

# 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- $\alpha$  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- $\alpha$  levels, and anti-drug antibodies were evaluated. Regulatory T cell response to infliximab was evaluated in vitro.

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**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- $\alpha$  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- $\alpha$  levels in the supernatant from wild-type *NOD2* patients cultured cells whereas the induction of FoxP3+ T cells and anti-TNF- $\alpha$  levels in the supernatant from variant *NOD2* patients cultured cells were significantly lower. TNF- $\alpha$  and IL-10 showed a correlation with the FoxP3+ T cell population percentage and serum levels of anti-TNF- $\alpha$ , 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- $\alpha$  was observed in patients with the associated perianal disease. **Conclusion** Anti-TNF- $\alpha$  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*

## Introduction

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