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ORIGINAL ARTICLE

# Outcome after a dose ''de-intensification'' strategy with anti-TNF drugs in patients with Crohn's disease

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**KEYWORDS**
Crohn's disease;
De-intensification;
Loss of response;
Tumour necrosis factor;
Infliximab;
Adalimumab

**Abstract**
*Background:* Dose ''intensification'' is a recommended strategy to recover therapeutic benefit in Crohn's disease (CD) patients who have lost initial response to anti-TNF therapy. Once patients have achieved remission, dose ''de-intensification'' can be used for cost and safety reasons.
*Objectives:* The primary aim of this study was to evaluate the long-term durability of remission after stepping down anti-TNF therapy. The secondary aim was to identify predictive factors associated with loss of response after ''de-intensification'' and to evaluate the effectiveness of a second ''re-intensification'' in patients who lost response after the treatment was stepped down.
*Methods:* We evaluated CD patients who received at least one standard anti-TNF dosage after achieving remission with ''intensified'' anti-TNF therapy.
*Results:* Twenty-four patients were included. The treatment was ''intensified'' because of partial response in 11 patients, loss of response in 10, and primary lack of response in 3. Eight of the 24 patients had lost response after a median follow-up of only 7 months after ''de-intensification'' of the anti-TNF therapy. The anti-TNF drug was ''intensified'' again in all 8 patients. Three patients did not respond to the new ''intensification'', two had partial response

*Abbreviations:* TNF, tumor necrosis factor alpha; CD, Crohn's disease; HBI, Harvey–Bradshaw index; 95% CI, 95% confidence interval.

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and three achieved remission. On univariate analysis, no predictive factors were identified for loss of response after treatment ''de-intensification''.
*Conclusions:* After only 7 months of follow-up, one-third of the CD patients who received ''de-intensification'' therapy lost response; of these, two-thirds did not achieve response after subsequent ''re-intensification''.


**PALABRAS CLAVE**
Enfermedad de Crohn;
Desintensificación;
Pérdida de respuesta;
Factor de necrosis tumoral;
Infliximab;
Adalimumab

**Resultado después de una dosis ''desintensification'' estrategia con medicamentos anti-TNF en pacientes con enfermedad de Crohn**

**Resumen**
*Antecedentes:* La ''intensificación'' del tratamiento anti-TNF podría ser una opción terapéutica en los pacientes con enfermedad de Crohn (EC) pierden la respuesta inicial a la dosis estándar. Una vez que los pacientes alcanzan de nuevo la remission podría plantearse la ''desintensification'' del tratamiento por motivos de costs y seguridad.
*Objetivos:* Primario evaluar la duración de la remisión a largo plazo tras la ''desintensificación'' del tratamiento anti-TNF. Secundario: Identificar los factores predictivos de recidiva tras la ''desintensification'' y evaluar la eficacia de una nueva ''intensificación'' en los pacientes que recidivaron tras la ''desintensificación'' del tratamiento.
*Métodos:* Se incluyeron pacientes con EC que recibieron al menos una dosis estándar de tratamiento anti-TNF después de alcanzar la remisión con el tratamiento ''intensificado''.
*Resultados:* Veinte y cuatro pacientes fueron incluidos. El tratamiento se ''intensificó'' por respuesta parcial en 11 pacientes, por pérdida de respuesta en 10 y por falta de respuesta primaria en 3. Ocho de los 24 pacientes perdieron respuesta después de una mediana de 7 meses de seguimiento tras la ''desintensification'' del anti-TNF. El tratamiento anti-TNF se ''intensificó'' de nuevo en los 8 pacientes. Tres de ellos no respondieron a la nueva ''intensificación'', 2 presentaron una respuesta parcial y 3 alcanzaron de nuevo la remisión. No se identificaron factores predictivos de recidiva después de la ''desintensificación'' del tratamiento.
*Conclusiones:* Después de sólo 7 meses de seguimiento, un tercio de los pacientes con EC en los que se ''desintensificó'' el tratamiento anti-TNF perdió la respuesta; dos tercios de ellos no lograron respuesta tras la ''re-intensificación''.


## Introduction

Tumour necrosis factor α (TNF) plays a pivotal role in the pathogenesis of several chronic inflammatory disorders such as Crohn's disease (CD), ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis or psoriasis. Anti-TNF drugs act by controlling inflammation through different mechanisms. Both infliximab and adalimumab are anti-TNF drugs; they bind specifically to TNF, preventing it to attach to specific receptors. Both have been proved to be effective in CD.[1–4]

Although infliximab and adalimumab are initially effective in a high proportion of patients, approximately 40% of patients treated with a maintenance regimen may lose the therapeutic response over time.[5–7] For patients who lose their initial response, consideration can be given to ''dose intensification'' to regain therapeutic benefit. Dose ''intensification'' can be achieved by increasing the infliximab dose from 5 mg/kg to 10 mg/kg every 8 weeks or by decreasing the interval between infusions to every 4 weeks or both; Adalimumab dose is ''intensified'' administering the drug every week instead of every other week.[5–8]

Efficacy of anti-TNF drug dose ''intensification'' to overcome loss of response in CD patients is high: in the ACCENT I study, increasing the infliximab dose to 10 mg/kg restored response in 90% of the patients with luminal CD who lose response to 5 mg/kg.[1] Furthermore, approximately 80% of patients who lost response while on 10 mg/kg every 8 weeks regained response after increasing the dose to 15 mg/kg.[1] Although there is less information available, similar figures have been reported with adalimumab: in the CHARM study, 45% of patients who lost response regained remission after increasing the dosage of adalimumab from 40 mg each-other-week to 40 mg weekly.[9]

There are both safety and economic concerns with this intensive treatment regimen in the long-term. Therefore, ''desintensification'' – the administration of the initial standard dose of anti-TNF – could be considered in patients who achieve remission with the ''intensified'' regimen. However, predictive factors of relapse after the ''desintensification'' of the treatment have not been identified. Therefore, it has not been established the group of patients that could benefit from the ''desintensification'' of the anti-TNF therapy. Furthermore, data on the durability of remission after ''desintensification'' of therapy are scarce.

The aim of the present study was to evaluate the long-term durability of remission after stepping down the anti-TNF treatment, in patients who achieved clinical