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Adalimumab for Crohn's disease: Long-term sustained benefit in a population-based cohort of 438 patients☆

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Abstract

Background and aims: Adalimumab is an effective therapy for induction and maintenance of Crohn's disease. However, results in clinical trials don't necessarily reflect daily clinical practice. Therefore, we assessed real-life long-term clinical response to adalimumab in a large population-based cohort and identified clinical parameters affecting response

Methods: All consecutive patients in North-Holland that started adalimumab between 2003 and 2011 were included, of which medical charts were reviewed. Response to induction therapy was assessed after 3 months. Sustained benefit of maintenance therapy was calculated from Kaplan–Meier survival tables depicting ongoing adalimumab treatment. Regression analyses were performed to identify factors predicting response to adalimumab therapy.

Abbreviations: OR, odds ratio; HR, hazard ratio; CI, confidence interval; TNF, tumour necrosis factor; CDAI, Crohn's Disease Activity Index; IBD, inflammatory bowel disease; CRP, C-reactive protein; SD, standard deviation; IQR, interquartile range; IFX, infliximab.

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Results: In total 438 Crohn's patients started adalimumab with 92.5% response to the induction phase. After 1 year 83.3% showed sustained benefit of maintenance treatment, followed by 74.0% after 2 years. Nevertheless, one third of patients were in steroid-free remission at the end of their follow-up. Response to induction was negatively affected by longer disease duration (OR 1.05; $p < 0.01$) and strictures (OR 3.73; $p = 0.04$). Increased CRP levels predicted higher rates of initial response (OR 0.31; $p < 0.01$). Concomitant thiopurines in the first 6 months of adalimumab treatment decreased the risk to fail maintenance therapy (HR 0.69, $p = 0.05$). Previous infliximab therapy did not affect response to adalimumab, however dose escalation was more often deemed necessary ($p < 0.01$).
Conclusion: Adalimumab was successful in the majority of patients, with 10% loss of response per subsequent year. Concomitant thiopurines might improve adalimumab maintenance treatment.

1. Introduction

In clinical trials adalimumab has been shown to be an effective therapy for remission induction and maintenance of moderate to severe Crohn's disease.[1,2] After a year, response to adalimumab was shown in 72% of patients, however complete remission was achieved in only 36–46% of patients.[1,3] This humanized antibody is directed against the pro-inflammatory cytokine tumour necrosis factor (TNF). Infliximab, a chimeric antibody, was the first anti-TNF available for Crohn's disease to show rapid improvement of symptoms, complete remission with endoscopic healing in almost half of Crohn's patients and a decreased need for surgery.[4–8] Both infliximab naive patients, as well as patients with primary or secondary loss of response to infliximab showed a beneficial response to adalimumab.[1,9–11] However, the GAIN trial, specifically designed to address the issue of response to adalimumab in infliximab failures, showed an absolute difference in remission induction of only 14% compared to placebo.[12] Clinical trials usually represent a subset of patients, since patients with high disease activity or significant co-morbidity do not meet inclusion criteria for participation. Furthermore, clinical trials use complex disease activity scores such as the Crohn's Disease Activity Index (CDAI), whereas in clinical practice we observe an extensive variability in symptoms and endoscopic lesions.[13] Therefore, the decision to commence, maintain, or discontinue medical treatment is usually based on the global physician's assessment, which constitutes a composite of symptoms, laboratory values, as well as endoscopic assessment. Hence, data from clinical trials cannot be directly extrapolated into daily clinical practice, and therefore, real-life data on efficacy and influential factors are essential to counsel a diverse population of Crohn's disease patients and improve treatment strategies. Since adalimumab was first introduced in 2003 and registered in 2007, long-term daily practice data on therapy response are still scarce. The aim of the present study was to assess long-term response to adalimumab in a large population-based cohort reflecting real-life daily clinical practice. Furthermore, we set out to identify clinical parameters affecting response to adalimumab.

2. Materials and methods

2.1. Study subjects

This retrospective cohort comprised all Crohn's patients who started adalimumab treatment in North Holland since its introduction in 2003. North Holland is a province of The Netherlands with 2.7 million inhabitants (20% of the Dutch population), with 18 hospitals including 2 tertiary referral centres and 16 regional hospitals. All hospitals were members of the so-called North Holland GUT club (Society of Gastroenterologists of North Holland). Each hospital could identify their patients ever starting adalimumab, through the records of the sole distributor of adalimumab in The Netherlands. Since adalimumab was introduced in 2003 in clinical trials, patients with a potential placebo treatment were excluded from this cohort. Furthermore, patients under treatment but with insufficient documented follow-up were excluded, since the outcome of adalimumab therapy could not be ascertained in these patients. Also patients with unclassified inflammatory bowel disease (IBD-U) or ulcerative colitis, diagnosed by the usual clinical, endoscopic and histological criteria [14] were excluded. If patients were referred to other hospitals or were otherwise lost to follow-up, they were censored at the date of last contact.

2.2. Data collection

All medical records were reviewed between January and May 2011 by two investigators (CPP and FMT). From all medical charts the following variables were recorded in a standardized manner using an Access database, which complied with the patient data protection act regulations: patient demographics, disease specific factors, Montreal classification,[15,16] duration of adalimumab therapy, imaging results within 3 months before adalimumab therapy (such as strictures reported on MRI or during colonoscopy), C-reactive protein (CRP) levels before and during treatment, and type of hospital (tertiary referral centre or regional hospital). Furthermore, methotrexate and thiopurines were considered to be concomitant immunosuppressive therapies. Both budesonide and prednisone were noted as concomitant steroids. Concomitant immunosuppressive therapies and steroids were assessed for the 6 months preceding start of adalimumab, the first 6 months of adalimumab therapy, and the subsequent 6 to 12 months of adalimumab treatment. Crohn's disease behaviour, noted to be the indication to start adalimumab therapy, was classified as luminal, fistulizing, both luminal and fistulizing or extra-intestinal activity. For patients who were previously treated with infliximab, treatment duration and the reason to cease infliximab were documented. Adalimumab therapy is initiated by a remission induction phase (160 mg and 80 mg

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