ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Review of the Landmark VARSITY Trial

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G&H Why is the VARSITY trial still important and clinically relevant?

BF The VARSITY trial was a landmark study that provided many insights into the treatment of ulcerative colitis. It was the first head-to-head study of biologics in moderate to severe ulcerative colitis, and compared the use of vedolizumab (Entyvio, Takeda) with adalimumab in a randomized controlled trial (RCT). Direct comparisons of drugs are very uncommon in the inflammatory bowel disease universe. Until very recently, the VARSITY study was the only direct comparison study. There is now one more—the SEAVUE trial, which compared ustekinumab (Stelara, Janssen) with adalimumab in Crohn's disease and was presented at this year's Digestive Disease Week.

Direct comparisons are important because of the number of treatment options that are currently available for inflammatory bowel disease. The biologics that have dominated the field of ulcerative colitis treatment over the past 20 years have been tumor necrosis factor (TNF) antagonists, starting with infliximab and then adalimumab. However, a number of new agents have been approved recently, including vedolizumab, ustekinumab, and tofacitinib (Xeljanz, Pfizer), which have all been compared against placebo. Clinicians want to know which of these agents is best for patients with regard to efficacy and safety. There are observational methods of obtaining data to answer this question, such as registries of patients, retrospective studies from large academic centers, administrative claims databases, meta-analyses and, more recently, network meta-analyses, in which researchers use statistical techniques to make inferences about relative efficacy. However, these types of data are observational and thus subject to problems such as bias, which the RCT was designed to overcome. A RCT controls bias because patients are assigned at random as opposed to being selected by an investigator. Literature has shown that observational studies tend to consistently overestimate treatment effects, and clinicians understand that such bias is not helpful.

In addition, randomization controls for confounders. Because patients are assigned to treatment at random, the factors that might influence the treatment effect, besides the treatment itself, are balanced between the groups, and the larger the sample size, the better these factors are balanced. The real beauty of randomization is that it balances known confounders as well as unknown or unmeasurable confounders between treatment groups, and thus isolates the experiment to exactly what the investigator is interested in, the relative efficacy and safety of drug A vs drug B. Thus, a RCT is the gold standard for obtaining high-quality evidence to directly compare drugs.

G&H What are the key findings of the VARSITY trial?

BF The primary hypothesis was that vedolizumab was superior to adalimumab. In total, 771 patients were randomized to the 2 treatment groups; 80% were naive to either drug, and 20% had disease that failed to respond to a TNF antagonist that was not adalimumab. The primary endpoint was the composite measure of clinical remission; patients had to stop bleeding in the rectum and had to show endoscopic improvement (eg, a decrease in Mayo endoscopic score from 2 or 3 to 0 or 1 at the end of induction). The study met its primary endpoint; at week

52, vedolizumab had a statistically significant difference (8.8%) in remission rates over adalimumab, which meant that vedolizumab was a superior treatment and that the primary hypothesis was met.

For the most part, the secondary endpoints lined up in favor of vedolizumab. These included symptom-based endpoints, such as the mean change in the Mayo score and the proportion of patients with a clinical response, defined by symptoms in distinction to endoscopy. Endoscopic improvement was also significantly better with vedolizumab. An outcome of particular interest to clinicians was rapidity of onset as evaluated by partial Mayo scores. TNF antagonists have a reputation for rapid onset of action for controlling symptoms, so it surprised some people that vedolizumab was successful in achieving higher response rates by week 6 during the induction period. Superior response rates relative to adalimumab were maintained until the end of the trial.

The one outcome measure that did not favor vedolizumab over adalimumab was corticosteroid-free remission. Although it was not statistically significant in favor of adalimumab, the point estimate favored that drug. However, a difference in corticosteroid-free remission would be expected to be accompanied by a difference in the corticosteroid doses used between the groups, which was not the case; there was no statistical significance in the average daily use of corticosteroids during the trial. In fact, the point estimate for this outcome favored vedolizumab. I interpret the inconsistent effect observed across corticosteroid-related endpoints as meaning that the difference seen in corticosteroid-free remission was likely because of chance.

G&H Are there any other important insights about efficacy or safety from the VARSITY trial?

BF An interesting, albeit underpowered, insight involves extraintestinal manifestations of inflammatory bowel disease. There has been some concern that vedolizumab might not be as effective for treating these conditions, the most common of which is arthritis/arthralgia. However, there was no difference between the 2 treatments in new-onset arthritis/arthralgia events or worsening of existing problems. Many clinicians would have expected adalimumab to have a lower rate of those manifestations.

In addition, it is important to point out that it is difficult to power a study based on safety endpoints because these drugs are generally safe. Vedolizumab has a special advantage over most drugs in that its immunosuppressive activity is confined to the gut through its mechanism of action. It specifically blocks T-cell trafficking into the intestinal mucosa, whereas other drugs, such as TNF antagonists, suppress the systemic immune system. There were no striking safety differences observed in the VARSITY trial, which is not surprising based upon the sample size. Tens of thousands of patients would be needed to show meaningful differences.

G&H What are the main limitations of the study?

BF One limitation is that it compares a very specific drug with vedolizumab. It is not clear whether the adalimumab results can be generalized to infliximab, which many clinicians consider to be the best TNF antagonist (although the only evidence to support this claim is a network meta-analysis).

Another limitation is that there was no dose adjustment in the trial for either drug. Although dose adjustment is off-label, it is not uncommon in clinical practice to intensify the dosing regimens for both vedolizumab and adalimumab. Some clinicians were concerned because the trial did not reflect how they use the drugs in clinical practice. However, both drugs were handicapped by this restriction, and vedolizumab was still superior.

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G&H What are the clinical implications of the VARSITY trial on the current treatment of ulcerative colitis?

BF The VARSITY trial demonstrated that vedolizumab is superior to a TNF antagonist that is widely accepted for the treatment of ulcerative colitis and is, in many jurisdictions, a market leader as far as the choice of clinicians and payers. It is difficult to choose adalimumab over vedolizumab for first-line therapy of ulcerative colitis based upon the results of the trial. That is why it is so important to perform direct comparisons between drugs. The study did not show that one drug was appreciably safer; nevertheless, it is problematic to conclude that there

is no difference in safety. We know that the safety profile of vedolizumab offers additional benefits because of its mechanism of action and the extensive observational data that have been generated.

G&H Has the trial actually affected current ulcerative colitis practice?

BF Yes, it has. Changing treatment choices is a gradual, evolutionary process, and it took a decade before many clinicians felt comfortable with biologics, starting with infliximab in ulcerative colitis. Now clinicians have become used to them; it will take time for newer drugs to supplant TNF antagonists. Not all gastroenterologists are aware of the most recent data from trials, which is one reason that change takes time. Nevertheless, gastroenterologists are becoming more and more aware of the VARSITY trial, and its robust, consistent, and clinically interpretable results are helping to change prescribing habits. In addition, it should be recognized that patient and physician preferences are not the only components that decide selection of treatment. In many jurisdictions, these preferences are constrained by payers, which is a common source of frustration for clinicians.

G&H How has the VARSITY study impacted clinical trial design and comparative-effectiveness research?

BF Although comparative-effectiveness studies are high-risk/high-gain, expensive ventures that are difficult to perform and require a large sample size, the VARSITY study has demonstrated that such research is feasible in ulcerative colitis and has created a blueprint for it. Interestingly, the SEAVUE trial, the only other comparative-effectiveness study completed thus far in inflammatory bowel disease, showed no difference between adalimumab and ustekinumab, which surprised many people. Ustekinumab has been assumed to be superior to adalimumab for a number of reasons; however, the study did not prove this assumption, possibly because of the limited sample size, which was considerably smaller than that of the VARSITY study. One conclusion that may be drawn is that direct comparisons should only be made with large sample sizes.

G&H What substudies or further analyses of the VARSITY trial are underway?

BF Several substudies are currently planned, but none have reached publication yet. There has been a good deal of interest in the prediction of early response and whether it tracks to long-term endpoints and prognosis. Furthermore, the VARSITY trial is one of the largest ulcerative colitis studies to look at histopathology as an endpoint. Histopathology is a hot topic right now and is thought to likely be a better prognostic marker than endoscopy, meaning that changes in achieving histologic remission in induction are more strongly associated with long-term clinical endpoints such as the need for colectomy, hospitalization, and returning to corticosteroid use. Vedolizumab was superior to adalimumab for histopathology endpoints. There will be additional research arising from the VARSITY trial regarding histopathology and other biomarkers such as C-reactive protein, which will be valuable because of the large sample size and long duration of follow-up.

G&H What further research is needed?

BF The difference between vedolizumab and adalimumab was meaningful; however, only approximately one-third of the patients achieved remission. In my opinion, a breakthrough approach in inflammatory bowel disease therapeutics will either come through precision medicine (identifying which patients are more likely to respond to a given agent based on pathologic pathways) or, more promisingly, packaging safe and effective agents into combination therapies.

Disclosures

Dr Feagan has received consultancy fees and research support from Takeda and AbbVie.

Suggested Reading

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