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CLINICAL AT

Trough Concentrations of Infliximab Guide Dosing for Patients With Inflammatory Bowel Disease

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This article has an accompanying continuing medical education activity on page e13. Learning Objective: Upon completion of this exam, successful learners will be able to discuss the impact of dose escalation of infliximab in Crohn's disease patients with low troughs; identify patients where dose reduction is appropriate based on symptoms, trough concentrations, and inflammatory markers; and review timing and frequency of testing for anti-infliximab antibody testing.

See Covering the Cover synopsis on page 1261; see editorial on page 1268.

BACKGROUND & AIMS: Infliximab, a tumor necrosis factor antagonist, is effective for treating patients with Crohn's disease (CD) and ulcerative colitis (UC). We aimed to determine whether dosing based on therapeutic drug monitoring increases rate of remission and whether continued concentration-based dosing is superior to clinically based dosing of infliximab for maintaining remission in patients with CD and UC. **METHODS:** We performed a 1-year randomized controlled trial at a tertiary referral center, including 263 adults (178 with CD and 85 with UC) with stable responses to maintenance infliximab therapy. Doses were escalated or reduced using an algorithm to reach a target trough concentration (TC) of 3–7 μg/mL in all patients (optimization phase). Patients were randomly assigned (1:1) to groups that received infliximab dosing based on their clinical features (n = 123) or continued dosing based on TCs (n = 128) (maintenance phase). The primary end point was clinical and biochemical remission at 1 year after the optimization phase. **RESULTS:** At screening, 115 of 263 patients had a TC of infliximab of 3–7 μg/mL (43.7%). Of 76 patients with TCs <3 μg/mL, 69 patients (91%) achieved TCs of 3–7 μg/mL after dose escalation. This resulted in a higher proportion of CD patients in remission than before dose escalation (88% vs 65%; $P = .020$) and a decrease in the median concentration of C-reactive protein, compared with before the dose increase (3.2 vs 4.3 mg/L; $P < .001$); these changes were not observed in patients with UC. Of 72 patients with TCs >7 μg/mL, 67 patients (93%) achieved TCs of 3–7 μg/mL after dose reduction. This resulted in a 28% reduction in drug cost from before dose reduction ($P < .001$). Sixty-six percent of patients whose dosing was based on clinical features and 69% whose dosing was based on TC achieved remission, the primary end point ($P = .686$). Disease relapsed in 21 patients who received clinically based dosing (17%) and 9 patients who received concentration-based dosing (7%) ($P = .018$). **CONCLUSIONS:** Targeting patients' infliximab TCs to 3–7 μg/mL results in a more efficient use of the drug. After dose optimization, continued concentration-based dosing was not superior to clinically based dosing for achieving remission after 1 year, but was associated with fewer flares during the course of treatment. ClinicalTrialsRegister.eu number: 2011-002061-38.

Keywords: Monoclonal Antibody; Personalized Medicine; Pharmacokinetics; Therapeutic Drug Monitoring.

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Biological therapies have revolutionized the management of chronic inflammatory diseases, such as rheumatoid arthritis, spondylarthropathies, psoriatic arthritis, and inflammatory bowel diseases (IBD). Results from pivotal clinical trials showed that infliximab (Remicade) is effective for inducing and maintaining clinical remission in patients with Crohn's disease (CD) and ulcerative colitis (UC).[1,2] Infliximab is a chimeric IgG1 monoclonal anti-tumor necrosis factor (TNF) antibody and is

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Abbreviations used in this paper: **ATI, antibodies to infliximab; CD, Crohn's disease; CRP, C-reactive protein; HBI, Harvey-Bradshaw Index; IBD, inflammatory bowel disease; IQR, interquartile range; PMS, partial Mayo score; QALY, quality adjusted life years; TC, trough concentration; TNF, tumor necrosis factor; UC, ulcerative colitis.**

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administered as an intravenous infusion with weight-based dosing (5 mg/kg) and a regimen that includes an induction phase (intravenously at weeks 0, 2, and 6) followed by maintenance treatment (intravenously every 8 weeks) in responder patients.[3] Despite its proven efficacy, up to 60% of patients with an initial response later experience secondary loss of response requiring dose escalation or a switch to another TNF antagonist to recapture response.[4,5] Loss of clinical benefit can be due to increased clearance of the drug in the presence or absence of antibodies to infliximab (ATI).[6–8] Cohort studies and post-hoc analyses showed that serum infliximab trough concentrations (TCs) are correlated with clinical response, clinical remission, and mucosal healing in patients with IBD.[9–12] In general, low infliximab TCs and the presence of ATI are associated with worse clinical outcomes and an infliximab TC within the interval of 3–7 μg/mL during maintenance therapy correlated with sustained clinical outcomes.[11–15] TNF antagonists account for a large part of the health care costs of IBD.[16] Decreasing the drug in patients with supra-optimal TCs would lead to important cost savings and potentially also to fewer adverse events.[17] Stratified dosing based on therapeutic drug monitoring has not yet been evaluated prospectively.

Our aim was to compare the efficacy, cost-effectiveness, and safety of concentration-based dosing to clinically based dosing of infliximab in a cohort of CD and UC responder patients treated with infliximab maintenance therapy, that is, the Trough Concentration Adapted Infliximab Treatment (TAXIT) randomized controlled trial.

Methods

Design Overview

This randomized controlled trial was conducted at the University Hospitals Leuven, an academic and tertiary referral center from August 2011 to April 2013. The protocol was approved by the Institutional Review Board (ClinicalTrialsRegister.eu number, 2011-002061-38). All patients provided written informed consent.

Setting and Participants

Eligibility criteria included age of at least 18 years and a diagnosis of moderate-to-severe CD or UC confirmed by endoscopy and histology. Patients needed to be treated with maintenance infliximab therapy for at least 14 weeks and needed to be in stable clinical response. Stable clinical response was assessed by the treating physician and defined as being symptom-free (full responder) or having clear clinical improvement with an obvious decrease of disease activity, but with clinical symptoms still present (partial responder). Stable doses of concomitant immunomodulators were permitted (azathioprine or methotrexate) when initiated before the study, oral corticosteroids were allowed at a low dose if kept stable throughout the study. At screening, the infliximab dosing regimen was allowed to differ from the standard dosing regimen of 5 mg/kg every 8 weeks (eg, because of previous secondary loss of response in patients in whom response was restored). Patients who were on a nonstandard higher dosing regimen because of secondary loss of response to infliximab therapy at the time of screening were ineligible and patients with ATI >8 μg/mL equivalents, which was previously shown to be a clinically relevant cut-off.[7]

Randomization and Intervention

Upon inclusion, we randomly assigned patients (1:1) to receive clinically based or concentration-based dosing of infliximab during the maintenance phase. All patients were first dose optimized to have an infliximab TC within the interval of 3–7 μg/mL (optimization phase) according to the TAXIT algorithm (Figure 1). Individual infliximab TCs were evaluated at each infusion and the dosing regimen was changed for the next infusion according to the algorithm, until

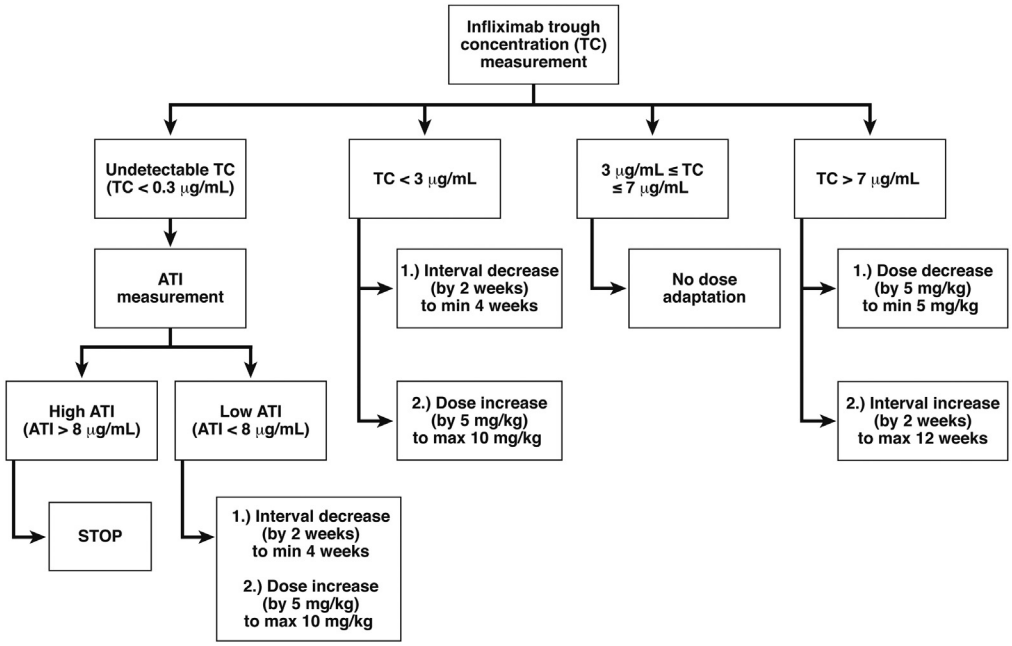

Figure 1. TAXIT algorithm based on infliximab TC and ATI to achieve infliximab TC of 3–7 μg/mL. max, maximum; min, minimum. ATI are μg/mL expressed in equivalents.