequently the incidence of CRC increased in the general membership population by almost 75%. Mortality from CRC was 2 fold higher in the IBD population. Of note, Kaiser Permanente has no formal medical group policy regarding neoplasia surveillance in IBD patients.

Comments: This study is the largest performed using a non-referral population in the US and showed a significantly increased risk of colon cancer among IBD patients that did not change over time. This is somewhat contrasting to other recent population-based studies showing a decreasing incidence of CRC in patients with IBD (Jess et al. — Gastro ’06; Wintzer et al. — CGH ’04; Soderlund et al. — Gastro ’09). No information was provided on the disease extent, duration and degree of inflammation. The prevalence of PSC was low. Whether the low use of surveillance colonoscopy, or the infrequent use of immunomodulators and biologics have contributed to these findings is unclear. Colon cancer remains an important cause of morbidity and mortality in patients with IBD and further surveillance and diagnostic options are clearly needed. (Herrinton LJ et al. — Gastro ’12;143:382-9).


2) IL-17a antagonist (secukinumab) not effective for Crohn’s disease.

Approximately 50% of patients do not respond or fail standard and anti-TNF biologic therapy. Few alternatives exist for this patient population. Interleukin-17a (IL-17A) is elaborated by the T helper 17 (Th17) subset of T cells and exhibits potent pro-inflammatory properties in animal models of autoimmunity, including collagen-induced arthritis, experimental autoimmune encephalomyelitis, and experimental autoimmune uveitis. Elevated levels of IL-17A have been found in the intestinal mucosa of patients with Crohn’s disease, where it is associated with overexpression of IL-23. In this multi-center randomized phase 2a trial, investigators studied the efficacy of secukinumab (AIN457), a fully human selective anti-IL-17A monoclonal antibody in patients with moderate to severe Crohn’s disease. At baseline, about 50% of patients were on steroids, 30% on Aza/6-MP and 12% previously received a-TNF therapy (all randomized to secukinumab). At 6 weeks, neither secukinumab nor placebo recipients experienced a significant improvement although the CDAI decreased more in the placebo group compared to the active group. There were also more side-effects including infections in the secukinumab group. There was <0.1% probability that secukinumab reduces CDAI by more than 50 points compared to placebo. Post-hoc analyses showed that patients with elevated inflammatory markers (elevated CRP and calprotectin) did worse with secukinumab.

Comments: Despite preliminary studies suggesting that IL-17 antagonists may be effective in Crohn’s disease, this good quality study failed to indicate a positive response. Furthermore, patients treated with this IL-17A antagonist seem to fare worse both as far as Crohn’s disease and infectious complications compared to the control group. The study was slightly imbalanced (all anti-TNF failures were block randomized to drug) and there were fewer patients on Aza/6-MP in the active arm group. Nevertheless, this study raises important doubts about the effectiveness of blocking IL-17 in Crohn’s disease. In fact, the present data may suggest that IL-17A may be protective in Crohn’s patients, although this hypothesis needs to be proven. It is unclear if a higher dose of drug may be effective yet there are safety concerns. Secukinumab at doses lower or equal to 10 mg/kg was effective in non-controlled phase 2 studies for patients with rheumatoid arthritis and plaque psoriasis (Hueber et al. — Sci Transl Med ’10). In any event, there is a chance that other IL-17 compounds may have different outcomes, but I think the likelihood overall is low. The strategy of IL-17 blockade may need to be re-visited or it is possible that this is another case where the same mechanism of action has different outcomes in patients with different immune-mediated disorders. (Hueber et al. — Gut 2012;61:1693-1700).


3) Surgery rates in Crohn’s disease still high in population-based study.

Medical treatment for Crohn’s disease has changed dramatically in the last 15 years with the advent of immunomodulators and especially biologics. The impact of these medications on the risk of surgery in Crohn’s patients is controversial. Investigators used medical records from Olmsted County, MN to evaluate the natural history of a cohort of 313 newly diagnosed Crohn’s patients from 1970–2004 and followed through 2009 for a median follow-up of 12 years. Fifty percent of patients underwent at least 1 major abdominal surgery and 10% had at least 3. The cumulative risk of surgery was 38, 48 and 58% at 5, 10 and 20 years after diagnosis. Baseline predictors of surgical risk were small bowel location (HR 3.4), smoking, male gender, penetrating disease at diagnosis (HR 2.7) and early use of steroids. The use of 5-ASA was associated with a lower risk in univariate analysis and the use of anti-TNF agents with a higher surgical risk. The rates of major abdominal surgery remained stable over time.
**Comments:** Although these findings are not novel, they offer a glimpse on the natural history of Crohn’s disease during the immunomodulator and at least part of the biologic era. As expected from a retrospective study, the effect of various immunosuppressives cannot be teased out since there is an obvious bias to use more effective medications in patients with more complicated and severe disease, who also carry a higher risk for surgery. The other clinical markers, however are helpful to assist clinicians in identifying patients who are at higher risk of complications and therefore require more aggressive medical therapy. Prospective studies are necessary to determine if either immunomodulators or biologics alter the natural history of disease. (Peyrin-Biroulet et al. - Am J Gastroenterol 2012; 107:1693–1701)