EVIDENCE-BASED GI
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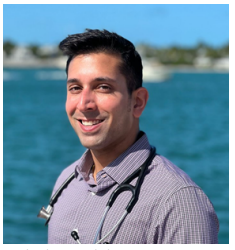
IBD

Therapeutic Drug Monitoring of Maintenance Infliximab Is Beneficial for Patients with Immune-mediated Inflammatory Diseases



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This article reviews Syversen SW, Jørgensen KK, Goll GL, et al. Effect of Therapeutic Drug Monitoring vs Standard Therapy During Maintenance Infliximab Therapy on Disease Control in Patients With Immune-Mediated Inflammatory Diseases: A Randomized Clinical Trial. JAMA 2021; 326(23):2375-2384. doi: 10.1001/jama.2021.21316. PMID: 34932077

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STRUCTURED ABSTRACT

Question: Is proactive therapeutic drug monitoring (TDM) of infliximab levels and anti-infliximab antibodies beneficial during maintenance therapy for patients with stable immune-mediated inflammatory diseases?
Design: Randomized, parallel-group, open-label clinical trial.
Setting: Twenty hospitals in Norway.
Patients: A total of 454 adults with stable psoriasis, psoriatic arthritis, rheumatoid arthritis, spondyloarthritis, Crohn's disease, or ulcerative colitis receiving maintenance infliximab therapy were enrolled between June 2017 and December 2019. Patients were followed through December 2020.
Interventions: All patients were randomized 1:1 to TDM with associated infliximab dose or dose interval changes based on trough infliximab levels and antibodies or standard therapy without infliximab level or antibody monitoring.
Outcome: The primary outcome was sustained disease control (i.e. without a flare requiring change in treatment, change in infliximab dose/interval, or addition of immunosuppressive therapies such as corticosteroids) for 52 weeks. Secondary outcomes included time to disease worsening, patient/physician global assessments of disease activity, remission status, adverse events, and inflammatory markers, among other outcomes.

Data Analysis: Logistic regression was used to analyze the primary outcome with treatment group and stratification factors as covariates. Secondary outcomes were assessed using Cox proportional hazards regression (for time-to-event endpoints), mixed-effects logistic regression (for binary outcomes), and linear regression (for continuous outcomes).
Funding: The study was funded by the Norwegian Regional Health Authorities.
Results: Sustained disease control without disease worsening (primary outcome) at 52 weeks was observed in 73.6% in the TDM group and 55.9% in the standard therapy group, with an estimated adjusted difference of 17.6% (95% CI 9.0%-26.2%, p<0.001). A stratified analysis by use of concomitant immunomodulators showed similar results. The hazard ratio for disease worsening with standard therapy compared to proactive TDM was 2.1 (95% CI 1.5-2.9). Disease activity, remission status, and adverse event rates were similar between intervention arms.

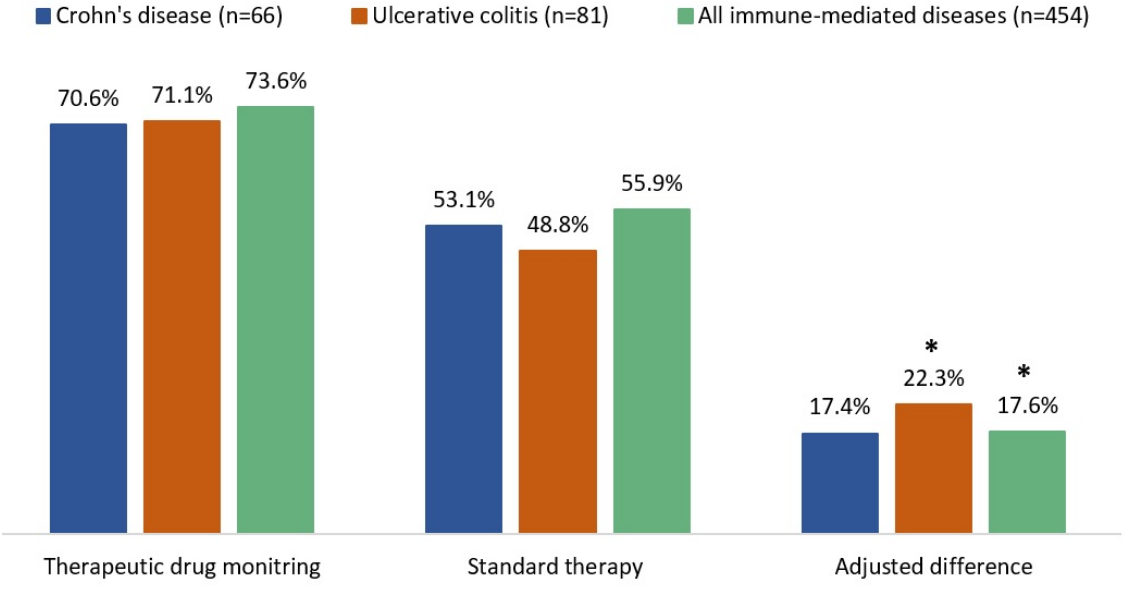

Figure 1. Sustained disease control without worsening.
*Statistically significant results

COMMENTARY

Why Is This Important?

Anti-tumor necrosis factor alpha (TNF) agents such as infliximab are needed to reduce the risk of disease exacerbations and improve quality of life among patients with moderate-to-severe inflammatory bowel diseases (IBD). However, up to 50% of patients with IBD who initially respond to anti-TNF agents lose their clinical response over time.[1] Observational studies have demonstrated that subtherapeutic serum infliximab levels and development of neutralizing anti-infliximab antibodies have been associated with loss of clinical response in this population.[2,3]

Prior clinical trials assessing proactive TDM for infliximab include the TAILORIX (122 Crohn's disease patients) and TAXIT (263 IBD patients) trials, both of which did not demonstrate a statistically significant benefit of TDM for their primary outcome of clinical remission.[4,5] However, TDM was associated with fewer disease flares during the course of therapy in the TAXIT trial.[4] Therefore, additional RCT data is needed to determine if there may be a benefit of proactive TDM for infliximab.

Key Study Findings

In this RCT of 454 patients with stable immune-mediate inflammatory diseases treated with maintenance infliximab, Syversen et al. found that proactive TDM was associated with a lower risk of disease worsening and less anti-infliximab antibody formation over 52 weeks of follow-up compared to standard care. The efficacy of proactive TDM persisted after stratification by immunomodulator use and in sensitivity analyses that varied the definition of disease worsening, strengthening the study's primary findings. These data support the use of a treat-to-target approach using trough drug concentrations and anti-drug antibody levels during maintenance infliximab therapy for autoimmune diseases.

Caution

The study assessed multiple autoimmune diseases, among which IBD represented 147/454 (32.4%) patients. While a statistically significant

favoring TDM was found for ulcerative colitis, the same result was not statistically significant for Crohn's disease, though the overall effect was similar and lack of statistical significance likely reflects that only 61 study patients had Crohn's disease. Larger randomized trials of proactive TDM are therefore needed for the IBD population.

My Practice

I utilize proactive TDM to guide my therapeutic decisions for all of my patients receiving infliximab treatment. I monitor trough infliximab concentrations and anti-infliximab antibody levels immediately prior to the first maintenance infusion and prior to subsequent infusions that follow a change in dose. For low infliximab trough concentrations without antibodies, I typically increase the dose in 2.5 mg/kg intervals to a maximum of 10 mg/kg. If there is a low infliximab concentration with low levels of antibodies present, I will often increase the dose and consider the addition of an immunomodulator. If there is absent drug with high levels of antibodies, I will switch to a new agent. Even though there is limited data for other anti-TNF agents, I still practice more proactive TDM for therapies such as adalimumab.

For Future Research

It remains unclear if the efficacy of proactive TDM is unique to infliximab therapy or if similar effects are present with other anti-TNF agents. Additionally, Syverson et al. did not demonstrate a significant benefit of proactive TDM for Crohn's disease, likely due to the sample size reductions when assessing individual diseases. Larger randomized trials in IBD and cost effectiveness analyses comparing proactive to reactive TDM would be helpful to justify the proactive approach for anti-TNF therapies in the IBD population.

Conflicts of Interest

Jessica R. Allegretti, MD, MPH is a consultant for Baccain, Janssen, Merck, Morphic, Pandion, Pfizer, Salix, Servatus, and Takeda; serves on the advisory boards for Artugen, Finch Therapeutics, and Iterative Scopes; and has received research support from Finch Therapeutics, and Merck.

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