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Life After SONIC

by Amar R. Deshpande, Maria T. Abreu

As our understanding of the underlying mechanisms of disease has improved, the treatment algorithm for Crohn's disease has undergone myriad changes over the last few decades. With the release of six month results from the Study of Immunomodulator Naïve Patients in Crohn's Disease (SONIC) study at ACG 2008, we for the first time have a head-to-head comparison of immunomodulators, biologics, and combination therapy, with combination therapy shown to be better than either alone. While this groundbreaking data is exciting, it raises as many questions as it answers. So what do we do with the SONIC data in the context of our current understanding of the treatment of Crohn's disease? To answer that complex question, it is important to first look back at the history of treatment to see how we got to this point.

For decades, Crohn's was treated with 5-ASAs for maintenance and steroids for induction and flares, with operative management reserved for refractory disease and complications. In 1980, Present and colleagues first showed in a prospective fashion that use of the immunomodulator 6-MP led to improvement in disease activity and steroid discontinuation, and Feagan and his North American Crohn's Study Group colleagues followed this up 15 years later with evidence of efficacy using methotrexate (1,2). Soon after, an entirely new class of drugs blocking the action of TNF-α emerged (3). Since that time, several studies have shown efficacy of infliximab and other TNF-α antagonists (adalimumab and certolizumab pegol) in treating moderate to severe disease, fistulae, and extraintestinal manifestations, as well as in maintaining clinical response.

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With two categories of drugs from which to choose (immunomodulators and biologics), the next question is which to choose first and when to use both. Early experience demonstrated significant reduction in antibody formation to infliximab when 6-MP was given concurrently. This popularized dual (or combination) therapy, as decreased antibody production leads to fewer infusion reactions and less loss of response (4). However, these data were derived in the era of episodic dosing. A post-hoc analysis of ACCENT 1 has shown that the diminution in antibody production is more dependent on dosing schedule (more antibodies in episodic versus maintenance dosing) than on the concurrent use of immunomodulators (5).

The other recent data to support dual therapy was D'Haens and colleagues' "Top Down/Step Up" trial (6). This two year trial randomized patients with active disease naïve to immunosuppression to early combination therapy (the "top down" approach) or conventional "step up" therapy, starting with steroids and then escalating treatment to immunomodulators and then biologics. At 26 and 52 weeks, early combination therapy was statistically significantly more likely to result in steroid-free and surgery-free clinical remission than was conventional therapy (the primary endpoints). Though this difference was lost at 78 and 104 weeks, the study was designed to evaluate early therapy, with <20% of patients in the early combination group (those with persistent disease activity) receiving maintenance infliximab after three dose induction.

Advocates for combination therapy, however, have to deal with two major concerns: infectious complications and the risk of malignancy. In their case control study, Toruner and colleagues showed that the odds ratio for development of an opportunistic infection increases as the number of immunosuppressive medications increases (7). However, many of these infections were mild and easily treated (mucosal Candida, non-disseminated HSV), and much of the risk for

opportunistic infections seemed to be driven by corticosteroids. This finding was supported by the TREAT registry, in which risk of serious infection (and mortality) was related to steroids and narcotics, not immunomodulators or biologics (8).

As for malignancy, a recent interim report shows a doubling of the risk of non-Hodgkin's lymphoma (NHL) in patients with IBD compared to the general population, with about 75% of those patients having taken thiopurines (9). A prior study had shown a four-fold increase in lymphoma in IBD patients on thiopurines versus those not on them (10). But, no specific data exists directly comparing those on thiopurine monotherapy versus combination therapy. At DDW 2008, using data from the SEER database, Siegel and colleagues did show an increased risk of NHL in those taking biologics compared with those just on thiopurines (11). Since the majority of patients on biologics were thiopurine-exposed, that group may resemble a combination therapy group, with a number needed to harm of ~5,000 (6/10,000 for biologics versus 4/10,000 for thiopurines). The big recent concern, particularly in the pediatric population, has been the development of hepatosplenic T-cell lymphoma (HSTCL) in those on combination therapy (12). The numbers are still small, with a recent review describing the 16 known cases of IBD-associated HSTCL since 1998, all of which occurred with combination therapy (13). Given the low incidence and prior reports of HSTCL in patients on thiopurine monotherapy, it is difficult to make a determination on the true risk of this rare and lethal lymphoma on combination versus monotherapy.

With these concerns for higher rates of infection and malignancy in combination therapy as a backdrop, the Infliximab Maintainance/Immuno Suppressives Discontinuation (IMID) study earlier this year looked at the role of stopping the immunomodulator in patients on dual therapy with disease in remission for at least six months (14). Two years later, the primary endpoint of needing to stop or change the dose of infliximab (implying decreased biologic effect) and CDAI were no different in those that continued versus those that stopped the immunomodulator. Though this seems to imply that the immunomodulator can be stopped, there was a trend at two years to higher CRPs and lower infliximab trough levels in the group that stopped the immunomodulator; this has been shown to lead to decreased remission rates and worse endoscopic disease (15). So perhaps the combination of the two classes of drugs has a long-term benefit too, not just the short-term benefits seen in the D'Haens study. An important caveat is that patients in the IMID study could have been on immunomodulators prior to biologic therapy; they were not started together as in the the D'Haens trial.

Though posthoc analyses have looked at the role of immunomodulators in biologic therapy (with conflicting results), there had been no prospective data on monotherapy versus combination therapy until 2008. The first trial, COMMIT, compared infliximab to infliximab plus methotrexate in those requiring steroids for active disease (16). At one-year, there was no difference between the two groups in steroid-free remission at week 14 (induction) and remission at week 50 (maintenance).

The second trial, SONIC, looked at the more commonly used thiopurine class of immunomodulators and was a late-breaking abstract at ACG 2008 (17). Patients with moderate to severe disease and naïve to both immunomodulators and biologics were randomized to receive azathioprine monotherapy, infliximab monotherapy, or combination therapy. At 26-weeks, the primary endpoint of steroid-free clinical remission was achieved in statistically significantly more patients in the combination group than either monotherapy group, and the infliximab monotherapy group also did statistically significantly better than the azathioprine monotherapy group. With respect to mucosal healing at 26-weeks, again the combination therapy group did better than either monotherapy group.

So does this mean we should revert back to combination therapy given the results of SONIC, despite the concerns of infections and malignancy? First, it is important to realize the data from SONIC was only out to six-months; one-year data is expected in 2009. Crohn's disease commonly affects those in childhood, adolescence, and young adulthood, so it is a disease with which we have to deal for decades, not months. All of our studies are plagued by short-term outcomes, not over five-to-10 years or powered for the right issues like prevention of surgery. Unfortunately, we do not have long-term data involving any of the biologics, so we are left to extrapolate short-term data to the long term, a potentially dangerous proposition.

Second, each of the biologic trials has slightly different entrance criteria, primary endpoints, and management algorithms. As an example, all patients on azathioprine in the SONIC study were started on a fixed-dose of 2.5 mg/kg/day. There was no metabolite monitoring or dose escalation, so perhaps the immunomodulator arm was handicapped by subtherapeutic levels. In that case, looking at longer term data or allowing dose escalation may result in the differences between the treatment groups narrowing. Taking the results of varied trials, compiling the data, and applying them to individual patients can often lead to more contradictions than solutions.

In any case, perhaps the most important point is that neither biologics nor immunomodulators (nor their combination) is the panacea. All of the major biologic trials (which included immunomodulator failures) have a one-year clinical remission rate of 35%–45%. Add to this the likelihood that we will need to treat some people for upwards of 60-years, and it becomes obvious that neither monotherapy nor combination therapy is the ultimate solution. To that end, smaller molecule TNF-α antagonists, which would theoretically minimize immunogenicity and therefore, loss of response, are being actively studied. Further, there are multiple ongoing trials looking at blocking alternative, non TNF-α-mediated pathways of inflammation. As examples, natalizumab is an α4 integrin blocker that is already approved for use in Crohn's disease, and gut-specific α4 integrin blockers that would minimize neurologic side effects are in trials as well.

So life after SONIC provides no simple answer as to how to definitively approach therapy of Crohn's disease. What it does tell us is that in those patients with moderate to severe Crohn's disease who are naïve to therapy, combination therapy is better than monotherapy up front. The real question is what to do long term once we have (hopefully) achieved remission. Do both need to be continued indefinitely? Can the biologics be stopped once started? The top-down study suggests yes. For patients with a lot to lose (extensive disease, multiple surgeries, complex fistulas), it makes the most sense to continue both. For patients who within one-year of combination therapy can tell when they are due for their next dose of the biologics, stopping the biologic is not an option, but stopping the immunomodulator may be. Finally, thiopurine monotherapy continues to be a very reasonable option for steroid-dependent patients who can wait eight-to-12 weeks for their effect. We look forward to longer term data from SONIC. ■

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