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ORIGINAL ARTICLE—ALIMENTARY TRACT

Anti-TNF-alpha loss of response is associated with a decreased percentage of FoxP3+ T cells and a variant *NOD2* genotype in patients with Crohn's disease

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Abstract

Background Anti-TNF-α therapies interact with the tolerogenic response in patients with Crohn's disease, modulating inflammation. However, drug levels and the genetic background may affect this interaction.

Methods Patients with Crohn's disease in remission on biologic monotherapy were enrolled in this study. FoxP3+ lymphocytes, *NOD2* genotype, serum cytokine, anti-TNF-α levels, and anti-drug antibodies were evaluated. Regulatory T cell response to infliximab was evaluated in vitro.

Results Fifty-seven patients were included. Thirty-nine patients (68.4 %) were receiving non-intensified biologic therapy whereas 18 patients (31.6 %) were under an intensified biologic schedule due to loss of response. Eleven intensified patients (61.1 %) showed a variant *NOD2* genotype vs 9 on non-intensified biologics (23 %, $p < 0.01$). Percentage of FoxP3+ T cells and serum free anti-TNF-α levels were significantly higher in patients with a wild-type vs variant *NOD2* genotype, either under non-intensified or intensified schedule. Increasing amounts of infliximab significantly increased the expression of FoxP3+ T cells and anti-TNF-α levels in the supernatant from wild-type *NOD2* patients cultured cells whereas the induction of FoxP3+ T cells and anti-TNF-α levels in the supernatant from variant *NOD2* patients cultured cells were significantly lower. TNF-α and IL-10 showed a correlation with the FoxP3+ T cell population percentage and serum levels of anti-TNF-α, irrespective of *NOD2* genotype. Eight variant *NOD2* patients (66.6 %) vs 4 wild-type *NOD2* patients (8.8 %) showed a perianal phenotype ($p = 0.01$). A significant reduction of the percentage of FoxP3+ T cells and serum levels of anti-TNF-α was observed in patients with the associated perianal disease.

Conclusion Anti-TNF-α loss of response is associated with a decreased percentage of FoxP3+ T cells and a variant *NOD2* genotype in patients with CD.

Keywords Crohn's disease · FoxP3+ regulatory T cells · Anti-TNF-alpha · *NOD2*

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Introduction

The etiology of Crohn's disease (CD) is multifactorial and includes aspects regarding the interaction between the host