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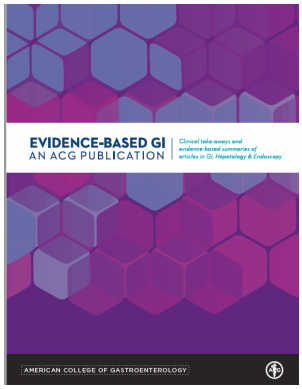

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The New Frontier of Combination Therapy for IBD: The VEGA RCT

Dr Tarun Chhibba
Guest Contributor

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Associate Editor

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IBD

This summary reviews Feagan BG, Sands BE, Sandborn WJ, et al. Guselkumab plus golimumab combination therapy versus guselkumab or golimumab monotherapy in patients with ulcerative colitis (VEGA): a randomised, double-blind, controlled, phase 2, proof-of-concept trial. Lancet Gastroenterol Hepatol 2023; 8: 307-20 .

Correspondence to Bharati Kochar, MD, MS. Associate Editor. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: Is combined treatment with guselkumab (Tremfya, Janssen Biotech, Horsham, PA), an IL-23 antagonist monoclonal antibody, and golimumab (Simponi, Janssen Biotech, Horsham, PA), a tumor necrosis factor (TNF)-antagonist monoclonal antibody, superior to golimumab or guselkumab alone for the treatment of moderate to severe ulcerative colitis?

Study Design: The VEGA study is Phase 2 proof of concept, randomized, double-blind, placebo-controlled trial (RCT) to compare 3 arms of therapy: (1) guselkumab and golimumab in combination (2) guselkumab monotherapy and (3) golimumab monotherapy.

Setting: Patients were recruited from 54 hospitals in 9 countries.

Patients: Study inclusion criteria included: age 18-65 years; confirmed diagnosis of ulcerative colitis 3 months prior to screening**;** moderate-to-severe disease activity defined by baseline Mayo score of 6-12 including an endoscopy subscore of ≥ 2; no prior treatment with anti-TNF, anti-interleukin (IL)12/23 or anti-IL23 agents; and inadequate response or failure to tolerate "conventional therapy" or corticosteroid dependence. Multiple exclusion criteria were used, including pregnancy; ulcerative proctitis only; history of colonic resection; or severe disease likely to lead to colectomy within 12 weeks.

Study enrollment mandated a 2-week washout period for immunomodulators (6-MP, azathioprine, methotrexate), rectal corticosteroids, rectal 5-aminosalicylic acid (ASA) compounds, total parenteral or enteral nutrition and antibiotics being used to treat ulcerative colitis (UC) and intravenous (IV) steroids. Patients treated with JAK inhibitors, cyclosporine or 6-thioguanine were required to have a 4-week washout period. Concomitant immunomodulator use was not permitted. Patients treated with vedolizumab were required to have an 18-week washout period. For 5-ASA, budesonide, and prednisone equivalents of <20mg daily, the dose must have been stable for at least 2 weeks prior to enrollment.

Intervention: Patients were assigned to 1 of 3 intervention arms: (a) Combination therapy: guselkumab 200mg IV at weeks 0, 4 and 8 followed by 100mg SC every 8 weeks until week 32 + golimumab 200mg SC at week 0, then golimumab 100mg SC at weeks 2, 6 and 10; (b) Guselkumab monotherapy: guselkumab 200mg IV at weeks 0, 4 and 8 followed by 100mg SC every 8 weeks until week 32; or, (c) Golimumab monotherapy: golimumab 200mg SC at week 0, then 100mg at week 2 and every 4 weeks until week 34. Placebo administrations were provided to maintain masking.

Outcomes: The primary outcome was clinical response at week 12, defined as 30% decrease in the baseline Mayo score including a minimum decrease of ≥3 points with a decrease in rectal bleeding score of ≥1 point or a rectal bleeding score of 0 or 1. The major secondary outcome was clinical remission at week 12, defined as Mayo score of ≤2 with no individual subscore of >1.

Other secondary endpoints at week 12 and 38 included: 7-day and 60-day corticosteroid-free clinical remission; symptomatic remission: stool frequency

subscore of 0 or 1 with no increase from baseline and rectal bleeding subscore of 0; endoscopic improvement: Mayo endoscopy subscore of 0 or 1 with no friability; histological remission at week 38; improvement in quality of life: inflammatory bowel disease (IBD) Questionnaire increase ≥ 16 points from baseline IBDQ score.

Analysis: The analysis was powered (80%) to detect a 20% difference in the primary outcome of clinical response at week 12. All randomly assigned patients who received 1 dose of study medication were included in the modified intention-to-treat analysis.

Funding: Janssen Research and Development funded this trial; Janssen, Inc is the manufacturer of both guselkumab and golimumab.

Results: Between 2018 and 2021, 358 patients were screened to identify 214 eligible patients: 48%-58% male, 92%-94% white, average disease duration of 5 years, and average Mayo score just under 9.

At week 12, there was a significantly greater clinical response in the combination compared to golimumab monotherapy arm (83% vs 61%, *P*=0.003), but no significant difference between the combination therapy and guselkumab therapy arm (83% vs 75%, *P*=0.216). For the major secondary outcome, clinical remission was more common in the combination therapy compared to guselkumab monotherapy arm (37% vs 21%, *P*=0.041) but not the golimumab monotherapy arm (37% vs 22%, *P*=0.058). The proportion of patients who achieved endoscopic improvement, endoscopic normalization and histologic remission were highest in the combination therapy arm compared to the monotherapy arms at weeks 12 and 38 (**Figure 1)**. Also notably, the proportion of patients who achieved a corticosteroid-free clinical remission at week 12 was significantly higher in the combination therapy arm than the monotherapy arms.

Incidence of serious adverse events were low: at week 12, 1% in the combination therapy arm, 1% in the golimumab monotherapy arm and 3% in the guselkumab monotherapy arm experienced a serious adverse event. In the combination therapy arm, this serious adverse event was a serious infection. No opportunistic infections occurred, and rates of infection (any type) was

12%-14% in all 3 arms. At week 50 follow up, there was 1 malignancy noted in the guselkumab monotherapy arm and 2 deaths, 1 in the combination therapy arm and 1 in the guselkumab monotherapy arm.

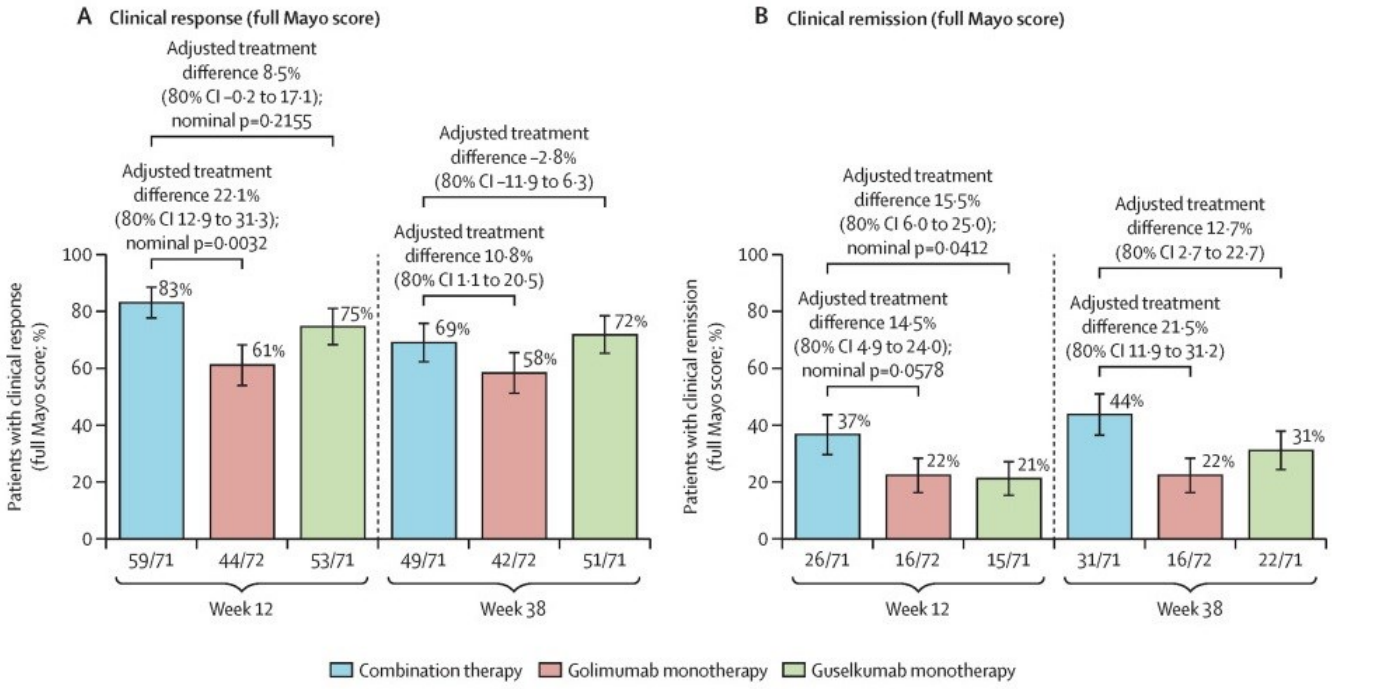

Figure 1. Clinical response and clinical remission at weeks 12 and 38 for golumumab monotherapy, guselkumab monotherapy, and combination therapy. Reprinted from *Lancet Gastroenterology Hepatology*, Feagan BG, Sands BE, Sandborn WJ et al. Guselkumab plus golimumab combination therapy versus guselkumab or golimumab monotherapy in patients with ulcerative colitis (VEGA): a randomised, double-blind, controlled, phase 2, proof-of-concept trial. Pages 307-320. Copyright 2023, with permission from Elsevier.

COMMENTARY

Why Is This Important?

The publication of the SONIC[1] and U-SUCCESS[2] RCTs, which demonstrated the superiority of azathioprine plus infliximab over monotherapy for corticosteroid-free clinical remission in Crohn's and UC, revolutionized management of IBD. Multiple monoclonal antibodies with different mechanisms of actions are now available to treat UC, including vedolizumab, which is an anti-integrin antibody, anti-IL-12/23 monoclonal antibodies, like ustekinumab and risankizumab, as well as small molecules, like ozanimod, a sphingosine-1 phosphate inhibitor, and updacitinib, a selective JAK1 inhibitor. However, as monotherapy, these treatments produce clinical remission in only a minority of patients. Therefore, identifying optimal combination therapies that achieve higher remission rates *and* acceptable safety profiles is a huge knowledge gap in IBD management. While this proof of concept trial did not meet the primary outcome, it demonstrates that

prospective combination biologic agents can be safe and it's a critical step forward for the feasibility of these regimens.

Key Study Findings

In patients with moderate-severe UC who were naïve to biologic therapies, combination therapy with guselkumab and golimumab is safe and superior to golimumab monotherapy for clinical response at week 12 and just missed achieving statistical superiority compared to both monotherapies for clinical remission at week 12.

Other important secondary outcomes, such as endoscopic and histologic remission, were highest in the combination therapy arm of this relatively small trial.

Caution

The patient population was limited to patients that did not have prior treatment with anti-TNF agents or other biologic agents. Also, the sample size was relatively small and was underpowered to show differences <20% in clinical response rates.

My Practice

Combination biologics or combination biologic with JAK inhibitors is increasingly common in tertiary IBD practice. These should not be first or second line treatment strategies, but reserved for those with the most refractory disease. However, the VEGA trial asks an interesting question: should we be considering combination biologics as a strategy upfront? While the findings don't directly make the strongest argument for this, those in the combination arm, which only included combination therapy until week 10 with golimumab administration ending then, did have a numerically higher chance of experiencing clinical response and remission even as early as week 12. Perhaps more powerfully, this trial demonstrated that combination biologics are not unsafe.

Since guselkumab is not yet formally approved for the treatment of IBD, I am not using this in practice. However, I use golimumab in practice for patients who report a robust response to infliximab or adalimumab in the past, but are unable to restart the medication for a host of reasons. While golimumab is only formally FDA approved for the treatment of ulcerative colitis, when needed for refractory patients, I have requested approval to use it "off label" in patients with Crohn's disease as well.

My most commonly used combination advanced therapy for IBD is now vedolizumab in combination with a JAK inhibitor (JAKi). JAK inhibitors have potent inductive properties and the added benefit of not being immunogenic–meaning we can start and stop them as needed. Using this strategy over the span of a 1-2 years, I have even de-escalated patients to

vedolizumab monotherapy. Similarly, more recently, I have patients with whom I am treating with combination JAKi and anti-interleukin medications with the eventual goal of de-escalating to monotherapy with the anti-IL. Additionally, for those patients who have the most refractory disease that are either not good candidates for surgical management or decline surgical intervention, I am also turning to combination biologics – anti-TNFs with vedolizumab or anti-TNFs with anti-IL agents. This is in recognition of the fact that a multimodal approach is often needed to address severe disease. But it is always important to remind patients and include expert surgeons in the conversation because surgical management may need to be part of this multi-modal approach.

Whether it is for the treatment of IBD alone or the IBD with other medical conditions, including those that are not widely thought of as immune mediated inflammatory diseases, such as hypercholesterolemia or migraines, combination biologics is becoming a mainstay of treatment strategies. However, insurance companies pose great barriers to this strategy that incurs increased upfront investment. Trials like VEGA have the added benefit of providing the proof of concept needed to argue with insurance companies to approve appropriate care for patients.

For Future Research

VEGA joins an increasing cadre of active comparator clinical trials in IBD, which should be the norm, as placebo is no longer a viable comparator for medications. This trial sets the stage for understanding the clinical role of combination biologics. The mechanistic implications of combination biologics should be better elucidated. Furthermore, we need strategies beyond clinical acumen to identify which patient requires which medication or combination of medications.

Conflicts of Interest

Dr. Chhibba reports no conflicts of interests. Dr. Kochar reports serving as an advisory board member for Pfizer Pharmaceuticals.

Note: The authors of the article are active on social media. Tag him to discuss their work and this EBGI summary!

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Bruce Sands

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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

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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.

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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

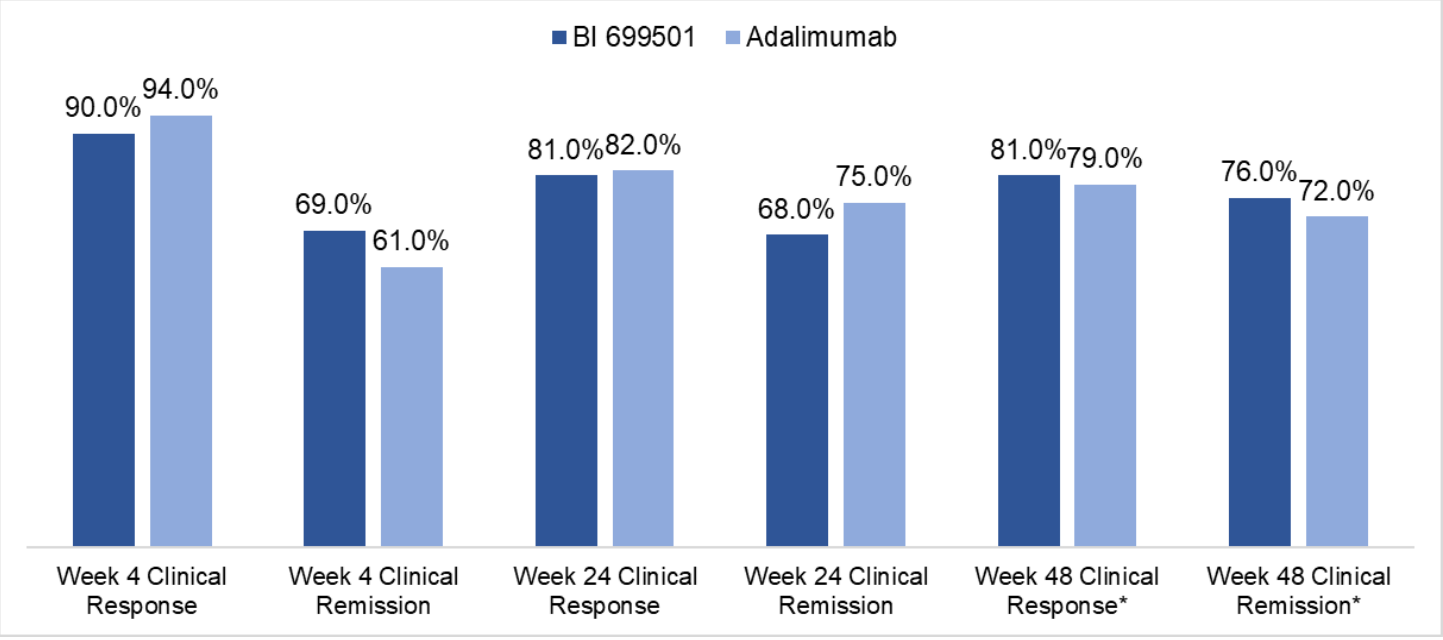

Figure 1. Efficacy endpoints. *At week 24, patients in the adalimumab group switched to BI 699501.

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.

Dr. Allegretti has received grant support from Janssen Pharmaceuticals, Pfizer Pharmaceuticals, and Merck Pharmaceuticals, and has served as a consultant for Janssen Pharmaceuticals, Pfizer Pharmaceuticals, AbbVie Pharmaceuticals, Ferring Pharmaceuticals, Merck

Pharmaceuticals, Bristol Myers Squibb, Seres Therapeutics, Finch Therapeutics, Iterative Scopes, and Takeda Pharmaceuticals.

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HEPATOLOGY

Hepatitis C Virus Testing and Treatment: A Call to Action

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This summary reviews Kapadia SN, Zhang H, Gonzalez CJ, et al. Hepatitis C Treatment Initiation Among US Medicaid Enrollees. JAMA Netw Open 2023;6(8):e2327326.

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STRUCTURED ABSTRACT

Question: Hepatitis C virus (HCV) infection is curable with direct-acting antiviral (DAA) agents, but treatment is thought to be underutilized, especially among individuals with low socio-economic status. What are the variations in treatment access and initiation in Medicaid patients with newly diagnosed HCV?

Study Design: Retrospective cohort study using Medicaid claims data in patients age 18 to 64 years old with a new diagnosis of HCV in 2018 were included.

Setting: United States including Washington DC and Puerto Rico. Data from Rhode Island, Tennessee, and Kansas were omitted as they were missing race and ethnicity data for more than 50% of sampled individuals.

Patients: 87, 652 patients with 51% males, the majority (46%) aged 50 to 64 years old (40% aged 30 to 49 years old; 14% aged 18 to 29 years old), with 46% non-Hispanic White. 49% had a history of active injection drug use at diagnosis.

Outcome: The primary endpoint was HCV treatment initiation with DAAs within 6 months of diagnosis.

Data Analysis: Univariate analyses for all independent variables using X^2 testing. Multivariable logistic regression models were used to identify factors associated with treatment initiation.

Funding: Grants from National Institute of Diabetes, Digestive, and Kidney Diseases, National Institute on Drug Abuse, Patient-Centered Outcomes Research Institute (PCORI), Troup Fund of the Kaleida Health Foundation.

Results: Of the total patients, only 20% (n=17, 927) received DAAs within 6 month of initial HCV diagnosis. Female sex, younger age of 18-29 year old (odds ratio [OR]: 0.65; 95% confidence interval [CI]: 0.50-0.85), and active injection drug use (0.84; 95% CI: 0.75-0.94) were associate with decreased treatment rates (in regression analysis). In terms of ethnicity, Asian race (OR, 0.50; 95% CI, 0.40-0.64), American Indian or Alaska Native race (OR, 0.68; 95% CI, 0.55-0.84), and Hispanic ethnicity (OR, 0.81; 95% CI, 0.71-0.93) were associated with decreased treatment initiation (adjusted for state fixed effects).

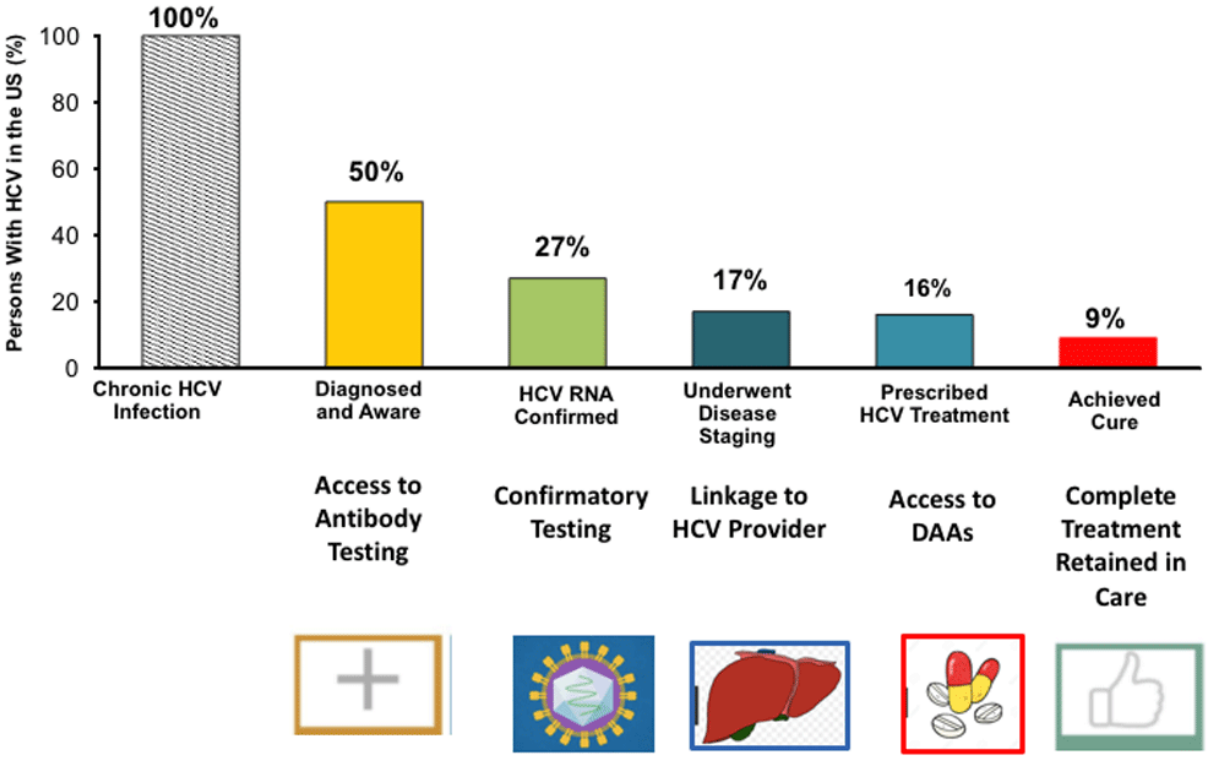

Figure 1. Hepatitis C virus (HCV) cascade of care.

Of the 3.5 million Americans estimated to be infected with HCV, 50% have undergone anti-HCV testing, the first step in the cascade of care. Next, confirmation testing for viremia (HCV RNA testing) is needed. Once infection is confirmed, linkage with a provider who is expert in HCV treatment is needed (primary care or specialist) and additioal steps include testing for HCV genotype and staging of liver disease. Once treatment is prescribed, there are additional steps to get the medication approved and the patient to complete the treatment. As shown, there are multiple points along the cascade of care where interruption can occur, leading to decreased numbers of persons achieving HCV cure. Current HCV elimination efforts are focused on reducing gaps along the cascade of care. Figure and legend from reference 3.

COMMENTARY

Why Is this Important?

Introduced in 2014, DAA therapy has transformed the landscape of HCV management and treatment. Combination use of DAAs has resulted in highly effective interferon-free regimens with a current sustained virologic response (SVR) above 90%, regardless of genotype, severity of the liver disease, renal function, and whether or not the patient was previously treated.[1] Additionally, HCV treatment has decreased rates of HCV related cirrhosis, hepatocellular carcinoma, and liver transplantation.[2]

However, despite curability, HCV remains a public health problem, especially among younger populations (aged 20-39 years old) and driven largely by those who inject drugs. Of the 189 million people affected globally and more than 4 million in the US, most are expected to achieve HCV cure because of the remarkable effectiveness of DAA therapy.[3] However, there exists dramatic gaps in the HCV care cascade (Figure 1) that allow those that are diagnosed with HCV to get to treatment access and care.

Specifically in patients with Medicaid, disparities in treatment can differ across states with some states requiring different durations of sobriety, need for advanced fibrosis, or specialist consultation in order to receive treatment.

Key Study Findings

Only 20% of patients with Medicaid started HCV treatment within 6 months of diagnosis. In particular, female sex, active intravenous drug use, younger age and certain minoritized racial and ethnic groups (Asian, Hispanic, or American Indian or Alaskan native) were associated with less treatment initiation.

Caution

The study is limited to only Medcaid patients so it is unclear whether this treatment underutilization applies to those with private insurance or the older Medicare population. Additionally, given the lack of granular data in the Medcaid claims database, the true disparity of HCV treatment may be greater as many patients with HCV may be undiagnosed or not linked to healthcare.

My Practice

In my hepatology practice, those who are referred for hepatitis C treatment are initially seen with baseline labs (comprehensive metabolic panel, complete blood count, international normalized ratio) and Hepatitis A and B serologies in addition to HIV if not previously checked. While genotype for hepatitis C is less important now given our pan genotypic regimens, most insurance companies require it and is important to know in the rare treatment failure. A fibrosis test is also used to risk stratify

for advanced fibrosis – in our clinic we use transient elastography. If the patient is fasting on the day of their visit, we will often obtain elastography same day and after labs are resulted, submit to insurance companies.

However, because we are specialists, we are often referred those with known Hepatitis C. Many locations in the US do not have easy access to GI or hepatology. Many primary care practices, including ours at the University of Chicago, will treat hepatitis C. Additionally, programs like Project ECHO (at centers throughout the United States) can provide telehealth education and case based curriculum in HCV to expand treatment access at community health centers and primary care practices in underserved neighborhoods.[4] The American Association for Liver Disease and the Infectious Disease Society of America have produced an excellent resource for HCV management: www.hcvguidelines.org, which provides updated guidance about appropriate diagnosis and treatment, too.

For Future Research

Exploring whether similar disparities in treatment initiation are seen in those with private insurance and the Medicare population will be important. Additionally, interventions in the critical points in the HCV care cascade as described above are needed to increase not only treatment initiation but sustained viral rates and cure.

Conflict of Interest

Dr. Paul has no relevant conflicts of interest.

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EVIDENCE-BASED GI
AN ACG PUBLICATION

Proton Pump Inhibitors Do Not Cause Dementia: Refuting Sensationalized Claims in a Post-Modern Epidemiologic Era

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This summary reviews Mehta R, Kochra B, Zhou Z, et al. Association of Proton Pump Inhibitor Use with Incident Dementia and Cognitive Decline in Older Adults: A Prospective Cohort Study. Gastroenterology 2023; 165: 564-72.

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STRUCTURED ABSTRACT

Question: Is proton pump inhibitor (PPI) use associated with an increased risk of dementia or cognitive decline?

Design: Prospective cohort study based on post hoc analysis of randomized controlled trial (RCT).

Setting: ASPirin in Reducing Events in the Elderly (ASPREE) trial.

Patients: Patient population consisted of 18,934 older (≥ 65 years old) Australian and US adults with no cardiovascular disease, dementia, cognitive impairment, or physical disability and at least 5 years of life expectancy at enrollment between 2010-2014. All patients were randomized to receive low-dose (100 mg) aspirin vs placebo. No difference in mortality, dementia, or physical disability was identified, although aspirin-treated patients were more likely to have major hemorrhage events (hazard ratio [HR] = 1.38; 95% confidence interval [CI]: 1.18-1.62) during median 4.7 years of follow-up.

Interventions/Exposure: At baseline, 4667 study patients were using PPIs (24.6%), 368 used H2 receptor antagonists (1.9%) and remainder did not receive medications for gastric acid suppression.

Outcome: Since dementia and cognitive impairment were secondary outcomes of the ASPREE RCT, study patients underwent 4 cognitive tests at baseline and again at years 1, 3, 5 and final visit. Individuals with suspected dementia based on these tests were referred for definitive cognitive and functional assessments. Adjudication of dementia diagnosis was determined by a panel of neurologists, neuropsychiatrists and geriatricians using DSM-4 criteria and required presence of memory impairment plus either aphasia, apraxia, agnosia, or executive dysfunction. Panel was blinded to study patient characteristics and medication use.

Patients also had annual study visits where they were asked to bring all of their current medications as part of annual assessment. Additional potential confounders were assessed at baseline visit and annual visits, including demographic data, smoking status, alcohol consumption, body mass index, chronic kidney disease, hypertension, and diabetes.

Data Analysis: Intention-to-treat analysis. Hazard ratios (HR) calculated using Cox proportional hazards model after adjusting for baseline covariates. A "time-varying" repeated exposures analysis was performed to assess the association between new use of PPIs after age 65 with incident dementia. Finally, a network analysis was constructed using a co-occurrence matrix to determine which medications were most often used concomitantly in PPI users.

Funding: National Institute of Health. ASPREE RCT supported by National Institute on Aging, National Cancer Institute, and Medical Research Council of Australia.

Results: Among 18,934 study patients, 14,267 patients were PPI nonusers and 4667 patients were PPI users with mean age: 75.2, female: 55%-59%, White: 83%-92%, mean body mass index (BMI): 28-29, former/current smoker: 44%-46%. PPI users were more likely to be White, have lower education level, higher depression score, have chronic kidney disease, and were more likely to be using anti-hypertensive medications, statins, non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants and benzodiazepines.

During total of 84,995 person-years of follow-up (median 4.5 years per person), 572 incident cases of dementia were diagnosed with 449 in PPI nonusers and 123 in PPI users. After adjusting for age, sex, years of education, race/

ethnicity, smoking status, alcohol consumption, body mass index, family history of dementia, chronic kidney disease, type 2 diabetes, hypertension, depression scores, baseline cognition and receiving aspirin or placebo at baseline, there was no difference between PPI nonusers, PPI users, and H2RA users for dementia or cognitive impairment (**Table 1**). Using additional data from the ASPREE-XT, 120,194 person-years of follow-up (median 6.3 years per person) also did not show any association: HR = 0.91; 95% CI: 0.78-1.07. Finally, using time-varying analyses to assess associations between sustained PPI use use (increasing duration of PPI use) and incident dementia, no association was identified: multivariate HR = 0.96; 95% CI: 0.91-1.00.

Medication	Dementia	Cognitive Impairment
PPI (n = 4667)	aHR = 0.88 (95% CI: 0.72-1.08)	aHR = 1.00 (95% CI: 0.92-1.09)
H2RA (n = 368)	aHR = 1.00 (95% CI: 0.59-1.74)	aHR = 1.02 (95% CI: 0.79-1.31)

Table 1. Multivariate Hazard Ratio for Dementia and Cognitive Decline for PPI Users and H2RA Users Compared to Non-Users.
Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; PPI, proton pump inhibitor.

COMMENTARY

Why Is This Important?

In August 2023, Northius et al published their retrospective analyses of the Atherosclerosis Risk in Communities (ARIC) Study in Neurology and reported that PPI use "for > 4.4 years by individuals ages 45 years and older is associated with a higher incidence of newly diagnosed dementia".[1] Unfortunately, this led to a multitude of headlines in the lay media similar to this from Bloomberg: "Could Medicines for Heartburn Be Causing Dementia?"[2] Of course, as has happened with many similar reports from epidemiologic studies, this was followed by many phone calls and visits from concerned PPI users. Understandably, even primary care providers and specialists who lack epidemiologic training may be misled by these reports. Fortunately, this excellent study from the Clinical and Translational Epidemiology Unit at Massachusetts General Hospital, helps reassure patients and clinicians that PPI use does not cause dementia.

Some additional "bottom lines" may be helpful. Although observational studies linked PPIs with multiple adverse events like pneumonia, diabetes, and all-cause mortality, RCTs and prospective cohort studies[3-4] have not demonstrated any association, much less a causal relationship. This is unsurprising. Retrospective observational studies are inherently susceptible to multiple potential flaws such as misclassification of diagnosis (e.g., using post-hospitalization *International*

Classification of Diseases- 9th edition codes to identify dementia) or failure to adjust for confounders (e.g., alcohol use, chronic kidney disease, family history of dementia), which were both present in the study by Northius et al. Interestingly, earlier observational studies linked multiple medications, including antihypertensives, NSAIDs, aspirin and PDE5 inhibitors (e.g., sildenafil) with dementia, but subsequent RCTs and prospective cohort studies failed to confirm those findings.

As eloquently expressed by George Davey Smith[5], there is an "epidemic of epidemiologic reports of 'risk factors' for disease from studies that cannot realistically contribute to causal understanding," although, these studies utilize graphs, tables, and language inferring causation. Ultimately, in a post-modern epidemiologic world, there should be a greater reliance on the classic Bradford-Hill criteria[6] before any suggestion of a causal relationship is made.

Key Study Findings

After appropriate adjustment for potential confounders, there was no association between PPI use and dementia: HR = 0.88 (95% CI: 0.72-1.08).

Using additional data from the ASPREE -XT, 120,194 person-years of follow-up (median 6.3 years per person) also did not show any association: HR = 0.91; 95% CI: 0.78-1.07. Finally, using time-varying analyses to assess associations between sustained PPI use (increasing duration of PPI use) and incident dementia, no association was identified: multivariate HR = 0.96; 95% CI: 0.91-1.00.

Caution

Observational studies always have a risk of confounding, which means that there may be unmeasured variables associated with PPI use and dementia which could impact the analysis. Although adjusting for multiple confounders was performed, only an appropriately-sized RCT can (usually) overcome this problem. Data on duration or dose of PPIs used prior to onset of study was not quantified. Also, it's essentially impossible to "prove" a negative outcome, although this well-designed study should be very reassuring to PPI users worried that PPI use may increase the risk of dementia.

My Practice

When my patients and primary care colleagues express concern about the safety of PPIs, I emphasize that properly designed studies have NOT demonstrated associations between PPI use and most publicized adverse events or diseases, including dementia, hip fractures, b12 deficiency, pneumonia, etc.[2-3] PPI use is probably associated with an increased risk of enteric infections[2], including recurrent *Clostridioides difficile* colitis, and there is contradictory data about whether PPI use could be associated with renal insufficiency, possibly due to rare episodes of acute

interstitial nephritis.

Unfortunately, since PPIs are over-prescribed in individuals with any digestive symptoms, I educate my patients that PPI use in poorly, but sensationalized, epidemiologic studies are essentially identifying patients with multiple co-morbidities and polypharmacy. Therefore, I encourage patients with erosive esophagitis, recurrent or complicated peptic ulcer disease, Barrett's esophagus, or chronic and frequent GERD symptoms that are only responsive to PPIs, to continue their medications (albeit at the lowest effective dose) and not be scared by media reports. Having said that, PPIs are overprescribed and should be de-prescribed if there isn't an appropriate indication.

For Future Research

In this post-modern epidemiologic era, authors of retrospective analyses of large databases should emphasize that these are hypothesis-generating studies, as opposed to hypothesis-answering, while applying Bradford-Hill criteria before making any suggestions of causality between an exposure and an adverse outcome.

Conflict of Interest

Dr. Schoenfeld has no relevant conflicts of interest.

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