1. **Mongersen – a new kid on the block for Crohn’s disease?**

Crohn’s disease-related inflammation is due to overexpression of a number of pro-inflammatory cytokines such as TNF-alpha, IL-1 and IL-12/23 but also to the relative down-regulation of other immune-modulatory cytokines such as TGF-β1. The latter is caused by increased levels of an intra-cellular protein called SMAD7 (the moniker is a combination of Sma = small body size and MAD = mothers against decapentaplegic, a protein found in the fruit fly). Mongersen is a single-strand anti-sense nucleotide that binds to the SMAD7 mRNA leading to its degradation. In this phase 2 study, investigators at several Italian centers randomized 160 patients with moderately active CD to receive 1 of 3 doses of mongersen administered PO or placebo for a duration of 14 days. The primary endpoint was clinical remission at day 15 (based on CDAI). The proportion of patients who met the primary endpoint was significantly higher in the mongersen 160 and 40 mg groups (65% and 55%) compared to the 10 mg and placebo groups (12% and 10%). Similarly the proportion of patients who achieved clinical response (CDAI-100) was significantly higher in the 160 and 40 mg groups compared to the placebo and 10 mg group. Interestingly, the response lasted for up to 80 days after the two week treatment period. There was a small decrease in the level of CRP in all mongersen arms irrespective of the dose but the median CRP drop was not statistically significant from placebo. The drug was well tolerated with relatively uncommon side-effects.

**Comments:**

The results of this study at first glance appear to be somewhat of a breakthrough and, in fact, the paper has received a great deal of attention from the scientific and lay press alike. However there are several limitations that have to be acknowledged and have been nicely highlighted in the associated editorial. First, the inclusion criteria and primary endpoint are based on relatively subjective indicators (CDAI) there was no endoscopic evaluation and the median CRP at baseline was quite low despite the alleged moderate to severely active disease. In fact, only a small minority of patients normalized their CRP at the end of treatment despite remarkable improvement in symptoms. On the other hand, other drugs such as vedolizumab have also shown [a modest] efficacy in Crohn’s disease despite non-significant improvements in the CRP. Another surprising finding was the durability of response of almost 3 months despite only 14 days of therapy. That may be a unique feature of TGF-beta modulators which needs to be confirmed in further studies. Virtually all patients were enrolled in a single country (Italy) and it is unclear if such results can be replicated elsewhere. Of note, another antisense ICAM-1 oligonucleotide inhibitor, alicaforsen, has shown some efficacy when given as an enema for UC but not when administered systemically for Crohn’s disease (Vegter et al. – Alim Pharmacol Therap ’13). If the current results with mongersen are confirmed in phase 3 studies, this drug may indeed be a game changer.


2. **More evidence to support biologic drug monitoring in patients with IBD**

Loss of response (LOR) to anti-TNF biologics is seen in up to 40% of patients within the first year and 5-10% within each subsequent year and is associated with low trough levels or anti-drug antibody formation. The role of therapeutic drug monitoring is still controversial given the variability of assays available and relative scarcity of outcome data. Investigators from multiple Israeli centers have performed a retrospective analysis...
of the outcomes of therapeutic drug optimization in pediatric and adult patients with IBD and secondary LOR to therapy. Among the 247 patients enrolled, the vast majority had Crohn’s disease, a third were treated with concomitant IMM and slightly more were receiving infliximab. Essentially all patients had objective evidence of active inflammation at the time of drug level assessment. Responsible clinicians were apparently blinded to the results of drug and antibody levels performed at a single central lab. Although there was a substantial overlap in baseline trough levels between patients who responded and those who failed an increased dose of biologic, trough levels of adalimumab > 4.5 mcg/mL and infliximab > 3.8 mcg/mL identified patients who failed to respond to dose increase or switching to another anti-TNF biologic with 90% specificity. Instead, an adequate trough level predicted a response to symptomatic therapy or switching to a different IMM with over 80% accuracy. In addition, high-level anti-drug antibodies were predictive of lack of response to dose intensification and instead were associated with response to switching to a different anti-TNF drug. A subanalysis of patients with evidence of active inflammation (elevated CRP or abnormal endoscopy) at the time of drug optimization yielded similar results.

Comments:

Although therapeutic drug monitoring for biologic drugs is far from perfect, this study adds to the evidence supporting drug optimization based on trough levels in patients with IBD. The retrospective design and lack of objective outcome indicators are important limitations of this study. Furthermore, the investigators used a “home-grown” assay so the results may be difficult to extrapolate to other settings. This is particularly relevant in what concerns the anti-drug antibody levels where titers (such as 1:160) are a more appropriate quantification method than concentrations given the polymorphic nature of these antibodies. Finally, it is difficult to compare “trough” levels between infusion drugs such as IFX who follow a simple distribution curve and injectable drugs such as ADA where the trough level is harder to define and interpret due to their different pharmacokinetics.


3. Can immunomodulators be withdrawn in Crohn’s patients on combination therapy?

The benefits of combination therapy with an anti-TNF biologic and IMM have to be balanced against the risks of increased immunosuppression. Prospective randomized studies in CD (SONIC) have demonstrated the benefit of combination therapy over mono-therapy in patients who are immunosuppressive naïve. However the benefit of continuing combo therapy in patients who previously failed IMM is unclear. Investigators from a single referral center in Belgium have performed a retrospective analysis of patients with CD who were treated with combination therapy prior to IMM withdrawal over a period of 11 years. All patients were in “durable” response for a median of 13 months prior to stopping the IMM and the vast majority stepped-up to combo therapy after failing an IMM (primarily thiopurine). IFX and anti-IFX (ATI) levels were obtained at several time points including before and after IMM discontinuation. Overall 38% of patients experienced a flare of which about half were rescued with dose escalation and the other half discontinued IFX due to loss of response a median of 29 months after the IMM was withdrawn. Loss of response was the main reason for stopping IFX. For the 52 patients who did not flare, trough levels of IFX remained stable during follow-up although a large proportion of patients with very low IFX levels at the time the IMM was withdrawn became undetectable. Only 4% of patients with detectable IFX developed antibodies (ATI). An IFX level > 5 µg/mL was associated with a low risk of loss of response, IFX dose escalation or surgery after IMM withdrawal. In contrast, 86% of patients with undetectable IFX flared after the IMM was stopped. An elevated CRP at the time of IMM discontinuation was also associated with a loss of response to the biologic or surgery during follow-up.
Comments:
Overall this is an interesting study which confirms previous observations from similar retrospective analyses; that IMM can be successfully withdrawn in a significant proportion of patients on combination therapy after a period of durable response, which in this case was approximately 13 months. The study also shows that low levels of IFX and elevated CRP are predictors of loss of response in this scenario. The retrospective nature of the study and the lack of a control group are obvious limitations. All of the patients in this cohort were on their first biologic and I doubt that the same favorable results can be replicated in patients who are on the second or third biologic and have demonstrated a high degree of immuno-reactivity to these drugs. However, I think this study provides some support for using biologic trough levels to predict the success of withdrawing IMM after a period of sustained response. Contrary to the algorithm proposed in the paper, in patients who are in remission with undetectable biologic levels after 12 months of co-therapy, I would withdraw the biologic and continue IMM as some of these patients may have “re-captured” the ability to respond to IMM (as was shown in the STORI study – Louis et al. Gastroenterol ‘12).