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In Case You Missed It

In Case You Missed It: Biosimilar BI 695501 Has Similar Safety and Efficacy To Adalimumab for the Treatment of Crohn's Disease: The VOLTAIRE-CD Study

IBD

Dr Jessica Allegretti
Associate Editor

Dr Rahul S. Dalal
Guest Contributor

Rahul S. Dalal, MD, MPH[1] and Jessica R. Allegretti, MD, MPH, FACG[2]

[1]Division of Gastroenterology, Hepatology and Endoscopy, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

[2] Medical Director, Crohn's and Colitis Center, Division of Gastroenterology, Hepatology and Endoscopy, Department of Medicine, Brigham and Women's Hospital; Associate Professor of Medicine, Harvard Medical School, Boston, MA

This summary reviews Hanauer S, Liedert B, Balser S, et al. Safety and efficacy of BI 695501 versus adalimumab reference product in patients with advanced Crohn's disease (VOLTAIRE-CD): a multicentre, randomised, double-blind, phase 3 trial. Lancet Gastroenterol Hepatol. 2021 Oct;6(10):816-825.

Correspondence to Jessica Allegretti, MD, MPH. Associate Editor. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: Does biosimilar BI 695501 (adalimumab-adbm; Cyltezo; Boehringer Ingelheim International, Rheim, Germany) have similar safety and efficacy as adalimumab (Humira; AbbVie Pharmaceuticals, Maidenhead, UK) for patients with moderate-severe Crohn's disease?

Design: VOLTAIRE-CD was a phase 3, randomized, double-blind study. Patients were randomized 1:1 to the biosimilar BI 695501 or adalimumab stratified by previous exposure to infliximab and simple endoscopic score for Crohn's disease. At week 24, patients were unblinded and those in the adalimumab group were switched to BI 695501.

Setting: 92 centers across 12 countries in Europe and the United States

Patients: 147 patients aged 18-80 years with moderately to severely active Crohn's

disease

Interventions: Biosimilar BI 695501 or adalimumab, 160 mg on day 1 and 80 mg on day 15 followed by 40 mg every 2 weeks via subcutaneous injection

Outcomes: The primary endpoint was the proportion of patients with clinical response (decrease in CDAI by ≥70 points) at week 4. The secondary endpoints were the proportions of patients with clinical response and clinical remission (CDAI < 150) at week 24. Clinical response and remission were also assessed at week 48, after patients in the adalimumab group switched to BI 695501 (at week 24). Adverse events were also assessed.

Data Analysis: Primary and secondary endpoints were analyzed using log-linked binomial models with prior infliximab exposure and study treatment as fixed effects and baseline SES-CD as a categorical effect.

Funding: Boehringer Ingelheim International.

Results: 147 patients were enrolled and received either BI 695501 (n=72) or adalimumab (n=75). At week 4, 61/68 (90%) and 68/72 (94%) had clinical response with BI 695501 and adalimumab, respectively (RR 0.95, 95% CI 0.87-1.03). At week 24, 55/68 (81%) and 59/72 (82%) achieved clinical response and 46/68 (68%) and 54/72 (75%) achieved clinical remission for BI 695501 and adalimumab, respectively. At week 48 (after patients in the adalimumab group switched to BI 695501 at week 24), 55/68 (81%) and 57/72 (79%) achieved clinical response and 52/68 (76%) and 52/72 (72%) achieved clinical remission in the BI 695501 and adalimumab (now switched to BI 695501) groups, respectively (**Figure 1)**. Drug-related adverse events were similar between treatment groups: 15/72 (21%) for BI 695501 and 17/75 (23%) for adalimumab during weeks 0-24 and 10/72 (14%) for BI 695501 and 11/75 (15%) for adalimumab during weeks 24 -56. The most common drug-related adverse events for BI 695501 included weight gain (4% for BI 695501), injection site erythema (3% for adalimumab), and upper respiratory tract infection (3% for adalimumab). No adverse events led to death.

COMMENTARY

Why Is This Important?

With the rising cost of medical care for patients with inflammatory bowel diseases, there is increasing pressure from insurance companies to substitute originator biologic treatments with biosimilars, which is felt to be a cost-saving strategy.[1] Previous research has demonstrated similar efficacy and safety of the biosimilar BI 695501 to adalimumab reference product for rheumatoid arthritis and plaque psoriasis.[2-4] VOLTAIRE-CD is the first study to demonstrate similar efficacy (i.e. non-inferiority) and safety of BI 695501 to adalimumab for the treatment of advanced Crohn's

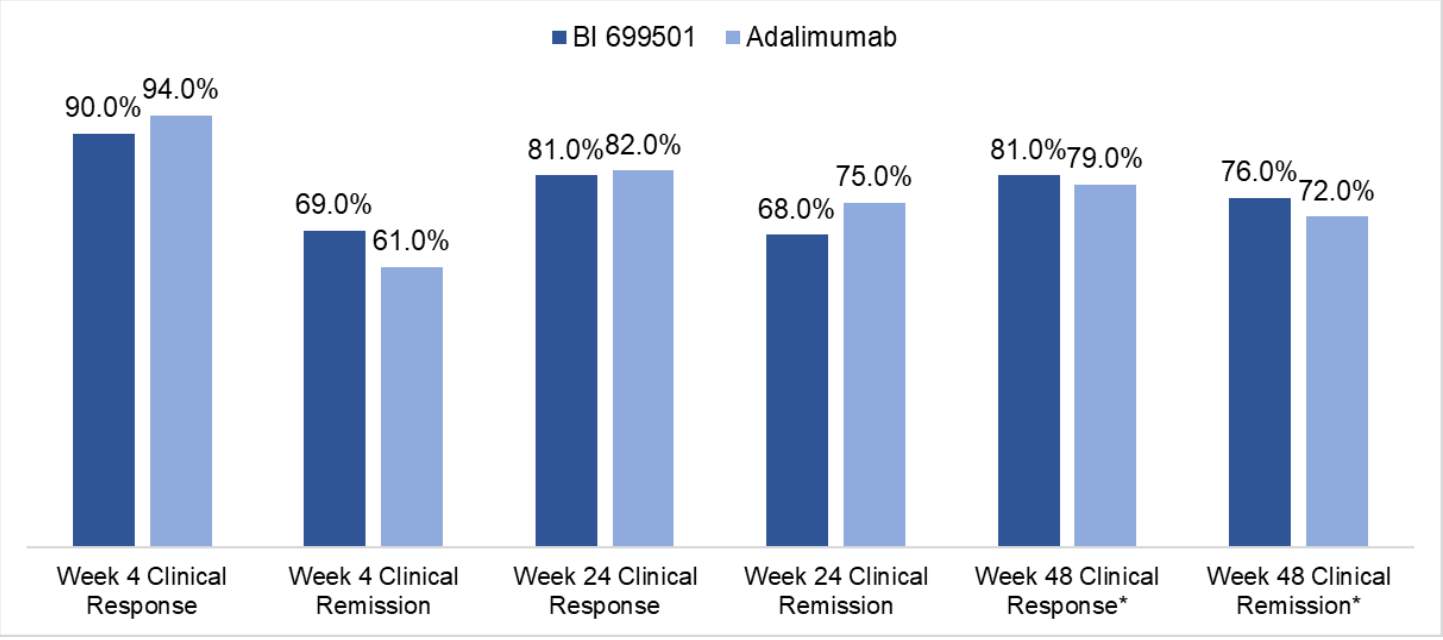

Figure 1. Efficacy endpoints. *At week 24, patients in the adalimumab group switched to BI 699501.

disease.

The availability of a cost-effective therapy with similar treatment efficacy to originator adalimumab may increase access and allow for earlier biologic treatment for many patients with moderate-to-severe Crohn's disease. The findings of this study may also help IBD providers counsel their patients and give reassurance when there are payer-mandated switches from adalimumab to a biosimilar.

When discussing biosimilars of biologic agents, some additional information may be helpful.[5] Biologic agents are proteins that are produced through recombinant DNA technology in living sources, such as bacteria or yeast, and posttranslational modifications of the resultant proteins occur within cell lines and can result in variations in the resultant protein products. This differs from non-biologic, small-molecule drugs which are produced through inorganic and chemical syntheses. The final small-molecule medications are identical. Thus, when competitive versions of small-molecule medications are produced by other pharmaceutical companies, they are called "generics" and are identical and bioequivalent to the original small-molecule medication. Since competitive versions of biologic agents aren't identical, due to the posttranslational changes, they are considered biosimilars as opposed to identical "generics." Biosimilars must be "highly similar" to the original biologic agent with "no clinically meaningful differences" by regulatory authorities prior to approval. "Interchangeability" is an additional designation for a biosimilar and means that it can be substituted for the original biologic agent even without the approval of the prescribing physician. In order for a biosimilar to also be labelled as interchangeable, it must

demonstrate that the biosimilar produces the same clinical result as the original biologic agent in any given patient, and that switching between the original biologic and biosimilar will not produce additional risks in adverse events, including increased immunogenicity or altered pharmacokinetics. Currently, BI 695501 (adalimimab-adbm; Cyltezo, Boehringer Ingelheim International, Rhein, Germany) is the only adalimumab biosimilar that also has interchangeability status in the US.

Key Study Findings

The study found that BI 695501 had similar safety and efficacy to adalimumab for moderate-severe Crohn's disease as measured by week 4 and week 24 clinical response and remission. Patients who switched from adalimumab to BI 695501 at week 24 maintained the treatment benefits of the original therapy through week 48.

Caution

This study did not assess long-term outcomes beyond 48 weeks. Therefore, the safety and efficacy of the biosimilar 695501 compared to adalimumab at later timepoints is not well-understood. For similar reasons, rare adverse events such as malignancy were not adequately assessed.

My Practice

In my practice, payer-mandated switches from originator anti-TNFs to biosimilars is becoming increasingly common. I generally try to keep my patients on the originator biologic when possible. However, I do not generally attempt to appeal a payer-mandated switch to a biosimilar as this may delay therapy. Data from studies like VOLTAIRE-CD help me to provide reassurance to my patients who worry about losing response to therapy after a switch to an adalimumab biosimilar for their Crohn's disease. Patients should be educated prior to a switch to a biosimilar to mitigate a potential nocebo effect.

For Future Research

Future research should examine the efficacy and safety of multiple biosimilar switches from originator adalimumab, as well as reverse switches from biosimilars back to adalimumab, as these scenarios have been observed among patients treated with infliximab and its biosimilars. Comparisons of the long-term safety, efficacy, and durability of BI 695501 to adalimumab are also needed for both Crohn's disease and ulcerative colitis.

Conflict of Interest

Dr. Dalal has received grant support from Janssen Pharmaceuticals and Pfizer Pharmaceuticals and has served as a consultant for Centaur Labs.

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