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Actual Anti-TNF Trough Levels Relate to Serum IL-10 in Drug-Responding Patients With Crohn's Disease

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Background: Patients with Crohn's disease (CD) responding to anti–tumor necrosis factor (anti-TNF) show great variability in serum drug levels, even within the therapeutic range. We aimed at exploring the role of inflammatory, genetic, and bacterial variables in relation to anti-TNF through levels in CD patients.

Methods: Consecutive CD patients receiving stable doses of infliximab or adalimumab were included. Clinical and analytical parameters were recorded. Cytokine response, bacterial DNA translocation, and several immune-related genes' genotypes were evaluated, along with serum through anti-TNF drug levels. A linear regression analysis controlled by weight and drug regimen was performed.

Results: One hundred nineteen patients were initially considered. Five patients on infliximab and 2 on adalimumab showed antidrug antibodies in serum and were excluded. One hundred twelve patients were finally included (62 on infliximab, 50 on adalimumab). Fourteen patients on infliximab and 15 on adalimumab (22.6% vs 30%, $P = 0.37$) were receiving an intensified drug regimen. C-reactive protein (CRP), fecal calprotectin, Crohn's Disease Activity Index, leukocyte count, and albumin levels in plasma were not significantly associated with infliximab or adalimumab levels in the multivariate analysis. Serum interleukin-10 (IL-10) levels were directly related to infliximab (Beta = 0.097, $P < 0.0001$) and adalimumab levels (Beta = 0.069, $P = 0.0241$). The best multivariate regression model explaining the variability of serum infliximab and adalimumab levels included IL-10. Predicted drug levels by this model robustly fitted with actual drug levels ($R^2 = 0.841$ for infliximab, $R^2 = 0.733$ for adalimumab).

Conclusion: Serum IL-10 is significantly related to serum anti-TNF levels in CD patients, showing how the disposition of anti-TNF drugs is significantly influenced by the degree of immunological activation.

Key Words: Crohn's disease, infliximab, adalimumab, interleukin 10, inflammation

INTRODUCTION

Anti–tumor necrosis factor (anti-TNF) therapy has been a major advance of the last 2 decades in the treatment of patients with Crohn's disease (CD). Anti-TNF induces and maintains remission in patients with moderate to severe luminal or fistulizing Crohn's disease that is refractory to conventional immunosuppressive therapy.[1–3]

Along with the use of this drug, safety and efficacy data from a vast number of patients have been recorded. From this experience, safety issues have emerged related to the increased risk of infections or cancer in some cohorts.[4–6] In terms of efficacy, therapy with anti-TNF is useful in approximately two-thirds of CD patients, whereas 13%–40% of patients show primary loss of response and 10%–20% show secondary loss of response.[7–10]

The mechanisms underlying loss of response are multifactorial and include disease characteristics (phenotype, location, severity), drug metabolism (pharmacokinetics, pharmacodynamic, immunogenicity), and treatment strategy (dosing regimen).[11–15] These factors, among others, have pushed the need for evaluating serum drug levels in IBD patients[16–18] as an effort toward finding an objective tool useful to guide a safer and more efficient anti-TNF therapy. However, the pharmacokinetics variability observed in many different studies keeps this topic under constant discussion.[19, 20]

Our group has described the frequent presence of bacterial translocation in CD patients, along with the value of bacterial DNA (bactDNA) detection as an independent risk