Practical considerations in prescribing anti-TNFα therapy to your Crohn’s disease patients

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As gastroenterologists who frequently treat patients with Crohn’s disease, we have been faced with an explosion in the treatment options at all severities of disease.

In patients with mild colonic inflammation, we can choose among 8 oral formulations of mesalamine: sulfasalazine, mesalamine w/eudrigit (Asacol), Asacol HD, MMX mesalamine (Lialda), extended release mesalamine (Apriso), balsalazide (colazal), olsalazine (dipentum). The active ingredient (and hence mechanism of action) is identical in all of these medications. What separates them includes drug coating, varying mechanisms to control of release of active agent, pH sensitivity vs. release by colonic bacteria, tolerability, dosing frequency, pill burden, compliance, and of course, cost. Much time and effort is spent by the various manufacturers (at least for those still under patent) to distinguish among these choices, but there are no trials that are true head to head comparisons among these agents, so treating physicians are left to grapple with surrogate comparisons.

The development and FDA approval of the first anti-TNFα therapy in 1998 for the treatment of moderate to severe Crohn’s disease heralded a new generation of biological therapies with specific, molecularly targeted actions. The results among true responders included dramatic clinical and endoscopic improvements, avoidance of surgery, fistula healing, and a significantly improved quality of life. Even more remarkable, they did not need to suffer through a long period before noticing clinical improvement as was common with the use of immunomodulators; and many patients can either avoid or minimize their steroid dosing, avoiding well known short and long term complications.

Since the introduction of the first biologic, infliximab, for the treatment of Crohn’s disease, two other anti-TNFα therapies have been approved for the same indication (adalimumab/Humira, certolizumab/Cinzia). As with the mesalamines, we are again in the position of choosing among drugs with similar mechanisms of action (binding of TNFα, apoptosis of inflammatory T-cells), but with notable differences in structure and pharmacokinetics. Standard dosing for infliximab includes an IV infusion of the drug at 0, 2, 6 weeks, followed by every 8wk maintenance infusions. Adalimumab is a fully humanized (as opposed to the chimeric mouse component in infliximab) antibody and given as a subcutaneous injection every 2 weeks. Loading dose of adalimumab involves an initial 4 simultaneous injections (160mg) followed by 2 simultaneous injections (80mg), then one injection (40mg) every two weeks. Certolizumab is a Fab fragment (as opposed to the whole antibody Fc + Fab in infliximab/adalimumab) joined to a polyethylene glycol molecule. The lack of an Fc portion prevents activation of complement and downstream antibody mediated cytotoxicity, but there does not appear to be any clinical relevance to this issue. Certolizumab loading is administered as 2 simultaneous subcutaneous (total 400mg) injections at 0, 2, 4 weeks, followed by monthly maintenance injections [Table 1]. Reconstitution of the drug is no longer required as the manufacturer now has pre-filled syringes. The major trials demonstrating efficacy of these agents reveal similar results in patients able to achieve and maintain clinical remission.
After presenting these options to a patient who is in need of biologic therapy, I am inevitably asked some variation of “doctor, which one is the best for me?” Extrapolating clinical trial data (with very rigid inclusion and exclusion criteria, their inimitable regimented follow up, results in comparison groups and subgroups) to the individual sitting in your exam room has always been a difficult exercise. Now we are asked to make an informed decision about which agent is the best, again in the setting where no true comparative effectiveness research is available to us. What is one to recommend in this vacuum of information? In a recent survey of American gastroenterologists, half of responding physicians surveyed offered all three anti-TNFα options to their patients. 

While we await the initiation of head to head trials (if ever) of the anti-TNFα agents, what criteria can we use to distinguish among the currently available choices and help our treatment naïve patients arrive at the “correct” choice? We recognize the cost and formulary restrictions are important considerations, but we have decided to approach this issue from the perspective that all options for anti-TNFα therapy are equally available to keep the discussion robust. There are many topics surrounding the use of anti-TNFα agents that lack strong data and consensus. Where a data gap exists, we provide guidance based on our experience from daily practice.

### Required testing prior to administration:

The FDA package insert for Anti-TNFα agents contains black boxed warnings for infections including tuberculosis (TB). All patients should obtain a chest film and tuberculin skin test (TST). If the patient has had a positive TST in the past, had BCG vaccination, or is concurrently on immunosuppressive therapy, then an interferon gamma release assay (IGRA, such as Quantiferon) test should be performed in lieu of a skin test. If there is evidence of latent TB, then patients should start antimycobacterial treatment prior to use of infliximab. There is no guideline on how long a patient has to be treated before it is safe to initiate Anti-TNF therapy. Our practice is to finish a 9 month course of INH therapy prior to starting anti-TNF therapy. If there is urgency to initiate treatment with a biologic, we will often coordinate care with an infectious disease expert in order to determine an appropriate duration of chemoprophylaxis prior to initiating anti-TNF therapy.

Anti-TNFα therapy can cause reactivation of hepatitis B in patients who are surface antigen or core antibody (sAg+ or cAb+) carriers. Hence all patients should be screened for hepatitis B status and administered prophylaxis if needed prior to starting therapy with anti-TNFα agents.

### Route of administration:

The first issue is whether the patient has a phobia
against self injections (a surprisingly high number in my patient population) in which case there is only one option. Additionally, I prefer a “tether” in patients who I suspect will have (or have already demonstrated) undependable follow up such as showing up to the office only in the setting of a flare or side effect. Particularly anxious patients also seem to prefer the comfort of knowing they are in a monitored setting during drug administration. The “tether” then becomes a mandatory visit to the infusion center in order to have infliximab administered. The infusion center will draw the basic labs after an IV is placed, thus saving the patient a separate visit to a phlebotomy lab. Initially, I schedule a clinic visit on the same day as the infusion allowing me to follow up the patient at least 3 times within 6 weeks essentially, shadowing the loading schedule. This allows a safe margin to detect any early side effects of therapy (i.e. infusion reaction, delayed reactions, drug induced hepatitis) that are the most worrisome initially as well as allowing us to determine whether any dose adjustment is necessary based on the clinical status of the patient. Additionally, the standard dose infusion is administered over 2 hours, often preceded with premedication with diphenhydramine and/or acetaminophen. The disadvantage is that patients will require up to 4 hours (travel to and from infusion center, 2 hour infusion) and may be left somnolent by the administration of IV diphenhydramine.

Other times, patients will have a preference for self-administered medications which saves a half-day trip to an infusion center and may be a better option for busy professionals who are comfortable with self-injection (or have a family member at home who can perform the task) and have dependable follow up. Both manufacturers provide home nursing support during the first few doses so that patients can learn the injection process right at home. I usually have the patient visit the manufacturer websites to watch the excellent videos on drug administration as a starting point:


Sometimes, patients will return with preferences based on the pen injector for adalimumab or the less frequent maintenance dose requirement for certolizumab. Increasingly, I have had patients who rely on the collective wisdom of disease specific internet support groups. Travelling through these sites, it is clear that intimate anecdotal experience (rather than population/trial data) carries the most weight. As social networking begins to envelope even private health matters, there is little doubt that more patients will be influenced by them.

The informed consent visit

As any attorney will tell you, consent is a process rather than a document. Often, a patient will require more information than we have time to elaborate or they have the ability to comprehend in one visit. Do we believe a patient will understand mechanism of action, options in therapy, major and minor risks of therapy, and need for monitoring and follow up all in one conversation? It’s not uncommon for me to ask the patient to bring the most involved family member for a visit simply to go over the major treatment options. While we have heard of individual practitioners having patients sign an informed consent form prior to starting biologic therapy, it has not been our practice, and there is no nationally published data on the subject.

Uncharted territory

Infliximab, FDA approved for treatment of Crohn’s disease in 1998, benefits from the broadest experience with theories often tested using this medication first (i.e. post-operative recurrence, injection treatment of rectal strictures). Adalimumab was FDA approved for treatment of Crohn’s disease in 2007 and certolizumab followed in 2008. Up to half of respondents in one survey felt that the efficacy and adverse reaction profiles of the currently available anti-TNFα therapies were indistinguishable, but many questions with the newest anti-TNFα therapies remain unanswered.

1. What should be done in case a patient loses response to a previously effective Anti-TNFα agent? Given infliximab’s approval for treatment of moderate to severe Crohn’s disease 9 years before any alternatives were available, the majority of patients who had lost response to an Anti-TNFα drug had loss of response to infliximab. Hence, the majority of data of the utility of a second anti-TNFα
drug revolves around those who had lost response to infliximab, estimated to be as much as 10% per year. Studies on the use of infliximab after use of adalimumab or certolizumab have yet to be published. The largest study to date is GAIN which looked at patients with either primary or secondary loss of response to infliximab and were treated with adalimumab. In the adalimumab group, 21% were in remission at 4 weeks (vs. 36% of naïve patients in the adalimumab induction study, CLASSIC I). There is currently a lack of data on which to base any firm recommendations on patients who require a second biologic drug if they have failed infliximab. Given the relationship of the development of antibodies to infliximab (ATI) and declining efficacy, some groups advocate checking trough levels of infliximab and antibodies to infliximab prior to changing therapies. However, we are not aware of data that that updosing infliximab (i.e. 10mg/kg) in patients without ATI’s is more effective than in patients with ATI’s. Hence, we empirically attempt a trial of dose intensification (either decreasing the interval to q4wk or increasing the concentration to 10mg/wk every 8wk) before changing strategies. There is no commercially available assay to test drug levels of adalimumab or certolizumab. We also await the presence of data on patients who have failed SQ anti-TNF as the initial therapy and have been switched to a drug with an alternative mechanism of action, such as natalizumab.

2. What is the preferred therapy for patients with perianal fistulizing disease?
Perianal fistulizing disease may be seen in up to a third of Crohn’s patients and a clinically difficult management issue. The first placebo controlled trial of infliximab revealed a fistula closure (mean duration 3months) rate of 55% in the treatment group and 13% in the placebo group. There have been two double blind RCT’s which confirm efficacy of infliximab in fistula healing as the primary endpoint. In the study examining perianal disease, the infliximab treatment arm had a greater response (defined as >50% fistula closure during consecutive visits) compared to the placebo arm (69% vs. 31%). In patients who had lost their response to a dose of 5mg/kg every 8 weeks of infliximab, 57% regained their response after having their dose increased to 10mg/kg every 8 weeks. For adalimumab, there has been one study with a secondary end point for fistula healing (CHARM) and a follow up study of those fistula healers at one year of continued maintenance therapy. Adalimumab (given as either weekly or every other week (eow) 40mg subcutaneous injections was better than placebo in fistula healing (33% vs. 13%) over a period of 56 weeks. It took 16 weeks from the onset of therapy to find a statistical difference between treatment and placebo arms. Certolizumab evaluated fistulating disease subpopulations in their PRECiSE 2 and PRECiSE 3 data and found fistula closure rates higher in treatment groups than in placebo. Fistula closure (defined as >50% of draining fistulas without drainage at 2 consecutive visits) was greater in the Certolizumab arm compared to the placebo arm (54% vs. 43%). At this time, the strongest available data for perianal fistula closure is with infliximab, but studies suggest benefit can be found with adalimumab and certolizumab. Again, because of differences in definitions of fistula closure, design and evaluation, and follow up periods between studies, it is not possible to make an equivalent comparison of efficacy. Finally, we hasten to add that our perianal fistula patients are co-managed with a colorectal surgeon with experience in the management of Crohn’s disease.

3. What is the preferred management strategy in patients who experience adverse events during treatment with Anti-TNFα agents?
A majority of physicians have encountered adverse events due to treatment with Anti-TNFα therapy which have required discontinuation of the drug. Some risks of anti-TNFα therapy, such as risk of latent TB reactivation, appear constant regardless of the specific drug used. However, other risks such as drug induced hepatitis, lupus like reactions, or psoriasis, may resolve after switching to an alternate anti-TNFα therapy. Hence, we await further data on both pathophysiological mechanisms underlying autoimmunity caused by anti-TNFα treatment as well as better data on switching medications to avoid adverse reactions.

4. What should I do for patients who intend to or become pregnant?
All of the currently FDA-approved anti-TNF therapies are pregnancy category B, suggesting they are low risk in pregnancy, but this is based on limited data. It is unlikely there will ever be randomized controlled
trials of anti-TNFα efficacy in pregnant patients. We expect the strongest data will be available from the multi-year PIANO registry which enrolls pregnant patients with IBD (over 700 patients to date) and follows their course through pregnancy and 12 months post-partum. Placental transfer of infliximab have been documented, but has not yet resulted in any immediate neonatal infections or inability to mount appropriate antibody responses to vaccination of the child (Mahadevan DDW 2010). It is our practice to continue ongoing anti-TNF therapy through the pregnancy, though others have advocated avoiding infliximab dosing during the 3rd trimester when placental uptake is the greatest. There has been in vitro evidence which suggests that Certolizumab is not transferred into the placenta, possibly because it’s missing the Fc portion of the antibody. This is supported by data on 4 patients who were exposed to Certolizumab during pregnancy, without any detectable drug in the newborn (DDW 2010, personal communication with Dr. Mahadevan). While the data are still scant, for those who are already maintained on anti-TNF therapy (or for those who require their first dose during pregnancy), it may be prudent to switch to certolizumab in patients who intend on getting pregnant in the near term. Early reports suggest that infliximab is not present in the breast milk of mothers who have been recently dosed with the drug. Data for adalimumab and certolizumab in breast milk is, to our knowledge, not yet available. Overall, we educate new mothers about the paucity of data in this area, but do not discourage them from breast feeding their infants despite ongoing treatment with Anti-TNFα therapy.

Given the paucity of reliable outcomes data on the effects of drug treatment in pregnant patients we attempt to enroll all pregnant IBD patients in the multicenter PIANO registry headed by the UCSF Center for Colitis and Crohn’s disease.

5. Should all of my patients on Anti-TNF agents also be on concomitant immunomodulators?

The SONIC trial established that treatment with combination infliximab (5mg/kg q 8week) and azathioprine (2.5 mg/kg daily) in patients with moderate to severe Crohn’s disease who were immunomodulators and biologic naïve were more often in steroid free remission than those who were treated with either infliximab or azathioprine monotherapy alone (57% vs. 44% vs. 30% respectively). No similarly rigorous studies have been performed for adalimumab or certolizumab, but there is little reason to suspect the trend would be different. While this study suggests patients do better initially, it does not provide information on whether combination therapy should be continued indefinitely and certainly does not provide long term safety information. Available data already suggest that combination therapy increases risk of infection and lymphoma. One study found that patients in clinical remission on combination therapy did similarly well after half the group had azathioprine withdrawn from their treatment regimen.

In our own practice, our goal is to establish clinical remission first either in a step up approach or with biologics initially. We add a second agent (either immunomodulators therapy or infliximab) if monotherapy is not enough to achieve clinical steroid free remission. Almost all of our patients have an interest in being on the “least” amount of medication that will keep them in remission. After one year, in patients in clinical remission, we are open to a trial of discontinuing immunomodulator therapy. Additional data will required before we can fully risk stratify patients who will require long term combination therapy. Currently, we use surrogates such as normalization of CRP level and endoscopic mucosal healing to identify patients who may stay in long term remission on monotherapy with Anti-TNFα agents.

Conclusions:

We present the clinical decision making involved when helping a patient to choose among the currently available Anti-TNFα therapies. There are differences between treatment naïve patients and those who have failed one anti-TNF therapy or are have disease complications such as fistulas. The oldest Anti-TNF therapy, infliximab, has been available since 1998 and has the broadest data available in Crohn’s subpopulations. However, the more recently developed subcutaneous anti-TNF drugs offer the promise of “cutting the tether,” though we continue to await the results of randomized studies in Crohn’s subpopulations.
References:


28. Christian Albrechts University K, Germany, 2. Fremantle Hospital, Fremantle, WA, Australia, 3. Herlev Hospital, Copenhagen, Denmark, 4. University of Chicago Medical Center, Chicago, IL, United States, 5. UCB, Slough, United Kingdom, 6. Mayo Clinic, Rochester, MN, United States. Certolizumab Pegol Is Effective At Maintaining Response and Remission in Patients With Fistulising Crohn's Disease: 3-Year Results From the Precise 3 Study. Gastroenterology 2010.


