ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Comparative Effectiveness Research in Inflammatory Bowel Disease: The VARSITY Study and Beyond

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G&H What is comparative effectiveness research?

BS Comparative effectiveness research refers to the comparison of health care interventions that already exist and is a way of identifying which of these work best for patients in specific circumstances—in other words, which have the greatest benefits and the least harms. Comparative effectiveness research was sparked in part by the stimulus package that President Barack Obama passed in 2009, which earmarked funds for this type of research, with the goal of reducing health care costs. There is also a sense that comparative effectiveness research incorporates the viewpoint of patients to understand what they value.

G&H How does this type of research differ from other types?

BS There are different approaches that may be used in comparative effectiveness research. In its simplest form, it consists of simple randomization schemes in which patients are randomized to different drugs that have already been approved. This is different from the type of research that is normally conducted in the development of a new drug, which mainly consists of randomized, controlled trials that compare a new drug entity to placebo to establish whether the drug is efficacious. Here, the researchers are looking at efficacy rather than effectiveness. In real life, effectiveness incorporates the notion not only of the efficacy of a drug but whether the drug is going to work considering all of the limitations of how it is taken, if patients actually take it, and a variety of other real-life factors.

G&H Why are comparative effectiveness studies needed in inflammatory bowel disease?

BS Inflammatory bowel disease (IBD) currently has a variety of drugs with different modes of action, and the number of drugs and modes of action is increasing. However, the more drugs that are added to the IBD armamentarium, the less certain doctors are of how to position, sequence, and combine the drugs to maximize effectiveness and safety for patient care. Therefore, there is a need for comparisons of drugs and treatment strategies to guide clinical practice.

G&H What are the main benefits and challenges associated with these studies?

BS As discussed above, these studies can provide the guidance needed when multiple options are available. On the other hand, these types of studies are usually large and complex to conduct. In the past, there have only been relatively small studies directly comparing drugs in IBD, and these studies were limited in scope. Comparative effectiveness studies are starting to become more common, and the results of one such study (VARSITY) were recently published.

G&H Why was this comparative study conducted?

BS As mentioned, there is a growing number of different classes of agents for the treatment of IBD. There are biologic agents, which appeared 20 years ago first with the approval of infliximab and then other anti–tumor necrosis factor (TNF) agents such as adalimumab, golimumab (Simponi, Janssen), and certolizumab pegol (Cimzia, UCB). In addition, there are newer biologic agents that work in mechanistically different ways: vedolizumab (Entyvio, Takeda), which is an anti-α4β7 integrin antibody, and ustekinumab (Stelara, Janssen), which is an anti-interleukin (IL)-12 and -23 antibody. However, there has been very little information about which of these agents are advantageous over others and which should be used first or second in the treatment paradigm. There are a number of ways of obtaining the answers, but the best is to use direct comparison in blinded randomized, controlled trials. Another way is to perform a systematic review and network meta-analysis, the latter of which is a sophisticated form of meta-analysis that compares different drugs and attempts to standardize them according to placebo responses and head-to-head comparison in each study. Another approach to considering comparative effectiveness involves the evaluation of real-world data collected from routine health care, registries, and electronic medical records; however, this method has the potential for bias because, inherently, some patients are chosen for one drug or another based upon personal characteristics, demographics, or characteristics of their disease. Usually, researchers use logistic regression or other means of adjusting for potential confounders. Sometimes researchers attempt to use propensity score-matching analysis to compare like patients, but none of these methods are as rigorous as a direct head-to-head trial, which is what my colleagues and I used in the VARSITY study.

G&H How, specifically, was the VARSITY study designed?

BS The study, which was funded by Takeda, was designed as a head-to-head, double-blinded, double-dummy, randomized, controlled trial of vedolizumab against adalimumab. Because vedolizumab is an intravenous drug and adalimumab is a subcutaneously delivered drug, patients assigned to treatment with vedolizumab received placebo subcutaneous injections and, on the other hand, patients assigned to adalimumab received placebo intravenous infusions. Treatment was assigned in a 1-to-1 fashion, and blinding was maintained. Patients received standard induction and maintenance dosing without the ability to dose escalate because of the difficulty that would cause to maintain blinding. Patients were followed for 52 weeks, and then for another 18 weeks by telephone. The primary endpoint was the proportion of patients who achieved clinical remission at week 52, and key secondary endpoints included the proportion of patients who achieved endoscopic improvement (a Mayo sigmoidoscopic score of 0 or 1 at week 52) and corticosteroid-free clinical remission (patients using oral corticosteroids at baseline who were able to discontinue and achieve clinical remission at week 52).

G&H What were the key study findings?

BS At the primary endpoint of clinical remission at week 52, vedolizumab was superior to adalimumab. This endpoint was achieved by 31.3% of patients assigned to vedolizumab as compared to 22.5% assigned to adalimumab, for a treatment difference of 8.8% with superiority with vedolizumab that was highly statistically significant. In terms of endoscopic improvement, there was an overall statistically significant difference of 11.9%, with superiority with vedolizumab (39.7%) compared to adalimumab (27.7%). For corticosteroid-free clinical remission, there was no significant difference between the 2 treatments, although numerically higher rates were achieved in the adalimumab arm compared to the vedolizumab arm (21.8% vs 12.8%, respectively). The mean oral corticosteroid dose at week 52 was similar with both treatments. There was no protocol-enforced corticosteroid tapering regimen; instead, tapering guidelines were provided but were loosely enforced to mimic clinical practice. To me, these results highlight the fact that in clinical practice, doctors do not often push patients very hard to taper completely off corticosteroids, even though doctors recognize the negative consequences of such treatment.

Although both drugs seemed to be very safe overall, there were numerically higher rates of various infections in the adalimumab arm than in the vedolizumab arm and higher rates of psoriasis, as is consistent with the known profile of anti-TNF agents. Thus, based on these study findings, both in terms of efficacy and safety, vedolizumab is the preferred first choice over adalimumab for the treatment of ulcerative colitis patients, particularly those who are anti-TNF–naive, in whom the superiority was most notable.

G&H What were the limitations of this study?

BS The editorial that accompanied the publication of this study in *The New England Journal of Medicine* pointed out that dose escalation was not permitted in either arm, which may not reflect real-world practice, where dose escalation may help either drug regain some efficacy. However, the results of the SERENE study, which were recently presented at United European Gastroenterology Week 2019, did not show that ultra-high dosing of

adalimumab was superior for induction compared to standard dosing in patients with ulcerative colitis. This might imply that it would not have mattered much if dose escalation had been allowed in the VARSITY study. Several objective findings seemed to suggest that the superior efficacy of vedolizumab was quite real, including the evaluation of histologic disease activity, where vedolizumab was clearly superior to adalimumab. Also, surprisingly, the efficacy of vedolizumab emerged earlier than that of adalimumab, which goes against the conventional wisdom that vedolizumab is an agent that is slow in onset.

G&H Are further analyses of the VARSITY study forthcoming? Are other comparative effectiveness studies underway?

BS There may be plans to further extend the follow-up of the VARSITY study beyond 1 year. There are a number of ongoing analyses looking at some of the histologic outcomes in relation to endoscopy, as well as a variety of analyses looking at the patient-reported outcomes in more detail.

I am aware of several other comparative effectiveness studies currently underway. The SEAVUE study, which is being conducted by Janssen, is comparing adalimumab to ustekinumab in Crohn's disease patients. There are also 2 studies on etrolizumab, which is an anti-β7 integrin antibody, in ulcerative colitis patients—1 study comparing the drug to adalimumab and the other study comparing the drug to infliximab. In addition, the EXPEDITION study is comparing brazikumab, an anti–IL-23 antibody, to vedolizumab in ulcerative colitis patients. No preliminary findings have yet been released for any of these studies, and I suspect that it will likely be a year and a half before any reporting occurs.

G&H What comparative effectiveness research would you like to see in IBD in the future?

BS In addition to direct comparisons of drugs, we need more studies that compare treatment strategies and different sequences of drugs. Also, we need studies that look at paradigms of treating to specific targets, such as what we saw with the CALM study, and treatment strategies that incorporate therapeutic drug monitoring. These are the types of comparative effectiveness studies that go beyond single agents and involve the full spectrum of drugs and treatment strategies that we have at our disposal.

It is important to continue to conduct comparative effectiveness studies and for the gastroenterology community to continue to refer patients into these studies. Patients do not lose by participating in such research because they receive an effective drug and do not receive placebo.

Dr Sands is a consultant for Takeda, Janssen, Allergan, Roche, Genentech, and AbbVie.

Suggested Reading

Cheifetz AS, Melmed GY, Spiegel B, et al. Setting priorities for comparative effectiveness research in inflammatory bowel disease: results of an international provider survey, expert RAND panel, and patient focus groups. *Inflamm Bowel Dis.* 2012;18(12):2294-2300.

Flasar MH, Cross RK. What is the need for comparative effectiveness studies in IBD? *Expert Rev Gastroenterol Hepatol.* 2014;8(8):851-854.

Salleron J, Danese S, D'Agay L, Peyrin-Biroulet L. Effectiveness research in inflammatory bowel disease: a necessity and a methodological challenge. *J Crohns Colitis.* 2016;10(9):1096-1102.

Sands BE, Peyrin-Biroulet L, Loftus EV Jr, et al; VARSITY Study Group. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. *N Engl J Med.* 2019;381(13):1215-1226.