1. Is IBD incidence in young children increasing?

The Paris pediatric modification of the Montreal classification defines very early onset IBD (VEO-IBD, aka A1a) as a disease phenotype that is distinct from that of other children. VEO-IBD is predominantly colonic with a lower risk of ileal disease. Researchers used a Canadian administrative database to determine the incidence, health service burden and outcomes of children with VEO-IBD in comparison with children with older age at diagnosis. All children diagnosed with IBD between 1994 and 2009 in Ontario, Canada, were identified and classified by disease onset < 6, 6-10 and > 10 years old. The incidence of IBD in children increased from 9.4 to 13.2/100,000 from 1994 to 2009. The incidence/year increased by 7.4% among children < 10 and 2.2% among children >10. Outpatient visits, hospitalizations and surgeries were less frequent among children < 6 than among children > 10 at any time point. The majority of patients < 6 were initially diagnosed as UC (61%) vs. children > 10 who were predominantly diagnosed with CD (58%). Patients < 10 at diagnosis were slightly more likely to have their IBD subtype diagnosis changed (UC – CD and vice-versa) compared to children > 10.

Comments: As in other recent studies from Canada, the incidence of IBD in children appears to be increasing by almost 40% in 15 years and particularly among the very young age group. While this rate is somewhat alarming, it is important to emphasize that these results are quite likely liable of multiple biases. Given the lower rate of outpatient visits, hospitalizations and surgeries, it follows that very young patients had milder disease at diagnosis which overall suggests a lead- and length-time bias (patients diagnosed earlier tend to have milder disease). This is likely in very large part due to increased IBD awareness among patients and physicians and improved access to gastroenterology care in this province of Canada. A similar phenomenon was described in Alberta, Canada (see IBD JC – Sept ’14). There is also no clinical or biological information available in these databases so information about disease location, severity and phenotype could not be extracted. Furthermore, biologic drugs were only approved after 2006 (for CD) and 2011 (for UC) and information about medication use was not provided. Nevertheless, there hasn’t been a single study world-wide suggesting that the incidence of IBD is decreasing although it may be stabilizing recently as we reached a “technological ceiling” in diagnosis. The increased incidence is now predominantly in the developing world which are seeing a “growth curve” similar to the Western world a few decades ago. This clearly suggests important environmental rather than genetic risk factors.

2. Long-term efficacy and safety of adalimumab for patients with Ulcerative Colitis

The efficacy of adalimumab for induction and maintenance of remission up to 52 weeks in patients with moderate-severe UC was demonstrated in the pivotal Ultra 1 and 2 studies which enrolled almost 1,100 patients. Patients who were still responding to therapy at 12 months were allowed to enter the open-label extension study, Ultra 3 for another 156 weeks. This paper presents the long-term efficacy and safety of adalimumab for UC up to 4 years from randomization. Of the 600 UC patients randomized to Ada at time 0, 199 remained on Ada after four years. Of the 588 patients who responded to therapy after 12 months and entered Ultra-3, a total of 360 remained on the drug after 3 years. The rates of clinical remission and mucosal healing were 32% and 42% at 12 months and 24.7% and 27.7% at 4 years, respectively. Of the 242 patients who entered Ultra-3 in remission, 63.6% remained in clinical remission 3 years later and 60% of the 409 patients who entered Ultra-3 with mucosal healing maintained it through week 144. During the first 12 months of Ultra-1 and Ultra-2, 25-30% of patients escalated to weekly Ada therapy and during the subsequent 3 years (Ultra-3), another 20% of patients required dose escalation due to loss of response. Overall more than 50% of patients who underwent dose escalation responded to therapy over the 4 year duration of the study. Clinical remission and mucosal healing rates were greater in anti-TNF naïve compared to aTNF-experienced patients. Patients with high CRP and low albumin were significantly more likely to lose response to Ada during the open-label phase. Corticosteroid-free remission rates also increased from 27% at 12 months to 40% at 4 years. The rate of side-effects and serious side-effects did not change during the open-label compared to the double-blind period of study although 3 patients developed B-cell lymphoma during Ultra-3.

Comments: Despite the obvious limitations of an open-label design, this report provides an estimate of the long-term efficacy and safety of adalimumab in patients with moderate-severe UC. The optimist will see the glass ¼ full while the pessimist will note the relatively modest long-term response and remission with anti-TNF drugs in UC. A few key points are important to emphasize: as it is the case with infliximab, the largest loss of response to Ada occurred in the first 12 months. Afterwards, patients who were responding or were in remission tended to do well long-term. In addition, patients who are anti-TNF treatment naïve tend to do better compared to those who are anti-TNF experienced. No data is provided in regards to co-therapy with immunomodulators, biologic trough levels and immunogenicity, although it is likely that antibody development is an important mechanism for loss of response in UC which is less subject to progressive structural damage compared to Crohn’s disease. Also, data from Ultra-2 and Ultra-3 suggests that Ada dose escalation to weekly therapy benefits approximately 50% of patients who recapture response or remission. Interestingly, low albumin and high CRP were
predictors of loss of response which indicates that some patients in clinical remission have incomplete mucosal or biological response and therefore are at higher risk of flares compared to those in deep remission.


3. Can infliximab be restarted after a drug holiday?

Only a limited number of biologic drugs are available for treatment of IBD. Infliximab is the longest biologic drug in use and therefore some patients are considered for a “second cycle” of IFX after a drug holiday. The efficacy and safety of this approach is unknown. Belgian investigators addressed this question in a retrospective cohort of 132 patients (109 CD and 23 UC) who restarted IFX after a drug holiday of minimum 6 months (range 6-125 mo). Most patients (n=100) discontinued their first course of IFX due to remission, pregnancy or personal choice and a majority had been treated with episodic therapy. All patients had undetectable ATI antibodies at the time of restarting IFX. Overall, restarting IFX was successful in 84.5% of patients at week 14, 70% at year 1 and 61% at the end of follow-up. Predictors of response with the second cycle of IFX were remission as the reason for discontinuation and the use of IMM with the second cycle of biologic. IFX trough levels were significantly higher and ATI levels lower after restarting therapy in responders compared to non-responders. ATI were a strong predictor of infusion reactions (HR 7.7) and IMM co-therapy (azathioprine, 6-MP, methotrexate) were associated with lower ATI levels after re-starting biologic and a lower rate of infusion reactions.

Comments: Although traditionally the loss of response to an anti-TNF biologic was considered an irreversible event, the current study indicates that recycling IFX is possible and effective for a substantial proportion of patients with IBD. Remission as the reason for discontinuation and co-therapy with IMM the second time, appear to be strong predictors of response. Although the conclusions are very optimistic, one has to keep in mind that this is a highly selected patient population. In practice, patients are more frequently facing the possibility of re-using a biologic after they failed it as well as other drugs in the same or different class. The other indication that this is a selected group of patients is the fact that all had undetectable ATI levels at the time of re-initiating IFX. In real life, a significant number of patients will remain ATI positive for years and re-using IFX in that group is associated with a high failure rate. Finally, it is unclear how many patients in whom IFX failed during the first cycle had surgery during the drug holiday and IFX was re-introduced as post-operative prevention therapy in patients with lower disease burden and substantially less structural damage thus introducing a bias in favor of restarting therapy. Nevertheless, this strategy seems applicable to a selected group of IBD patients and it is worth exploring particularly in patients who have interrupted the drug for non-medical reasons.

4. More on changing time trends in IBD – this time from Scandinavia

Several reports in the last 10 years have shown increasing incidence and prevalence (new and established cases) of IBD throughout the world. Growth in the developing countries in Asia and South America is outpacing the rate in the developed world. In this paper, investigators from Denmark evaluated changes in incidence, medical and surgical treatment in IBD patients over the last 35 years (from 1979-2011). They used data from several government-based administrative databases to compile data on new IBD diagnoses, types of medication used as well as surgical interventions which were classified as major or minor. During this period there were approximately 49,000 new IBD diagnoses of which 73% were ulcerative colitis (UC). There were more than 3-times as many new diagnoses of both CD and UC in the last 8 year period compared to the first 8-year period of the interval. The authors found that 5-year major surgery rates decreased from 44.7% during the first 7 years to 19.6% during the last part of the interval for CD and from 11.7% to 7.5% for UC (both statistically significant). During this time, there was a significant increase in the use of thiopurines and anti-TNF drugs parallel with a decrease in the use of 5-ASA and steroids. Particularly in CD, the use of 5-ASA had dropped by more than 50% over a decade whereas in UC the decline was less prominent. Interestingly, current use of both steroids and thiopurines was associated with an increased probability of major surgery in both UC and CD over time (compared to never use). In patients with UC duration more than 1 year, long-term use of steroids was associated with lower risk of surgery. There were not enough anti-TNF users to measure an association between aTNF use and surgery. The authors conclude that a surgery-sparing effect of the use of newer Immunomodulators was not found in this population.

Comments: The major strength of this study lies in the large study population but that’s about where the good things end. Otherwise there are multiple major confounders that make the interpretation of the results in this retrospective analysis quite difficult. One could easily arrive to the opposite conclusions simply by tweaking the working hypothesis. First, the dramatic increase in incidence of IBD over 30 years (3-fold) is likely spurious as the population growth in Denmark over this period was only 7.8% (from 5.1 mil to 5.5 mil according to Statistics Denmark). Thus, such an impressive growth has to be the result of improved disease awareness, access to specialist care and diagnostics and consequently enrichment of the IBD population with milder cases which don’t require advanced therapy or surgery. To support this, the absolute number of major surgeries in both UC and CD has actually increased over time (about 12%, in line with the population growth). Since the overall number of patients with severe disease requiring surgery has changed very little but the number of patients with mild disease has increased dramatically, statistical wizardry creates the impression of a significant drop in surgery rates which is obviously too good to be true. There is no information on disease
extent, severity and behavior or smoking habits, all factors that can influence response to medical therapy and need for surgery. Finally, some of the paradoxical associations between the use of thiopurines, steroids and the risk of surgery can be easily explained by selection bias (in this case confounder by indication). Patients with more severe disease are more likely to require both steroids and thiopurines and eventually surgery when these medications fail. The most glaring demonstration of this statistical flaw is represented by the lower rate of surgery among UC patients with long disease duration and recurrent steroid use. Obviously patients who receive yearly steroids with or without maintenance therapy are only able to do so because their disease is never severe enough to mandate surgery. Instead, it appears that some things in IBD care are universal, i.e. a prescription for prednisone is always handier than a conversation about immunosuppressive therapy regardless of the risks and benefits.