

COMMENTARY

Advances in Inflammatory Bowel Disease Therapeutics

Digestive Disease Week (DDW) 2016

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Hello. I am Dr Steve Hanauer from Northwestern University in Chicago. I am here at Digestive Disease Week (DDW) in San Diego. On behalf of Medscape, I would like to update you on some of the clinical advances in inflammatory bowel disease (IBD) presented at this year's meeting. I would like to focus on three separate topics: biologics and biosimilars, therapeutic drug monitoring in IBD, and advances in therapeutics that we can anticipate over the next year or so.

Biologics and Biosimilars

Let's begin with biologics and with biosimilars in particular. This is an important topic because the first biosimilar was approved by the US Food and Drug Administration (FDA) last year.^[1] And although it is not yet on the market, the biosimilar for infliximab is going to set the stage for subsequent biosimilar development and entry into the market in the United States. *[Editor's note: The FDA approved Inflectra (infliximab-dyyb) on April 5, 2016.]* Biosimilars have not been well understood by gastroenterologists to date because we have not seen them in our therapeutic armamentarium. They are already approved in a number of different countries, including in Europe and in Asia, and have entered into the marketplace with probably a substantial reduction in overall cost.

Biosimilars are different from the originator compounds in that the analysis and the development of biosimilars follow somewhat of a different pathway. Instead of doing clinical trials for all of the individual indications, biosimilars are approved on the basis of analytics. Sponsors need to demonstrate that their biosimilar is indeed as close to being identical to the originator. Although they will never be identical to the originators, they need to be as similar as possible as determined by a variety of analytics, including the chemistry and numerous functional assays. Then in several specific indications, not necessarily all of the indications for the originator, clinical trials are done to compare clinical outcomes and pharmacokinetics/pharmacodynamics of the biosimilar with the originator.

In the case of the biosimilar for infliximab, trials were done in rheumatoid arthritis and ankylosing spondylitis.^[2,3] The analytics demonstrated sufficient similarity for the FDA to approve the initial version of infliximab. Infliximab is still under patent in the United States, so it may be some time before we see it here. We have already seen trials (with long-term data) performed in Europe and in some countries where there has been a forced switch from the originator infliximab to the biosimilar.^[4,5] Happily, there have not been any signals of particular worry for clinicians.

This brings up an important topic regarding biosimilars because we are unlikely to see a large number of trials in either Crohn disease or ulcerative colitis. We are going to have to rely on the concept of extrapolation in that these biosimilars function in assays similar to the originator and have functioned similarly to the originator for other indications. Indeed, although we are not going to have much experience in IBD when they enter into the marketplace, I do believe we can have good security that these agents are going to function as the originator would.

The intent of biosimilars and this different pathway to approval is to reduce the overall cost. This is going to be an interesting concept because we do not know who is going to be saving money. For the most part, when it comes to biologic therapy, our patients are not actually paying for the drug. It is unlikely that the patients are going to be saving money. It does appear that the third-party payers are going to negotiate lower costs. At that level, society may benefit by the ability to have additional patients treated at the same overall cost. I would say that they are not to fear at the present time. We are going to have continued education regarding biosimilars. They are *fait accompli* at this point as they enter into the worldwide market.

Therapeutic Drug Monitoring in Inflammatory Bowel Disease

The next subject I would like to talk about that is being presented heavily at DDW is the concept of therapeutic drug monitoring

in patients with IBD. This is not a new concept. We have been accustomed to doing therapeutic drug monitoring with agents such as the thiopurines, including azathioprine and 6-mercaptopurine.

We have increasing evidence that therapeutic drug monitoring is going to be useful in the setting of biologic therapy for IBD. We have learned that biologic drug levels have been associated with clinical benefits, including remission and endoscopic healing in both ulcerative colitis and Crohn disease. These studies, for the most part, have been retrospective and have correlated therapeutic trough levels with good therapeutic outcomes. At this year's DDW, we have learned that even if patients have low levels of the biologics, they have a tendency to develop anti-drug antibodies.^[6,7] It may be necessary to not only have some drug on board, but above a particular drug level. This needs to be clarified for the different individual biologic agents.

Thus far with the anti-tumor necrosis factor (TNF) agents, we have seen similarities in drug levels for infliximab and adalimumab, although there is a bit of a range around each of these. We have already clarified how to use therapeutic drug monitoring to evaluate loss of response to an anti-TNF agent. We know that if patients have antibodies to the biologic that they will respond to an in-class switch—for instance, from infliximab to adalimumab or from adalimumab to infliximab or to another anti-TNF agent. On the other hand, if there are adequate drug levels and the patient has truly lost response, in that situation we need to change classes and move out of the anti-TNF class. Finally, if they have low drug levels but have not developed anti-drug antibodies, this means that the gas tank is not yet filled. We need to keep it filled up in order to sustain response.

This is not unique to anti-TNF agents. We are now seeing similar correlations with blood levels and the anti-integrins—in particular with vedolizumab—with data presented at this meeting.^[8,9] There are also correlations with ustekinumab drug levels and therapeutic responses.^[10,11] The problem has been that we have not been able to prospectively identify a means by which we can prevent loss of response. There have been several different trials, primarily in Europe, looking at whether we can use drug levels to either raise or lower dosing in order to optimize response. Thus far, in relatively small studies we have not been able to demonstrate a difference for patients who are in remission, whether or not their drug levels are high or low or whether they are treated simply on a clinical basis.

We need some additional prospective studies to better demonstrate the cost-effectiveness of therapeutic drug monitoring in IBD. I think that as the new agents such as ustekinumab come to market, we are going to be able to use the pharmacokinetics and pharmacodynamics to best predict and achieve better outcomes for our patients. However, we need are going to need prospective data.

Therapeutic Advances in the Near Future

My last topic is the new drugs for IBD that we can anticipate in the near future. There are some important presentations at this year's DDW on what I think are going to be the next two agents that are most likely to be approved for IBD. That is ustekinumab for Crohn disease and tofacitinib for ulcerative colitis.

We saw phase 2 data with ustekinumab in the CERTIFI study a few years ago that suggested that there would be a clinical response in patients with Crohn disease, either those who were anti-TNF naive or those who had received prior anti-TNF therapy.^[12] At this year's DDW, we see the long-term results with ustekinumab in Crohn disease. As predicted by the phase 2 studies, we indeed see improved induction and maintenance of clinical remission with ustekinumab.^[13]

What we have learned with biologic agents from other diseases and other classes, such as the anti-TNF agents, is that the doses needed in IBD are substantially higher than the doses required for the treatment of other autoimmune diseases. With ustekinumab, the most effective dosing was 6 mg/kg as an induction followed by 90 mg every other month as maintenance. The good aspect has been that this drug has been very effective, both in anti-TNF-experienced and anti-TNF-naive patients. But as we would anticipate, the more naive the patient is to treatment, the better the outcomes are going to be.

While both anti-TNF-experienced and -naive patients had better outcomes with ustekinumab compared with placebo, the absolute response rates were substantially better in the patients who were anti-TNF naive.^[13] This suggests, as we thought with all agents, that the earlier we treat, the better. One of the real advantages of ustekinumab is that we have a lot of clinical experience in the setting of psoriasis, and it has been quite safe without significant signals for neoplasia or even serious infections. It looks like ustekinumab will become another alternative. We will have to see regarding its positioning. It will likely be indicated for moderate to severe Crohn disease for patients who have failed conventional and/or biologic therapy. As I mentioned, we can expect to see the best results earlier in the course of the disease as an earlier intervention rather than

waiting until patients have had either complications of the disease or multidrug exposure.

In ulcerative colitis, we see very impressive data with tofacitinib at this year's DDW. Tofacitinib has been approved for rheumatoid arthritis. Similar to ustekinumab, the doses appear to be much higher for ulcerative colitis relative to rheumatoid arthritis. Nevertheless, tofacitinib has been shown to be effective in phase 3 studies for both induction and maintenance of moderate to severe ulcerative colitis.^[14] It looks like it will be another potential oral agent for ulcerative colitis, in particular for patients who have not responded to other therapies.

We see our therapeutic landscape already expanding in IBD. On my radar is anti-IL-23 therapy, which was presented in phase 2.^[15] There are also some therapies that affect lymphocyte trafficking, such as ozanimod, which is an S1P inhibitor that prevents lymphocytes from moving out of lymph nodes into the circulation or into the tissue. At DDW we have now seen a maintenance study with ozanimod in ulcerative colitis.^[16]

Happily, our therapeutic options are going to be expanding in IBD. Biosimilars are hopefully going to allow more patients to have access to this very important therapeutic option. We need to continue to optimize and personalize therapy on the basis of therapeutic drug monitoring. However, we need more prospective data regarding this so that we can do it in a more economic fashion. Finally, there are going to be several new drugs hopefully introduced into the marketplace in the very near future.

I want to thank you for listening. This is Dr Steve Hanauer on behalf of Medscape.

References

1. US Food and Drug Administration. FDA approves first biosimilar product Zarxio.
<http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm436648.htm> Accessed May 24, 2016.
2. Yoo DH, Hrycaj P, Miranda P, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. *Ann Rheum Dis.* 2013;72:1613-1620. [Abstract](#)
3. Park W, Hrycaj P, Jeka S, et al. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. *Ann Rheum Dis.* 2013;72:1605-1612. [Abstract](#)
4. Yoo DH, Prodanovic N, Jaworski J, et al. Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. *Ann Rheum Dis.* 2016 Apr 29. [Epub ahead of print]
5. Park W, Yoo DH, Miranda P, et al. Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study. *Ann Rheum Dis.* 2016 Apr 26. [Epub ahead of print]
6. Guidi L, Pugliese D, Marzo M, et al. Infliximab trough levels after dose optimization for loss of response predict outcome at one year. Program and abstracts of Digestive Disease Week 2016; May 21-24, 2016; San Diego, California. Abstract Sa1978.
7. Kurti Z, Vegh Z, Golovics PA, et al. Predictors of loss of response to adalimumab therapy; the importance of therapeutic drug monitoring in inflammatory bowel diseases. Program and abstracts of Digestive Disease Week 2016; May 21-24, 2016; San Diego, California. Abstract Sa1981.
8. Paul, S, Williet N, Claudez P, et al. Serum vedolizumab assay at week 6 predicts sustained clinical remission and lack of recourse to optimisation in IBD. Program and abstracts of Digestive Disease Week 2016; May 21-24, 2016; San Diego, California. Abstract Sa1939.
9. Osterman MT, Roblin X, Glover SC, et al. Association of vedolizumab drug concentrations at or before week 6 with remission at week 14 in moderately to severely active ulcerative colitis patients from GEMINI 1. Program and abstracts of Digestive Disease Week 2016; May 21-24, 2016; San Diego, California. Abstract 512.

10. Battat R, Kopylov U, Bessissow T, et al. Association of ustekinumab trough concentrations with clinical, biochemical and endoscopic outcomes. Program and abstracts of Digestive Disease Week 2016; May 21-24, 2016; San Diego, California. Abstract 696.
11. Adedokun OJ, Xu Z, Gasink C, et al. Pharmacokinetics and exposure-response relationships of ustekinumab during IV induction and SC maintenance treatment of patients with Crohn's disease with ustekinumab: results from the UNITI-1, UNITI-2, and IM-UNITI studies. Program and abstracts of Digestive Disease Week 2016; May 21-24, 2016; San Diego, California. Abstract Sa1934.
12. Sandborn WJ, Gasink C, Gao LL, et al.; for the CERTIFI Study Group. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *N Engl J Med.* 2012;367:1519-1528. [Abstract](#)
13. Sandborn WJ, Feagan BG, Gasink C, et al. A phase 3 randomized, multicenter, double-blind, placebo-controlled study of ustekinumab maintenance therapy in moderate-severe Crohn's disease patients: results from IM-UNITI. Program and abstracts of Digestive Disease Week 2016; May 21-24, 2016; San Diego, California. Abstract 768.
14. Sandborn WJ, Sands BE, D'Haens GR, et al. Efficacy and safety of oral tofacitinib as induction therapy in patients with moderate to severe ulcerative colitis: results from two phase 3 randomized controlled trials. Program and abstracts of Digestive Disease Week 2016; May 21-24, 2016; San Diego, California. Abstract 767.
15. Feagan BG, Sandborn W, Panes J, et al. Efficacy and safety of induction therapy with the selective IL-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: results of a randomized, double-blind, placebo-controlled phase 2 study. Program and abstracts of Digestive Disease Week 2016; May 21-24, 2016; San Diego, California. Abstract 812a.
16. Sandborn WJ, Feagan BG, D'Haens GR, et al. Ozanimod induces histological response and remission: results from the TOUCHSTONE study, a randomized, double-blind, placebo-controlled trial of ozanimod, an oral S1P receptor modulator, in moderate to severe ulcerative colitis. Program and abstracts of Digestive Disease Week 2016; May 21-24, 2016; San Diego, California. Abstract 857.

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Cite this article: Advances in Inflammatory Bowel Disease Therapeutics. *Medscape*. Jun 01, 2016.

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