

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Clinical Implications of Recent Findings From the EVOLVE Study



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G&H What is the EVOLVE study?

BB The EVOLVE (Entyvio Outcomes in Real-World Bio-Naive Ulcerative Colitis and Crohn's Disease Patients) study is a retrospective, multicenter, cohort study that focuses on understanding how both vedolizumab (Entyvio, Takeda) and anti-tumor necrosis factor (TNF) agents perform in patients with Crohn's disease and ulcerative colitis who are naive to anti-TNF agents. I am one of the investigators of this study, which was performed in multiple countries. This study is important because it focuses on the real-world experiences of patients who were never exposed to an anti-TNF agent. The majority of real-world studies examining the efficacy of vedolizumab have been focused on patients who previously failed anti-TNF agents, and the potential efficacy, and perhaps even safety, of treatment may be contingent on that particular point. This study is also important because it gives the opportunity to obtain a large enough sample to compare the performance of vedolizumab to anti-TNF agents. It can thus be considered to be a clinical effectiveness study to see how effective vedolizumab is in comparison to what has been traditionally used for patients with ulcerative colitis and Crohn's disease.

G&H What were the most important EVOLVE study findings from this year's Digestive Disease Week?

BB Digestive Disease Week (DDW) 2020 included 3 posters from the EVOLVE study. This study is very large

and has addressed many different points, but its findings from DDW 2020 focused on how effective vedolizumab is and its safety profile in comparison to anti-TNF agents for patients with ulcerative colitis and Crohn's disease. These patients were followed for a minimum of 2 years, and several endpoints, such as clinical remission, clinical response, and treatment persistence, were examined. The overall message is that, although both treatments perform reasonably well in general, there are signals to suggest that the efficacy of vedolizumab is better than that of anti-TNF agents in patients with ulcerative colitis. This finding is not surprising because it is consistent with the VARSITY study, which showed that vedolizumab works better than adalimumab in the setting of ulcerative colitis.

Also not surprising, but likely the most important finding, is that vedolizumab appears to have an advantage over anti-TNF agents in regard to toxicity profiles when used in patients with inflammatory bowel disease who are naive to anti-TNF medications.

G&H What other important findings were included in the posters?

BB Some people believe that vedolizumab may not be as effective as anti-TNF agents for the treatment of Crohn's disease. The EVOLVE study challenges that belief because the study does not show a clear advantage of either treatment for Crohn's disease.

It is also important to note that we did our best to try to adjust for inherent biases in the patients who received vedolizumab vs those who received an anti-TNF agent.

Particularly because vedolizumab is a new agent, there may have been a selection bias for sicker patients being given an anti-TNF agent, which could have impacted

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their performance on that agent. Similar to what has been done in other studies, we controlled for features that seem to be associated with a worse outcome and then viewed the data with that adjustment taken into consideration. One advantage of this study is its large sample size, which took patients from different countries around the world and allowed us to do our best to control for features that may have influenced the results that we were seeing.

G&H What are the clinical implications of these findings?

BB Probably most important is that doctors can now communicate to patients with confidence that vedolizumab is safer than anti-TNF agents in anti-TNF-naïve patients because a study has now clearly demonstrated this point. We have shown that patients who have never been on a biologic have a higher likelihood of developing serious adverse events, including serious infections, if they are started on an anti-TNF agent compared to vedolizumab. Doctors have always assumed this to be true but now have the science to back up this point.

In addition, there has been a suggestion that the benefit that occurs in patients may be similar regardless of whether they start on vedolizumab or on an anti-TNF agent. However, not showing a difference does not necessarily mean that the treatments are similar. It is difficult to draw a conclusion because the study was not powered for this particular purpose.

G&H Do the findings from this study have any other importance to the community?

BB At last year's meeting of the European Crohn's and Colitis Organisation, findings from the EVOLVE study focused on how anti-TNF agents worked after patients were exposed to vedolizumab. Patients who failed vedolizumab were started on an anti-TNF agent and followed for 6 months. We examined how well these patients did on an anti-TNF agent and compared the findings to patients who were started on an anti-TNF agent without any biologic exposure. We found that there was no difference between the 2 groups, meaning that the exposure of vedolizumab did not seem to impact the likelihood of achieving success on anti-TNF therapy. That is a very important discovery because the same is not true when those treatments are reversed; anti-TNF exposure impacts vedolizumab response rates.

G&H How do findings from the EVOLVE study impact the positioning of vedolizumab?

BB The EVOLVE data give us further confidence in setting up an appropriate algorithm and positioning biologics for the management of patients with ulcerative colitis and Crohn's disease. It appears that the most appropriate way to use biologics is to give vedolizumab first and then an anti-TNF agent. This is because of the impact that anti-TNF exposure has on vedolizumab response, as well as the fact that if a patient is started on vedolizumab and loses response, the EVOLVE study findings suggest that the patient has not burned any bridges. The patient has not compromised the effectiveness of anti-TNF therapy later on. The data also show that vedolizumab is safer.

It should be noted that this positioning refers to patients who are equally likely to respond to both treatments and for whom there is no reason why one agent would be preferred (unlike with, for example, patients who have a concomitant immune-mediated disease such as ankylosing spondylitis or uveitis, where anti-TNF therapy would help that disease as well).

G&H Based on the recent EVOLVE data, how does vedolizumab monotherapy compare to combination therapy with immunomodulators?

BB There was no difference, so perhaps it could be said that combination therapy does not offer an advantage. However, I think that it would be overstating our conclusions to say that this means that combination therapy is not needed. That may be the case, but this study does not have the power for this subgroup analysis to be confident that indeed a difference does not exist.

G&H Do the recent findings help determine which subgroups of patients (eg, in terms of disease phenotype) benefit most from the use of vedolizumab in the first-line setting?

BB I am not sure if the recent findings answered this question. In Crohn's disease, there was a higher proportion of patients who were started on an anti-TNF agent who had fistulizing disease. Those patients inherently do not respond as well, so we tried to control for that in the analyses to avoid bias against a good outcome with anti-TNF agents. Because we purposely tried to make the groups as similar as possible, we lost the ability to pick out subgroups where there was a signal that one agent would have worked better. Thus, we cannot comment on whether one agent or the other would be more effective in a particular phenotype. The only comment that can be made is that because vedolizumab has a better safety profile, patients who inherently have a higher risk of adverse events should probably be considered for that treatment, rather than an anti-TNF agent.

G&H What are the limitations of this study that should be taken into account?

BB There are several limitations because of the retrospective nature of the study. There are limitations associated with the targets themselves, such as clinical remission, because the outcomes were not prespecified and, therefore, collected in a systematic way. Among the usual limitations of retrospective research, the most important is that the patients are not randomized. As much as we try to control for confounding factors, there are unknown features that may have biased the results, hence the value of randomization. When a dataset is not randomized, there is always skepticism at interpreting significant findings because there may be some confounding factors that cannot be adequately addressed.

G&H What are the next steps in research?

BB There is some desire to expand the dataset by bringing in other countries, which may allow us to address other important issues. For example, all of the anti-TNF agents have been grouped together, but some people believe that one anti-TNF agent may work differently from another. Currently, we do not have enough patients on different anti-TNF agents to address that issue with any confidence. In addition, it would be useful to further refine sequencing and see if we can further understand the implications of drug exposure from one agent to another. Finally, anti-TNF agents and vedolizumab are no longer the only agents that are available, so we should explore the impact of other agents, such as tofacitinib (Xeljanz, Pfizer) or ustekinumab (Stelara, Janssen), with the same metrics that have been used in the EVOLVE study.

Disclosures

Dr Bressler has served as an advisor/speaker for Pfizer, Merck, Ferring, Janssen, AbbVie, Takeda, Celgene, and Genentech; has served as an advisor for Allergan, AMT, BMS, Gilead, and Protagonist; has received research support from Janssen, AbbVie, Takeda, Atlantic Pharmaceuticals, GSK, BMS, Amgen, Genentech, Merck, RedHill Biopharma, BI, Qu Biologics, Celgene, and Alvine; and has received stock options from Qu Biologics.

Suggested Reading

- Bressler B, Yarur AJ, Kopylov U, et al. Sa1748 Clinical effectiveness and safety of first-line biologic vedolizumab as a monotherapy or combination therapy in ulcerative colitis and Crohn's disease patients: results from the EVOLVE study. *Gastroenterology*. 2020;158(6 suppl 1):S407.
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- Sands BE, Peyrin-Biroulet L, Loftus EV Jr, et al. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. *N Engl J Med*. 2019;381(13):1215-1226.
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