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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

2 weeks later), followed by maintenance therapy of 40 mg every other week. If needed, dose escalation to 40 mg every week was recorded. Furthermore, the number and type of surgical interventions before and after start of adalimumab were assessed. From medical charts, all adverse events noted since the start of adalimumab were recorded. Permission to review medical charts was obtained from all 18 hospital's Medical Ethical Committees.

2.3. Endpoints and definitions

The primary endpoint of this study was long-term clinical response to adalimumab therapy. Clinical response was defined as ongoing adalimumab treatment at the end of follow-up or intended discontinuation whilst in remission or due to pregnancy wish. Response to the induction phase was assessed after 3 months of adalimumab treatment. When adalimumab was continued after 3 months, response to induction was considered to be favourable. In contrast, discontinuation of therapy within 3 months, due to adverse events or insufficient response, was recorded as failure of induction therapy. Patients continuing maintenance therapy after a favourable response to induction therapy were included for analyses on sustained benefit of maintenance therapy.

Moreover, with regard to a more stringent read-out for therapy efficacy, the number of patients in steroid-free remission at the end of their follow-up was assessed. This read-out is of importance since patients starting to lose response to adalimumab may have started concomitant steroid treatment and thereby clinical response may be overestimated. Steroid-free remission was achieved when patients were in clinical remission according to the global physician's assessment without concomitant steroids at the end of follow-up. Clinical remission was defined as complete cessation of diarrhoea, abdominal pain and closure of all draining fistulae. The global physician's assessment on clinical remission was retrieved from medical charts. In case of uncertainty, the treating physician was consulted to ascertain agreement of outcome. To correct for length of follow-up, steroid-free remission is shown per category of follow-up: until 1 year; 1 to 3 years; and 3 to 6 years of follow-up. Furthermore, the influence of adalimumab therapy on the subsequent need for abdominal surgeries was investigated. Moreover, all adverse events occurring since the start of adalimumab and documented in medical charts were assessed.

The secondary endpoints were concomitant medication, the need for dose-escalation, and identification of clinical parameters affecting response. The need for dose-escalation was at the discretion of the treating physician. Parameters affecting response to the initial phase of adalimumab were assessed separately from the maintenance phase. To assess the influence of treatment strategies, the hospital setting (tertiary referral centres versus regional hospitals) was investigated. Furthermore the influence of treatment period was investigated. Two treatment periods were compared: the first 5 years of adalimumab treatment (2003–2007) and the subsequent years (2008–2011). CRP levels were considered to be elevated above 5 mg/L.

2.4. Statistical analysis

Descriptive statistics were reported as frequencies and percentages (%). Normally distributed variables were presented as mean with standard deviation (SD), whereas skewed variables were presented as median with interquartile range (IQR). Categorical characteristics were compared by the Chi-square test, and continuous characteristics were compared using Student's t test. Kaplan–Meier analysis was used to determine adalimumab ongoing therapy. From survival tables, the 1- and 2-year clinical response (total cohort of 438 patients) and sustained benefit of maintenance therapy (405 patients with response to induction therapy) were calculated. The numbers of abdominal surgical interventions before and after adalimumab therapy were compared by non-parametric bootstrap analysis. With this method, samples of the same size as the original data set were drawn by sampling with replacement from the observed data. A bootstrap analysis with 1000 replications was performed to obtain distribution of surgical rate differences. From these bootstrapped distributions the 95%CI and *p*-values were calculated. Logistic regression analyses were performed to identify factors predicting failure of initial response. Results are presented as odds ratio (OR) for failure with 95% confidence intervals (95%CI). Cox proportional hazards regression analyses were performed to identify factors predicting failure of response to maintenance therapy. Results are presented as hazard ratio (HR) for failure with 95%CI. All variables with a *p*-value below 0.10 in univariate analysis were included in multivariate analysis. CRP levels at the start of therapy were not obtained for all patients. Similarly, only a subgroup underwent imaging before start of adalimumab. Therefore analyses on CRP levels and presence of strictures as predictive factors of response were performed in subgroups. *p*-Values below 0.05 were considered statistically significant. Data were analysed with SPSS® software version 19.0 (SPSS Inc., Chicago, IL, USA), STATA version 11.2 (STATA Corp. LP, College Station, TX, USA) and statistical software from the R-project for bootstrap.[17]

3. Results

3.1. Patient characteristics

In total, 504 IBD patients received at least 1 dose of adalimumab between 2003 and 2011. Thirty patients were excluded due to insufficient data to ascertain the outcome. Furthermore, 36 patients were excluded due to a diagnosis of ulcerative colitis or IBD-U. The final cohort thus comprised 438 patients (65.3% female) of whom demographics and clinical parameters are listed in Table 1. At the start of treatment, patients had a mean age of 38.5 years (SD 11.9), and median disease duration of 9.4 years (IQR 5.1–17.3). The median follow-up after the start of adalimumab treatment was 2.0 years (IQR 1.1–2.7). The majority of patients started adalimumab therapy for active luminal disease (69.6%), 12.6% for fistulizing disease, 14.2% for both luminal and fistulizing disease and 3.7% for extra-intestinal disease activity.

3.2. Clinical response to adalimumab treatment

Fig. 1A depicts a Kaplan–Meier curve of ongoing adalimumab treatment in the total cohort of 438 patients. Of the 438 patients starting adalimumab 405 patients (92.5%) showed a favourable response during the induction phase. Eighteen patients (4.1%) ceased adalimumab therapy in the first 3 months of treatment due to insufficient response and 15 patients (3.4%) had to stop adalimumab within 3 months treatment due to adverse events. In total, 53 patients (12.1%) had to stop treatment due to adverse events. All adverse events since the start of adalimumab are listed in Table 2. After a favourable response to induction therapy, loss of response to maintenance therapy was reported in 17.0% of patients at the end of their follow-up. Fig. 1B depicts a Kaplan–Meier curve of ongoing adalimumab maintenance treatment, in the 405 patients who continued adalimumab maintenance therapy after a favourable initial response. The subsequent estimated sustained benefit of maintenance therapy after 1 year was 83.3% (95%CI 79.6–87.0), followed by 74.0% (95%CI 69.1–78.9) after 2 years of therapy.

Steroid-free remission at the end of follow-up was achieved in 20.3% of patients with a follow-up length up to 1 year. Furthermore, in the subgroup of patients with a follow-up between 1 and 3 years, 31.6% of patients were in steroid-free remission, succeeded by 40.4% of patients with 3 to 6 year follow-up. The number of abdominal surgical interventions did not differ before or after adalimumab therapy for the 405 patients on maintenance treatment (before 8.00/100 patient years; after 9.34/100 patient years; 95%CI: −1.29–3.88; $p = 0.31$).

Table 1 Patient demographics.

Patient demographics of the total cohort ($n = 438$)	
Gender (% female)	65.3
Age at start of adalimumab (mean years, ±SD)	38.5 (± 11.9)
Disease duration at start (median years, IQR)	9.4 (5.1–17.3)
Montreal classification[a] *(%)*	
Age at diagnosis: A1/A2/A3	13/76/11
Location of disease activity: L1/L2/L3/L4	25/28/47/9
Disease behaviour: B1/B2/B3/p	53/24/23/37
Extra intestinal manifestations (%)	
Arthralgia	44
Cutaneous	13
Uveitis/conjunctivitis	5
Oral aphthous lesions	4
Surgeries before start (%)	
Small bowel resections	34
Large bowel resections	21
Perianal surgeries	21
Strictureplasty	6
Concomitant medication (%)	
Thiopurines[b]	
- Continuation of previous treatment	28
- Only during first 6 months adalimumab	11
- Initiation after 6 months adalimumab	2
Steroids[c]	
- Continuation of previous treatment	20
- Only during first 6 months adalimumab	11
- Initiation after 6 months adalimumab	3
Methotrexate	
- Continuation of previous treatment	7
- Only during first 6 months adalimumab	3
- Initiation after 6 months adalimumab	2
Previous infliximab therapy (%)	62 (total)
Successful infliximab	7
Failure of infliximab	52
- Primary nonresponse	7
- Loss of response	20
- Adverse events	25
Outcome unknown	3

[a] Montreal classification:- Age at diagnosis: A1: <17 years, A2: 17–40 years, and A3: >40 years;- Maximal location of disease: L1: ileal, L2: colonic, L3: ileocolonic, and L4: upper disease;- Maximal disease behaviour: B1: non-stricturing, non-penetrating, B2: stricturing, B3: penetrating, and p: perianal disease.
[b] Thiopurines: azathioprine/6-mercaptopurine/6-thioguanine.
[c] Steroids: prednisone/budesonide.

3.3. Concomitant medication

Steroids were used by 138 patients prior to the start of adalimumab, which was discontinued in 52 patients in the first 6 months of adalimumab treatment and in 54 patients in the subsequent 6 to 12 months of adalimumab treatment. 30 patients had to commence steroids in the first 6 months. Prior to the start of adalimumab, thiopurines were used by 179 patients (40.9%), of whom 124 patients continued in the first 6 months of adalimumab therapy. Concomitant thiopurine therapy was initiated in 32 patients in the first 6 months of adalimumab treatment.

3.4. Dose escalation

Up to 40% of patients needed dose escalation during their course of adalimumab treatment, after a median period of 5.7 months (IQR 2.8–13.6). Dose escalation was more often deemed necessary in patients previously treated with infliximab than for infliximab-naïve patients (49.8% and 26.8%, $p < 0.01$). This association did not reflect longer disease duration in patients previously treated with infliximab (data not shown).

3.5. Clinical parameters affecting response to adalimumab

Other than disease duration (univariate analysis only) (Table 3), none of the parameters investigated affected response to induction therapy. A longer duration of disease before the start of adalimumab increased the risk to fail induction therapy (OR 1.05; 95%CI 1.02–1.09, $p < 0.01$). In 197 patients, imaging was performed within 3 months before the start of adalimumab treatment. In this subgroup, univariate analysis showed that intestinal strictures were associated with an increased risk to fail induction therapy (OR 3.73; 95%CI 1.07–12.92, $p = 0.04$). CRP levels before the start of therapy were obtained from 344 patients. In multivariate analysis, patients with higher CRP

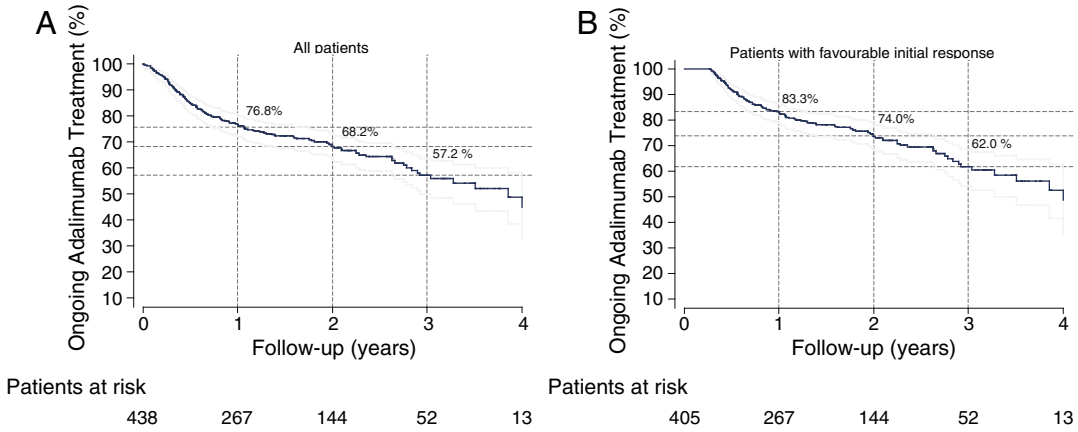

Figure 1 Kaplan–Meier curves of ongoing adalimumab treatment. A) Clinical response is depicted in a Kaplan–Meier curve of ongoing adalimumab treatment in the total cohort of 438 Crohn's patients. Calculated from survival tables, clinical response of the total cohort was observed in 76.8% of patients after 1 year, followed by 68.2% after 2 years and 57.2% after 3 years. B) Clinical response to maintenance treatment is depicted in a Kaplan–Meier curve of ongoing adalimumab treatment, only for the 405 patients with initial response during the first 3 months of adalimumab therapy. Sustained benefit of maintenance treatment was present in 83.3%, 74.0% and 62.0% of patients after 1-, 2-, and 3-years respectively.

levels were more likely to respond to the induction therapy (OR 0.40, 95%CI 0.17–0.91, $p = 0.03$).

Regarding maintenance therapy, only concomitant thiopurines in the first 6 months of adalimumab therapy decreased the risk of failure in multivariate analysis (HR 0.69, 95%CI 0.48–0.99, $p = 0.05$) (Table 4 and Kaplan–Meier curves in Fig. 2). Both patients that were using thiopurines prior to adalimumab and continued thiopurines, and patients who commenced thiopurines in the first 6 months of adalimumab were included in this analysis. Two hundred and seventy patients (61.6%) were previously treated with infliximab (Table 1). The median time between last infliximab infusion and start of adalimumab was 2.7 months (IQR 0.6–19.5). Previous failure to infliximab did not influence adalimumab maintenance therapy, as is depicted in Fig. 3. Though treatment strategies could differ between tertiary referral centres and regional hospitals, this did not influence response to adalimumab therapy. Regression analyses on parameters affecting response in the total cohort of 438 patients showed similar results as the 405 patients with maintenance treatment (data not shown).

4. Discussion

This study is one of the first real-life large population-based multi-centre cohort studies on long-term adalimumab response in Crohn's disease patients. Response to the induction phase was favourable in the vast majority (>90%) of patients, and of these patients 83% experienced sustained benefit of maintenance therapy after one year of treatment, with 10% loss of response per subsequent year. Nevertheless, concomitant steroids were deemed necessary in approximately a third of patients. Elevated CRP levels were associated with higher rates of response to induction therapy, whereas the presence of strictures and longer disease duration were more frequently associated with failure of response to the induction phase of adalimumab treatment. Concomitant use of thiopurines in the first 6 months of adalimumab predicted an improved outcome of maintenance therapy. Notably, previous treatment with infliximab did not affect response to adalimumab, however dose escalation was more frequently deemed necessary.

A recent retrospective Belgian cohort described an initial response to the remission induction phase in 84% of patients, with 71% failure-free survival of the total cohort after 14 months.[18] Similar analysis in the present population-based Dutch cohort showed a comparable failure-free survival of about 70% after 14 months. However, previous smaller retrospective series described somewhat lower rates of response to adalimumab.[19–21] In the present cohort several factors were identified to affect response to adalimumab. Concomitant thiopurine treatment in the first 6 months of adalimumab therapy was significantly associated with higher rates of maintenance therapy. This finding is in accordance with previous smaller cohort studies suggesting that concomitant thiopurines decrease the probability for adalimumab dose escalation and loss of response,[20,22,23] especially in the first 6 months of treatment.[24] Interestingly, the majority of patients did not start thiopurines in the first 6 months of adalimumab treatment, but continued previous thiopurine therapy. In line with this finding, a nationwide Dutch pharmacotherapeutic study including 2685 patients revealed that concomitant thiopurine treatment was indeed associated with a lower risk of adalimumab discontinuation.[25] One explanation could be that the induction phase of adalimumab is more effective with concomitant thiopurines that are continued in the first 6 months of therapy, resulting in a reduced inflammatory load, which could maintain remission of disease. In contrast with this beneficial effect of combination therapy, the risk of infections or other adverse events should be taken into account in the treatment of each individual patient. For infliximab, the SONIC trial confirmed superiority of concomitant thiopurines to infliximab monotherapy for the induction of steroid-free remission.[4] As for randomised

Table 2 Adverse events reported since the start of adalimumab treatment (n = 438).

	(n)	(%)
General events	103	23.5%
Oedema	13	2.9%
Arthralgia/myalgia	9/8	3.8%
Migraine/headache/ dizziness/nausea	2/9/6/ 6	5.2%
Fatigue and malaise	8	1.8%
Dyspnoea	7	1.6%
Loss of vision/loss of taste	4/1	1.1%
Paresthesia extremities	6	1.4%
Dysmenorrhoea	4	0.9%
Others present in less than 3 patients per event [a]	20	4.6%
Skin reactions	93	21.2%
Skin rash/injection site reaction	30/12	9.6%
Itching/injection pain/ fear of injection	12/8/1	4.7%
Hair loss/alopecia areata	8	1.8%
New eczema/increased eczema	16/3	4.3%
Lichen simplex/M. Andrews-Barber/ lupus like reaction	1/1/1	0.7%
Infections	90	20.5%
Upper respiratory tract infections or sinusitis	17	3.9%
Skin infection/cartilage inflammation/toxic dermatitis	15/2/3	4.6%
Fever episodes	7	1.6%
Pneumonia/pleural TBC	6/1	1.6%
Arthritis/psoriatic arthritis/ tendinitis/coxitis	1/1/1/ 2	1.1%
Shigella/salmonella enteritis	1/1	0.5%
Herpes zoster/warts	5/2	1.6%
Fungal infection: skin/oral/ oesophagus/vagina	1/3/1/ 2	1.6%
Eye infection/stromal herpes keratitis	2/1	0.7%
Gingivitis/periodontitis	2/2	0.9%
Urinary tract infection/other infectious AE unknown	5/3	1.8%
Others present in one patient [b]	3	0.7%
Malignancies during ADA treatment, relation unknown	7	1.6%
Prostate carcinoma	1	0.2%
Cervical cancer	1	0.2%
Dysplasia cervix with human papillomavirus	1	0.2%
Basal cell carcinoma	1	0.2%
Mantle cell lymphoma (†)	1	0.2%
Possible dysplastic naevi	1	0.2%
Giant cell tumour of the wrist	1	0.2%

† Patient died.

[a] Dysmenorrhoea, insomnia, lymphopenia, palpitations or tachycardia, abnormal liver test, swollen lymph nodes, hypertension, increase hay fever, erectile dysfunction, striae, jaw pain, fainting, increase in weight, obstinate behaviour, chest pain, and poor wound healing.

[b] Bacteraemia with central line present, auto-immune hepatitis, and endocarditis (group B streptococcus).

Table 3 Clinical parameters affecting response to the induction phase of adalimumab treatment (n = 438).

Univariate analysis	OR for failure	95%CI	p-Value
Gender (female)	0.80	0.39–1.66	0.56
Disease duration (years)	1.05	1.02–1.09	<0.01
Age at diagnosis (Montreal)			
A1	1.00	Reference	–
A2	0.69	0.27–1.77	0.44
A3	0.59	0.14–2.49	0.47
Location of disease (Montreal) [a]			
L1	1.00	Reference	–
L2	0.91	0.36–2.27	0.84
L3	0.66	0.28–1.57	0.35
Disease behaviour (Montreal)			
B1	1.00	Reference	–
B2	1.11	0.48–2.57	0.80
B3	0.75	0.29–1.95	0.56
Tertiary referral centre	1.19	0.58–2.47	0.63
Period of treatment	0.31	−0.68–1.29	0.54
Concomitant steroids	1.72	0.79–3.75	0.18
Concomitant thiopurines	0.66	0.30–1.45	0.30
Concomitant methotrexate	0.96	0.28–3.30	0.95
Previous infliximab	0.93	0.44–1.95	0.84
Previous surgeries	1.52	0.72–3.22	0.27
Strictures at imaging [b]	3.73	1.07–12.92	0.04
CRP level >5 mg/L at start of adalimumab treatment [c]	0.31	0.14–0.71	<0.01
Multivariate analysis	**OR for failure**	**95%CI**	**p-Value**
Disease duration (years)	1.07	0.99–1.16	0.08
Strictures at imaging [b]	3.31	0.94–11.66	0.06
CRP level >5 mg/L at start [c]	0.40	0.17–0.91	0.03

[a] No L4 patients failed the initial phase of adalimumab in this cohort.

[b] Subgroup analyses n = 197 patients.

[c] Subgroup analyses n = 344 patients.

controlled trials on adalimumab, thus far only a post hoc analysis of the CHARM trial showed no influence of concomitant immunosuppressive treatment on adalimumab therapy, however this analysis was limited by length of follow-up and study design.[1] Hence, only prospective trials can clarify the additive effect of thiopurines on adalimumab treatment. A recent query among Amsterdam gastroenterologists revealed that most tend to prescribe or continue concomitant thiopurine therapy next to adalimumab since the results of the SONIC trial were published, which is not according to current guidelines.

The frequent use of concomitant steroids should be taken into account as a potential confounder for clinical response defined as ongoing adalimumab treatment in this cohort. Concomitant steroids may lead to an underestimation of adalimumab therapy failures. However, most patients with concomitant steroids did not commence steroids in the first 6 months of adalimumab treatment, but continued previous steroid therapy. Due to the retrospective design of this study, it is not possible to determine the exact reason for the continuation of steroids. Nevertheless, during the first year

Table 4 Clinical parameters affecting adalimumab maintenance treatment in patients with initial response to the induction phase (n = 405).

Univariate analysis	HR for failure	95%CI	p-Value
Gender (female)	1.31	0.91–1.89	0.14
Disease duration (years)	1.02	1.00–1.03	0.09
Age at diagnosis (Montreal)			
A1	1.00	Reference	–
A2	0.81	0.51–1.27	0.35
A3	0.71	0.36–1.41	0.33
Location of disease (Montreal)			
L1	1.00	Reference	–
L2	1.04	0.65–1.66	0.86
L3	1.04	0.68–1.57	0.86
L4	1.10	0.15–8.04	0.93
Disease behaviour (Montreal)			
B1	1.00	Reference	–
B2	1.24	0.82–1.86	0.30
B3	1.20	0.81–1.80	0.36
Tertiary referral centre	1.27	0.89–1.80	0.19
Period of treatment	1.34	0.88–2.04	0.18
Concomitant steroids	1.14	0.78–1.67	0.49
Concomitant thiopurines	0.69	0.48–0.99	0.05
Concomitant methotrexate	1.42	0.88–2.30	0.15
Previous infliximab	0.89	0.62–1.27	0.52
Previous surgeries	1.07	0.76–1.50	0.71
CRP level >5 mg/L at start of adalimumab treatment [a]	0.74	0.51–1.07	0.11
Multivariate analysis	**HR for failure**	**95%CI**	**p-Value**
Disease duration (years)	1.02	1.00–1.03	0.84
Concomitant thiopurines	0.69	0.48–0.99	0.05

[a] Subgroup analyses n = 315 patients.

of adalimumab treatment, most of the previous steroid users were able to stop steroids and continue adalimumab. One important endpoint in many trials describing adalimumab efficacy is steroid-free remission considering complete clinical remission without concomitant steroid use. In contrast with the high number of patients with clinical response, defined as ongoing adalimumab treatment, only about one third of patients were in steroid-free remission at the end of their follow-up. Likewise, the randomised, double-blind 1-year CHARM trial, and the 2 year open-label extension ADHERE trial showed only 38% of patients in steroid-free remission, with 75% of those patients remaining in steroid-free remission during follow-up.[26]

The present study did not reveal an increased risk to fail adalimumab after previous infliximab therapy. These findings are in contradiction with other reports where infliximab naive patients have been reported to respond better to adalimumab than those with prior infliximab treatment.[12,18,27] In our cohort, not all patients discontinued infliximab due to failure or adverse events, some patients discontinued a successful infliximab treatment episode because of achieved remission. The reason for discontinuation of infliximab was not associated with the outcome of adalimumab therapy. Notwithstanding, previous infliximab failure was associated with an increased need for adalimumab dose escalation, which confirms a recently published prospective cohort.[28] In contrast, the randomised controlled SWITCH trial showed that after a complete response to infliximab, direct elective switching to adalimumab is associated with loss of efficacy and loss of tolerance after one year.[29] Therefore elective switching should be discouraged.

The strength of this cohort is that it is population-based, because it encompassed all Crohn's patients treated with adalimumab in the catchment area of 2.7 million inhabitants of The Netherlands. A high number of patients had a non-stricturing (B1) Montreal classification of disease behaviour when compared to previous cohorts. In regression analyses

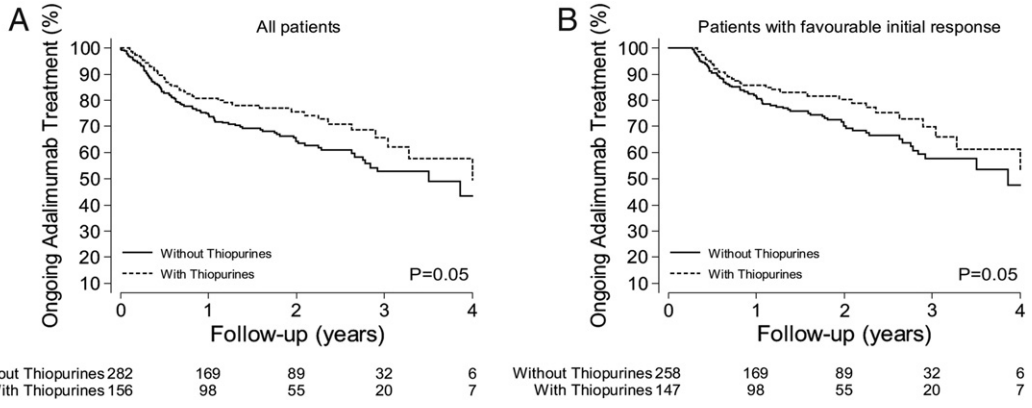

Figure 2 Kaplan–Meier curves of ongoing adalimumab stratified for concomitant thiopurine treatment. Concomitant thiopurine therapy reduced the risk of maintenance therapy failure in multivariate analysis (p = 0.05). A) Clinical response is depicted in a Kaplan–Meier curve of ongoing adalimumab treatment in the total cohort of 438 Crohn's patients, stratified for concomitant thiopurine therapy in the first 6 months of adalimumab treatment. B) Clinical response to maintenance treatment is depicted in a Kaplan–Meier curve of ongoing adalimumab treatment, only for the 405 patients with initial response during the first 3 months of adalimumab therapy. These data are stratified for concomitant thiopurine therapy in the first 6 months of adalimumab treatment.

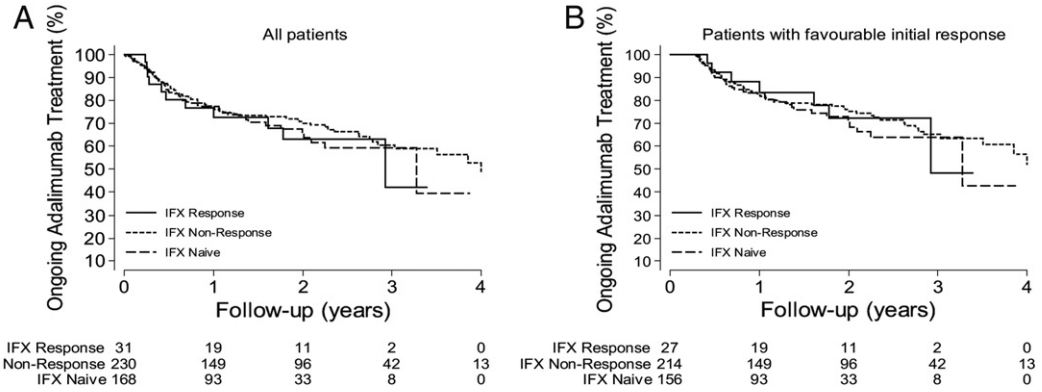

Figure 3 Kaplan–Meier curves of ongoing adalimumab stratified for previous infliximab therapy. Prior infliximab (IFX) therapy did not influence clinical response to adalimumab treatment. The reason of IFX discontinuation was unknown for 8 patients, therefore these are excluded. A) Clinical response is depicted in a Kaplan–Meier curve of ongoing adalimumab treatment in the total cohort of 438 Crohn's patients, stratified for previous infliximab. B) Clinical response to maintenance treatment is depicted in a Kaplan–Meier curve of ongoing adalimumab treatment, only for the 405 patients with initial response during the first 3 months of adalimumab therapy. These data are stratified for previous infliximab therapy.

disease behaviour did not affect response to the induction phase or maintenance phase of adalimumab treatment. Nevertheless, the lack of difference in the subsequent need for abdominal surgeries after adalimumab treatment might be partly due to the 53% B1 patients. Thus, the predictors for long-term clinical benefit, failure or surgery identified in this cohort may not be directly extrapolated to cohorts with a high percentage of patients with complicated or perianal disease. Longer disease duration was a predictor of failure of response to the initial phase of adalimumab, however only in univariate analysis. Previous smaller cohorts similarly suggested patients to have lower rates of remission and more relapses when starting adalimumab after a longer duration of disease.[30–32] The predictive value of CRP levels on disease activity and therapy response is still a subject of debate. In this study, elevated CRP levels were associated with higher rates of successful induction therapy. This may reflect a better initial response in patients with higher inflammatory disease activity, which was also shown in the CLASSIC I remission induction trial where a subgroup of patients with higher baseline CRP tended to have higher rates of remission.[2] Furthermore, elevated baseline CRP lowers the chance of treating unrecognized mere fibrostenosing disease. Other retrospective studies showed the opposite, where lower CRP levels were associated with higher rates of remission after 4 weeks, however this might represent a higher placebo response in patients with lower inflammatory load.[30] For infliximab, it has been shown that patients with higher levels of CRP respond better and early normalization of CRP levels correlates with sustained long-term response.[33]

To date, no prospective trial has compared head-to-head the efficacy of the two leading anti-TNF therapies for Crohn's disease: adalimumab and infliximab. Recently our group reported on 469 Crohn's patients with sustained benefit of infliximab in 83% after 1 year, followed by 73% after 2 years, and 62% after 3 years of maintenance therapy.[34] These figures are remarkably similar to the present adalimumab cohort, and suggest an equally sustained therapeutic benefit for both anti-TNF therapies. In contrast to the findings in the infliximab series, adalimumab did not result in a significant decrease in surgical interventions. However, it is important to consider the limiting factor of this study, i.e. the duration of 2 year follow-up in the present study in comparison with 10 years of follow-up for the infliximab cohort.

An important limitation of this study, inherent to a retrospective study, is the potential underreporting of adverse events, smoking status, and non-uniformity in assessment of outcome parameters such as the global physician's assessment. Both in prospective and retrospective trials, the assessment of therapy response is hampered by the lack of objective markers. So far, in daily clinical practice the only read-out available is the documented opinion of the treating physician and subsequent decisions that are made at the discretion of the treating physician, e.g. to stop ineffective therapy. However, the global physician's assessment is subject to considerable variation among physician's and limited reproducibility. Nevertheless, ongoing adalimumab therapy is the most valid retrospective reflection of therapy response. Moreover, in a retrospective study design it is not feasible to reliably check proper indication for starting a particular treatment, let alone differentiating an inflammatory from a fibrostenotic stricture. Hence, next to the total cohort, initial response to the induction phase, and response to the subsequent maintenance phase were described separately. Sustained benefit of maintenance therapy was analysed only in patients who continued maintenance therapy after a favourable initial response to adalimumab. Thereby, patients were excluded where there may not have been a proper indication and patients with fibrostenotic strictures (expected to benefit more from surgery than from immunomodulatory treatment) were filtered out. The large number of patients, long-term follow-up and the population based multi-centric design strengthens these data to accurately reflect real-life clinical practice.

In conclusion, the present long-term daily clinical practice series showed that the vast majority of Crohn's patients had a favourable response to induction and subsequently 83% sustained benefit of adalimumab after 1 year of treatment, with 10% loss of response each following year. However, only a minority achieved steroid-free remission during follow-up. Concomitant thiopurine therapy in the first 6 months may improve adalimumab sustained benefit. Moreover, previous

infliximab should not withhold adalimumab treatment, since patients losing response to infliximab can be treated successfully with adalimumab.

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Statement of authorship

CPP designed and carried out the study, performed statistical analyses and drafted the manuscript; EJE designed and carried out the study, performed statistical analyses and drafted the manuscript; FMT performed the research; MEH performed statistical analyses and contributed by critical revision of the manuscript; JMJ treated studied patients; GRAMD contributed by critical revision of the manuscript; PF contributed by critical revision of the manuscript; PCFS designed the study, treated studied patients and contributed by critical revision of the manuscript; HARET treated studied patients and contributed by critical revision of the manuscript; AAB designed the study, treated studied patients and contributed by critical revision of the manuscript; and CYP designed the study, treated studied patients, drafted the manuscript and contributed by critical revision of the manuscript. All authors read and approved the final manuscript.

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