Effectiveness of anti-tumour necrosis factor-α therapy in Danish patients with inflammatory bowel diseases

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ABSTRACT

INTRODUCTION: The objective of this study was to evaluate the outcome of anti-tumour necrosis factor-α (anti-TNF) treatment in a large cohort of patients with inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC) in clinical practice and to establish a cohort for future studies of genetic markers associated with treatment response.

METHODS: A national, clinically based cohort of previously naïve anti-TNF treated patients from 18 medical departments was established. The patients were screened for tuberculosis prior to treatment initiation. By combining the unique personal identification number of Danish citizens (the CPR number) from blood samples with data from the National Patient Registry, patients with International Classification of Diseases, Version 10 (ICD-10) codes K50-K63 were identified. Treatment efficacy reflected the maximum response within 22 weeks.

RESULTS: Among 492 patients with CD and 267 patients with UC, 74%/13%/14% and 65%/12%/24% were responders, partial responders and non-responders to anti-TNF therapy, respectively. More patients with UC than with CD were non-responders (odds ratio (OR) = 1.96, 95% confidence interval (CI): 1.34-2.87, p = 0.001). Young age was associated with a beneficial response (p = 0.03), whereas smoking ≥ 10 cigarettes/day was associated with non-response among patients with CD (OR = 2.33, 95% CI: 1.13-4.81, p = 0.03).

CONCLUSION: In this clinically based cohort of Danish patients with IBD treated with anti-TNF, high response rates were found. Heavy smoking was associated with non-response, whereas young age at treatment initiation was associated with a beneficial response among patients with CD. Thus, the results obtained in this cohort recruited from clinical practice were similar to those previously obtained in clinical trials.

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Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are characterised by a dysregulated inflammatory response. Severe cases of IBD are treated with infliximab or adalimumab (anti-tumour necrosis factor (TNF)), which are therapeutic antibodies targeting the pro-inflammatory cytokine TNF-α. They block the binding of TNF-α to its cell-surface receptors and limit downstream cell signalling pathways [1]. The efficacy of anti-TNF treatment has been established in clinical trials. These studies of carefully selected patients found that anti-TNF treatment was efficient [1-3]. The efficacy of such treatment in every-day clinical practice is less well established [4-10]. An evaluation of the outcome of anti-TNF treatment in clinical practice is needed to shape the future role of anti-TNF treatment [11]. Moreover, clinical trials suggest that approximately one-third of the patients do not respond to anti-TNF treatment [2]. Tools which may help the clinicians to identify those patients who are most likely to benefit from anti-TNF treatment are warranted.

The aims of the present study were twofold. First, we wanted to evaluate the outcome of anti-TNF treatment in a cohort of patients from clinical practice. Next, we wanted to establish a cohort for future studies on genetic variation associated with treatment response. Therefore, we established a clinically based cohort of previously naïve anti-TNF treated Danish patients with IBD from the 18 largest medical departments in Denmark.

METHODS

Patient identification

Prior to anti-TNF therapy, routine screening for *Mycobacterium tuberculosis* infection was performed as the treatment may lead to activation of latent infection. Therefore, we collected the unique personal identification number of Danish citizens (the CPR number) from all patients who had a blood sample analysed for *M. tuberculosis* at Statens Serum Institut (SSI, Copenhagen, Denmark) from 01.09.2009 to 30.03.2011 and at the Department of Respiratory Diseases B and the Department of Clinical Microbiology, Aarhus University Hospital (Aarhus, Denmark) from 01.01.2011 to 30.03.2011. The CPR numbers were linked to The National Patient Registry, and we examined 1,378 patient records from patients with ICD-10 codes of K50-K63, which included intestinal diseases, from 18 medical departments.

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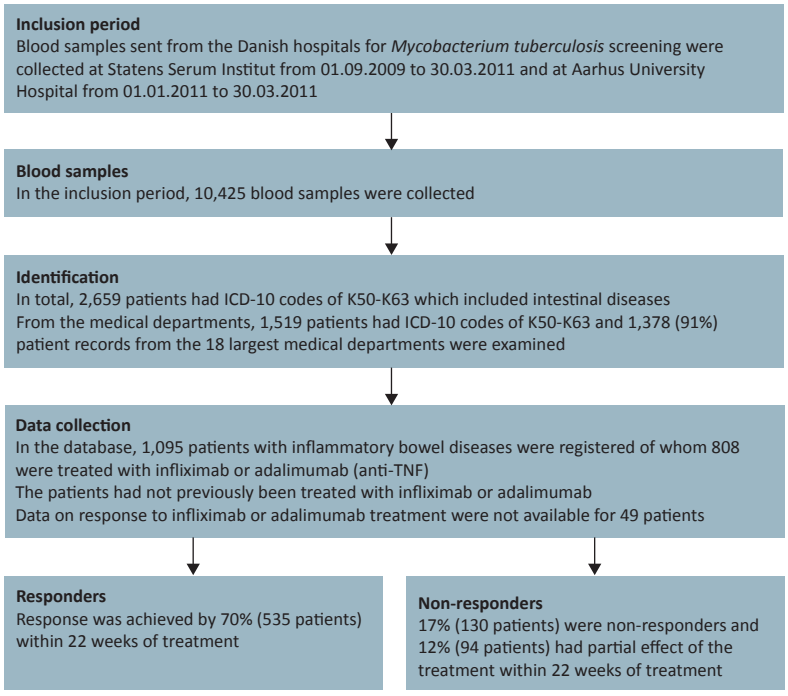
FIGURE 1

Flow diagram showing how blood samples and clinical data were collected from patients with inflammatory bowel diseases previously naïve to anti-tumour necrosis factor (TNF)-α therapy.



Database design and contents

In order to facilitate data acquisition, ensure data quality, and enable centralisation of data storage, a secure web-based database was constructed by Datamanagement (Datamanagement, Aarhus, Denmark).

Data were collected retrospectively from patient records. Data included information on disease (CD or UC), gender, year of birth, age at diagnosis, CD location and behaviour and UC distribution according to the Montreal classification, smoking status, the date of the first anti-TNF treatment (infliximab (Remicade; Centocor, Malvern, PA, USA) or adalimumab (Humira; Abbott Laboratories, North Chicago, IL, USA)), treatment indication, C-reactive protein (CRP), faecal-calprotectin (F-cal) and treatment efficacy (as described later). Furthermore, concomitant medication with azathioprine or methotrexate for up to 4 weeks and 5-aminosalicylates, intravenous or peroral glucocorticoids or antibiotics up to two weeks before the first infliximab or adalimumab treatment were registered.

Finally, operation codes KJF, KJG and KGH were extracted.

Treatment protocol

Indication for treatment was: Patients with moderate or severe disease who did not respond to prednisolone or immunosuppressive treatment. Patients were routinely treated with 5 mg/kg infliximab intravenously starting at week 0, 2, 6 and every eight weeks thereafter. As a standard, adalimumab was administered with 160 mg subcutaneously in week 0, 80 mg in week 2, and 40 mg every second week thereafter [12, 13].

Treatment efficacy

The 3-step scale used in previous studies was used to estimate efficacy eight and 22 weeks after anti-TNF treatment initiation in naïve patients and reflected the maximum response during the period [4-6, 11]. Patients with CD or UC with luminal disease were categorised as having: (A) no response, meaning no improvement or worsening of symptoms; (B) partial response, meaning some improvement of symptoms or reduction of steroid dose without worsening of symptoms; (C) response, meaning absence or almost absence of all clinical symptoms without increasing the steroid dose. Patients with fistulising CD were categorised as having: (A) no response, meaning no improvement or worsening of symptoms; (B) partial response, meaning reduced secretion or discomfort from fistulas or closure of one or some of the fistulas; (C) response, meaning closure of all fistulas evaluated by thumb pressure or no secretion.

Statistical analysis

A chi-square test or unpaired t-test was used to test if there was a statistically significant difference in response between patients with CD and UC and to examine if there was a difference in secondary parameters between responders and non-responders. Statistical analyses were performed using STATA version 11 (STATA Corp., Texas, USA).

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local Regional Ethical Committees (M20100153 and S-20120113) and the Danish Data Protection Agency (J. 2010-41-4719). The Local Regional Ethical Committees gave suspension for obtaining written informed consent.

Trial registration: Clinicaltrials NCT02322008.

RESULTS

Identification of cases

During the inclusion period, 10,425 blood samples from 9,217 individuals were collected as shown in **Figure 1**. From the medical departments, 1,519 patients had ICD-10 codes of K50-K63 and 1,378 (91%) patient records from 18 hospitals were examined. Among the examined 1,378 patient records, 1,095 patients with IBD were identified of whom 808 previously anti-TNF naïve pa-

TABLE 1

Clinical and demographic characteristics for anti-TNF-α naïve inflammatory bowel disease patients treated with anti-TNF-α.

	Crohn's disease				Ulcerative colitis				Inflammatory bowel disease			
	responder	partial responder	non-responder	p-value	responder	partial responder	non-responder	p-value	responder	partial responder	non-responder	p-value
Efficacy, n (%)	362 (74)	63 (13)	67 (14)	–	173 (65)	31 (12)	63 (24)	–	535 (70)	94 (12)	130 (17)	–
Gender, n (%)												
Male	163 (78)	28 (13)	19 (9)		88 (66)	17 (13)	28 (21)		251 (73)	45 (13)	47 (14)	
Female	199 (71)	35 (12)	48 (17)	0.02	85 (63)	14 (10)	35 (26)	0.46	284 (68)	49 (12)	83 (20)	0.03
Anti-TNF treatment, n (%)												
Infliximab	302 (74)	54 (13)	50 (12)		173 (65)	31 (12)	63 (24)	–	475 (71)	85 (13)	113 (17)	
Adalimumab	60 (70)	9 (10)	17 (20)	0.12	–	–	–	–	60 (70)	9 (10)	17 (20)	0.54
Indication for anti-TNF therapy, n (%)												
Flare up	265 (73)	47 (75)	51 (76)	0.76	146 (84)	26 (84)	55 (87)	0.68	411 (77)	73 (78)	106 (82)	0.29
Fistulising disease	48 (13)	12 (19)	9 (13)	1.00	–	–	–	–	48 (9)	12 (13)	9 (7)	0.60
Side effects to other medicine	11 (3)	1 (2)	2 (3)	1.00	14 (8)	0	2 (3)	0.25	25 (5)	1 (1)	4 (3)	0.63
Age, yrs, median (range)												
Age at diagnosis	24 (7-77)	23 (10-53)	27 (14-70)	0.17	31 (12-81)	32 (4-77)	31 (11-77)	0.64	26 (7-81)	25 (4-77)	29 (11-77)	0.07
Age at treatment	33 (13-80)	30 (17-72)	40 (16-75)	0.03	38 (15-84)	42 (7-80)	37 (17-81)	0.75	35 (13-84)	34 (7-80)	38 (16-81)	0.04
Time from diagnosis to treatment initiation, yrs, median (range)	5 (0-44)	7 (0-41)	6 (0-35)	0.42	4 (0-37)	4 (0-37)	3 (0-33)	0.39	4 (0-44)	5 (0-41)	4 (0-35)	0.89
Location, n (%)												
Ileal (L1)	91 (25)	12 (19)	24 (36)	0.07	–	–	–	–	–	–	–	–
Colonic (L2)	124 (34)	24 (38)	23 (34)	1.00	–	–	–	–	–	–	–	–
Ileocolonic (L3)	130 (36)	24 (38)	16 (24)	0.07	–	–	–	–	–	–	–	–
Proctitis (E1)	–	–	–	–	22 (13)	3 (10)	14 (22)	0.10	–	–	–	–
Left side (E2)	–	–	–	–	77 (45)	14 (45)	28 (44)	1.00	–	–	–	–
Extensive (E3)	–	–	–	–	58 (34)	7 (23)	16 (25)	0.27	–	–	–	–
Data not available	17 (5)	3 (5)	4 (6)	–	16 (9)	7 (23)	5 (8)	–	–	–	–	–
Smoking history, n (%)												
Current smoker	102 (28)	21 (33)	23 (34)	0.38	20 (12)	1 (3)	1 (2)	0.02	122 (23)	22 (23)	24 (18)	0.34
Former smoker	40 (11)	8 (13)	5 (7)	0.40	37 (22)	7 (23)	13 (21)	1.00	77 (14)	15 (16)	18 (14)	1.00
Never smoker	94 (26)	22 (35)	11 (16)	0.12	42 (24)	6 (19)	13 (21)	0.61	136 (25)	28 (30)	24 (18)	0.11
Data not available	126 (35)	12 (19)	28 (42)	–	74 (43)	17 (55)	36 (57)	–	200 (37)	29 (31)	64 (49)	–
> 5 cigarettes/day	43 (12)	3 (5)	13 (19)	0.11	5 (3)	0	0	–	48 (9)	3 (3)	13 (10)	0.74
> 10 cigarettes/day	31 (9)	3 (5)	12 (18)	0.03	3 (2)	0	0	–	34 (6)	3 (3)	12 (9)	0.25
Concomitant medication, n (%)												
Azathioprine	104 (29)	27 (43)	15 (22)	0.30	31 (18)	8 (26)	13 (21)	0.70	135 (25)	35 (37)	28 (22)	0.43
5-aminosalicylates	30 (8)	2 (3)	5 (7)	1.00	68 (39)	9 (29)	25 (40)	1.00	98 (18)	11 (12)	30 (23)	0.22
Glucocorticoids	107 (30)	22 (35)	24 (36)	0.31	88 (51)	12 (39)	31 (49)	0.88	195 (36)	34 (36)	55 (42)	0.23
Methotrexate	6 (2)	3 (5)	0 (0)	–	1 (1)	1 (3)	0 (0)	–	7 (1)	4 (4)	0	–
Antibiotics	23 (6)	8 (13)	5 (7)	0.79	15 (9)	4 (13)	6 (10)	0.80	38 (7)	12 (13)	11 (8)	0.58
CRP, patients with available data, n (%)												
Pre-treatment CRP, > 20 mg/l	74/216 (34)	16/49 (33)	14/46 (30)	0.73	33/97 (34)	6/24 (25)	14/47 (30)	0.71	107/313 (34)	22/73 (30)	28/93 (30)	0.53
> 25% decrease within 22 weeks	126/139 (91)	29/34 (85)	21/28 (75)	0.03	57/68 (84)	9/15 (60)	12/22 (55)	0.01	183/207 (88)	38/49 (78)	33/50 (66)	0.01
F-cal, patients with available data, n (%)												
Pre-treatment F-cal > 200 mg/kg	39/45 (87)	3/5 (60)	7/9 (78)	0.61	18/21 (86)	3/4 (75)	5/6 (83)	1.00	57/66 (86)	6/9 (67)	12/15 (80)	0.69
> 25% decrease within 22 weeks	25/29 (86)	1/2 (50)	0/4 (0)	0.01	10/13 (77)	3/4 (75)	1/2 (50)	1.00	35/42 (83)	4/6 (67)	1/6 (17)	0.01

CRP = C-reactive protein; F-cal = faecal-calprotectin; TNF = tumour necrosis factor.

tients were treated with infliximab or adalimumab. Forty-nine patients had to be excluded due to missing data.

Treatment efficacy

Data on efficacy were available for 759 patients and in-

TABLE 2

Adverse events to anti-tumour necrosis factor-α therapy causing treatment to be terminated. The values are n (%).

	Crohn's disease				Ulcerative colitis				Inflammatory bowel disease			
	responder	partial responder	non-responder	p-value	responder	partial responder	non-responder	p-value	responder	partial responder	non-responder	p-value
Skin rash	10 (3)	1 (2)	3 (4)	–	6 (3)	–	1 (2)	–	16 (3)	1 (1)	4 (3)	–
Allergy, unspecified	8 (2)	2 (3)	3 (4)	–	2 (1)	3 (10)	1 (2)	–	10 (2)	5 (5)	4 (3)	–
Dyspnoea	5 (1)	1 (2)	–	–	1 (1)	–	1 (2)	–	6 (1)	1 (1)	1 (1)	–
Joint and muscle pain	2 (1)	–	–	–	3 (2)	–	2 (3)	–	5 (1)	–	2 (2)	–
Infection, unspecified	1 (0)	1 (2)	1 (1)	–	1 (1)	–	–	–	2 (0)	1 (1)	1 (1)	–
Neuropathy	1 (0)	1 (2)	1 (1)	–	–	–	–	–	1 (0)	1 (1)	1 (1)	–
Serum sickness	–	–	1 (1)	–	–	–	–	–	–	–	1 (1)	–
Anaphylactic reaction	–	–	–	–	–	1 (3)	–	–	–	1 (1)	–	–
Cardiac failure	–	–	–	–	1 (1)	–	–	–	1 (0)	–	–	–
Other, unspecified	6 (2)	2 (3)	0 (0)	–	3 (2)	–	–	–	9 (2)	2 (2)	0 (0)	–
Total	33 (9)	8 (13)	9 (13)	0.27	17 (10)	4 (13)	5 (8)	0.80	50 (9)	12 (13)	14 (11)	0.62

cluded 535 (70%) responders, 94 (12%) partial responders and 130 (17%) non-responders (**Table 1**). The response rate was 65% (173 patients) and 74% (362 patients) among patients with UC and CD, respectively (odds ratio (OR) = 0.66, 95% confidence interval (CI): 0.48-0.91, p = 0.01). The non-response rate was 24% (63 patients) and 14% (67 patients) among patients with UC and CD, respectively (OR = 1.96, 95% CI: 1.34-2.87, p = 0.001). Among patients with CD, the response rate to infliximab and adalimumab treatment was 74% (302 patients) and 70% (60 patients), respectively (p = 0.12). The rate of non-response was 17% (48 patients) and 9% (19 patients) among females and males with CD, respectively (OR = 2.07, 95% CI: 1.13-3.81, p = 0.02).

Clinical markers associated with response

Heavy smoking was associated with a low response rate among patients with CD with 18% (12 patients) of the non-responders versus 9% (31 patients) of the responders smoking ten or more cigarettes per day (OR = 2.33, 95% CI: 1.13-4.81, p = 0.03) (Table 1).

Young age at treatment initiation was associated with a beneficial response among patients with CD, with a median age of 33 (13-80) and 40 (16-75) years among responders and non-responders, respectively (p = 0.03).

A high pre-treatment CRP level (CRP ≥ 20 mg/l, twice the upper limit of the normal range) or a high pre-treatment faecal-calprotectin level (faecal-calprotectin > 200 mg/kg) were not associated with anti-TNF response. However, a decrease in CRP or faecal-calprotectin level by ≥ 25% within 22 weeks after treatment initiation was associated with a beneficial response (OR = 3.93, 95% CI: 1.91-8.10, p < 0.01 and OR = 25, 95% CI: 2.52-248.19, p < 0.01, respectively).

CD location, UC distribution, treatment indication (flare-up, fistula or side effects to other medications), concomitant medication (azathioprine, 5-aminosalicylates, glucocorticoids, methotrexate or antibiotics) or overall smoking status were not associated with treatment response.

Adverse events

As shown in **Table 2**, 76 (10%) of the 759 patients treated with infliximab or adalimumab terminated the treatment because of adverse events. Treatment termination due to adverse events occurred in 10% and 9% of the patients with CD and UC, respectively, and in 9% and 11% of responders and non-responders, respectively.

The most severe adverse events were one case of serum sickness, one anaphylactic reaction and one case of cardiac failure. No deaths were reported.

Colectomy

Five partial responders with UC and 5 patients with CD and 23 patients with UC, who were non-responders, were colectomised within 22 weeks of treatment initiation. Four patients with UC who initially responded to anti-TNF therapy lost the effect and were colectomised within 22 weeks of treatment initiation.

DISCUSSION

Anti-TNF response was assessed in a clinically based cohort of 759 previously anti-TNF naïve Danish IBD patients sampled from 18 medical departments. Response was evaluated as the maximum response within 22 weeks of treatment initiation. We found that anti-TNF treatment of patients with CD and UC was effective with response rates of 74% and 65%, respectively. The response rate in our retrospective study may be slightly higher than in other studies due to the exclusion of 49

patients, many of whom may have been non-responders. Furthermore, we found a significantly higher rate of non-response among patients with UC than among patients with CD. Heavy smoking was associated with non-response, whereas young age at treatment initiation was associated with a beneficial treatment response among patients with CD.

The main result of the present study is that we achieved similar results in clinical practice as have been obtained in clinical trials with carefully selected patients [1-3]. Our results from the present large cohort support the previous findings of a high primary response rate in clinically based cohort studies [4-10]. Additionally, our findings of higher rates of non-response among patients with UC, among female patients with CD and among patients with CD smoking 10 or more cigarettes per day are in accordance with the results of previous, smaller studies [14, 15]. In addition, our findings that young age at treatment initiation was associated with a beneficial response among patients with CD and that a decrease of 25% or more of pre-treatment CRP or faecal-calprotectin levels was associated with a beneficial response are in accordance with the results of other studies [14, 16, 17]. The use of azathioprine and methotrexate has been associated with a beneficial response after short-term treatment and fewer infusion reactions among patients with CD and UC treated with anti-TNF [6, 14, 15]. We were unable to confirm this result, probably because of lack of power. The incidence of adverse events was in line with that reported in previous studies (Table 2) [1, 2]. Among patients with CD with fistulising disease, the response rate in our retrospective study, reflecting the best response within 22 weeks, was similar to the response rates reported in other prospective and retrospective studies [4-6, 11].

All in all, we found similar anti-TNF treatment results in this clinically based cohort as have been found in clinical trials and in the few previously published clinically based studies. The results indicate that this cohort may be used for future studies on genetic variation associated with treatment response [18-20]. Identification of clinically useful markers that may predict treatment response will help the clinician to stratify and thus select patients who will respond to anti-TNF therapy and to avoid treatment of patients who will not respond. Until now, biomarkers are used mainly in oncology for personalised therapy. Furthermore, knowledge on the underlying biological mechanisms may lead to the development of new, better targeted therapies.

The present study was a large nationwide Danish multicentre study of patients in clinical practice, including 759 previously anti-TNF naïve IBD patients. However, data were collected retrospectively and were not available for all patients, which prevented the calculation of a score, such as the Harvey-Bradshaw Index (HBI) or the Simple Clinical Colitis Activity Index (SCCAI), for determination of treatment response. Instead, the response was the best response within 22 weeks based on the physician's global assessment which has also been used in other retrospective studies. In the light of the obtained p-values and the number of statistical tests performed, we cannot exclude that our positive findings may be due to chance. Nor can we exclude that associations were not identified due to insufficient power.

CONCLUSION

This clinically based cohort of Danish patients treated with anti-TNF found high response rates. Heavy smoking was associated with non-response, whereas young age at treatment initiation was associated with beneficial treatment response among patients with CD. Thus, our clinical experiences were in line with results obtained from clinical trials.

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