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RAPID COMMUNICATION

Crohn's disease, fatigue, and infliximab: Is there a role for cytokines in the pathogenesis of fatigue?

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Abstract

AIM: To study the effect of infliximab on fatigue in relation to cytokine levels in Crohn's disease (CD) patients.

METHODS: Fourteen CD patients were blinded for treatment and received placebo at baseline, and infliximab 2 wk later, with a follow-up of 4 wk. Blood samples were drawn on a regular basis, and questionnaires on fatigue, depression, quality of life, and clinical disease activity were completed at regular intervals.

RESULTS: After placebo infusion, fatigue scores decreased within 3 d (3.5 points ± 1.1, $P \leqslant 0.01$), but returned to baseline values 14 d after this infusion. The drop of fatigue scores following infliximab infusion sustained until the end of the study (3.8 points ± 1.4, $P \leqslant 0.05$). Quality of life was increased at the end of the study compared to baseline values (138.6 ± 9.4 *vs* 179.4 ± 6.7; $P \leqslant 0.005$), whereas depression scores were decreased (20.4 ± 9.4 *vs* 11.3 ± 2.2; $P \leqslant 0.01$). No correlation between the severity of fatigue and the level of cytokines was observed.

CONCLUSION: The reduction of fatigue after infliximab infusion is subjective to a placebo effect. The effect of infliximab on fatigue, however, persists while the placebo effect disappears after a short period of time. A clear role of cytokines could not be substantiated.

Key words: Crohn's disease; Fatigue; Infliximab; Cytokines

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INTRODUCTION

Fatigue is a frequently reported symptom in inflammatory bowel disease (IBD) patients, even when the disease is in remission. It can be disabling when it has consequences for the patient's work, daily life, and quality of life. Recently, we reported fatigue in 40% of IBD patients with quiescent disease[1]. Our data also indicated that disease activity leads to a higher prevalence and level of fatigue. Despite the high prevalence, fatigue in Crohn's disease (CD) patients remains poorly understood as biochemical and haematological tests seldom provide an explanation. Studies in patients with chronic fatigue syndrome suggest an immunological basis for fatigue, mediated by cytokines[2-5]. Some of these cytokines also play a role in IBD, especially in active disease (TNF-α, IL-6, IL-10, IL-18)[6-11].

The treatment of CD has dramatically changed since the introduction of infliximab, a chimeric antibody against TNF-α. A clinical response was reported in two-thirds of the treated patients and even remission in one-third of the CD patients following treatment with infliximab[12-15]. Infliximab has a direct effect on circulating TNF-α and is thought to induce apoptosis of activated T-cells[15]. Patients frequently experience a rapid reduction of fatigue after treatment with infliximab. A previous, placebo-controlled study has shown a significant decrease of fatigue in CD patients treated with infliximab, based on a disease-specific health related quality of life questionnaire[16]. This finding has been confirmed by Persoons *et al*[17], although not in a placebo-controlled study.

The primary aim of this pilot study was to assess, in a placebo-controlled way, the role of cytokines in the pathogenesis of fatigue in CD patients, using infliximab. Furthermore, we measured the effect of infliximab on fatigue, clinical disease activity and depression scores, using validated questionnaires developed for these purposes.

MATERIALS AND METHODS

Patients

Fourteen consecutive CD patients from the Outpatient Department of Gastroenterology of the University Medical Centre in Utrecht were enrolled in the study. The diagnosis of CD was based on clinical, radiological, endoscopic and histological features[18]. Comorbidity, possibly resulting in fatigue (e.g. kidney or adrenal insufficiency, autoimmune diseases, malignancy, sodium depletion in case of an

Table 1 Demographic and clinical characteristics of the patients

Clinical characteristics	Included CD patients (n = 14)
Age (yr) (mean ± SD)	32.2 (± 8.6)
Disease duration (yr) (median; range)	7.5 (1-28)
Gender male (n)	5
Refractory, clinical active luminal disease (n)	9
Active (draining) fistulae (n)	5
Medication use	
Mesalamine (n) (range)	9 (1.5-3 g/d)
Azathioprine (n) (range)	12 (25-175 mg/d)
Prednisone (n) (range)	5 (10-50 mg/d)
Infliximab naïve (n)	8

ileostomy), was considered an exclusion criterion. Demographic and clinical characteristics of the included patients are presented in Table 1. Four patients, including 3 patients with fistulising disease, had a stoma (3 ileostoma, 1 colostoma). In 4 of the patients who used corticosteroids, the dose was tapered to two weeks after infliximab infusion. Doses of other medications were stable during the whole study period. None of the subjects used infliximab within 3 mo prior to study entry. The study was approved by the Medical Ethical Committee of the University Medical Centre Utrecht, and written informed consent was obtained from all subjects.

Study protocol

The study was designed as a single blinded study. All patients received placebo (i.e. saline) at baseline, followed by infliximab (5 mg/kg) at 2 wk. Patients with fistulae received one extra dose of infliximab, 4 wk after baseline. All patients were followed up for 4 wk after the last infliximab infusion. Fatigue scores were obtained every week (plus three days after each infusion), using the Multidimensional Fatigue Inventory (MFI). Depression scores were assessed every two weeks by the Center for Epidemiological Studies Depression scale (CES-D). Quality of life was measured at baseline and at the end of the study, using the Inflammatory Bowel Disease Questionnaire (IBDQ). Clinical disease activity was determined by the Crohn's disease activity index (CDAI), while in patients with fistulising disease the perianal Crohn's disease activity index (PCDAI) was employed as well. Blood samples were drawn every two weeks.

Questionnaires

Fatigue was assessed using the Multidimensional Fatigue Inventory (MFI-20) a 20-item self-report instrument designed to measure five fatigue dimensions: general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue[19-21]. Each scale consists of two items indicating fatigue and two items contraindicating fatigue, to limit possible influences of answering tendencies. A higher score indicates a higher level of fatigue (range 4-20). The questionnaire was developed and validated in the Netherlands[20]. In some studies the scale of general fatigue was preferred to the use of numerical rating scale because of its more favourable psychometric properties. Therefore, the general fatigue scale can be referred to as "fatigue"[19,22]. In the present study, we only used this scale. If fatigue is defined as the 95 percentile of the score on the general fatigue scale of a healthy control group, a score of 13 or higher indicates "fatigued"[1].

Quality of life was measured by the Inflammatory Bowel Disease Questionnaire (IBDQ). The IBDQ is a disease- specific health related quality of life questionnaire, containing 32 items, with a graded response range of 1 (worst) to 7 (best) and a total score of 32 to 224[23]. The 32 items can be divided into 4 dimensional scores, including bowel symptoms (10 items), systemic symptoms complaints (5 items), emotional well being (12 items), and social function (5 items). The subscale "systemic symptoms" contains two questions evaluating fatigue/energy loss. The IBDQ has been translated and validated in the Dutch language and proven to be valid, discriminative and reliable[24].

Depression scores were assessed every two weeks by the Center for Epidemiological Studies Depression scale (CES-D). The CES-D consists of 20 questions, 16 questions are related to feelings of mental depression (negative questions) and four questions are related to the absence of feelings of mental depression (positive questions). All questions refer to the situation during the last week, with a graded response range of 0 (< 1 d) to 3 (5 to 7 d). The total CES-D score ranges from 0-60. A high score reflects more feelings of mental depression and reduced psychological wellbeing. The CES-D has been translated and validated in the Dutch language[25,26].

Clinical disease activity

Crohn's disease activity index (CDAI): Disease activity was assessed using the CDAI[27], the most frequently used and accepted clinical activity score for Crohn's disease worldwide. A clinical response was defined as a reduction of 70 or more points of the CDAI score[13,15]. The CDAI was not computed for patients with a stoma (n = 4).

Perianal Crohn's disease activity index (PCDAI): The PCDAI was used to measure the severity of perianal Crohn's disease in patients with fistulising disease[28]. The PCDAI incorporates 5 items: discharge, pain, restriction of sexual activity, type of perianal disease, and degree of induration. Each category is graded on a 5-point Likert scale ranging from no symptoms (score of 0) to severe symptoms (score of 4). A higher score indicates more severe disease.

Cytokine, biochemical and hematological tests

The cytokines TNF-α, interleukin (IL)-6, IL-10, and IL-18 were assessed before, two weeks after each infusion, and 4 wk after the last infliximab infusion, using the Luminex Multiplex system which is described in detail previously[29,30]. Biochemical and haematological tests (e.g. haemoglobin, C-reactive protein CRP) were performed at the same time as the cytokines were assessed. A CRP under 7 mg/L was considered normal.

Statistical analysis

The distributions of the data were evaluated by means of descriptive statistics (mean or median; SEM or range). Paired Student t tests or Wilcoxon Signed Ranks tests

Table 2 Decrease in general fatigue score and CDAI score after infusion mean ± SEM

t/D	General fatigue		CDAI score	
	Placebo	Infliximab	Placebo	Infliximab
D 3	3.5 ± 1.1[b]	2.4 ± 1.5		
D 7	3.5 ± 1.1[b]	3.5 ± 1.6[a]	40 ± 10.6[b]	63 ± 18.9[b]
D 14	1.9 ± 1.1	2.6 ± 1.2[a]	39 ± 13.3[a]	65 ± 27.1[a]
D 21	.	3.6 ± 1.4[a]		72 ± 28.9[a]
D 28	.	3.8 ± 1.4[a]		68 ± 36.2

[a]$P \leqslant 0.05$, [b]$P \leqslant 0.01$ *vs* baseline. CDAI: Crohn's disease activity index.

were performed for comparisons before and after the different infusions. Dichotomous variables were expressed as frequency (%), and differences between frequencies were analysed using the McNemar test. Partial correlation coefficients were computed between general fatigue and the IBDQ, the CES-D, the decrease in clinical activity scores, cytokines, and haematological tests. $P < 0.05$ was considered to be significant. Statistical analysis was performed with the SPSS version 11.5 for Windows.

RESULTS

Fatigue scores

Table 2 shows the average decrease of fatigue score (subscale "general fatigue") after placebo and infliximab infusion. At baseline the mean general fatigue score (± SEM) was 15.8 (± 1.00). Three and 7 d after placebo infusion, a significant decrease in fatigue was measured compared to the baseline values. Fourteen days after placebo infusion, the fatigue scores had returned to baseline value. After infliximab infusion, the fatigue score dropped significantly after 7 d, and this effect sustained until the end of the study (4 wk after the last infliximab infusion).

If fatigue is defined as a score on the general fatigue scale of 13 or higher[1], 86% of the patients was fatigued at baseline. Of these patients, 33% responded to the placebo infusion, leaving 57% of all participating patients fatigued. After infliximab administration, this percentage reduced to 36% and 21% of all participating patients after 2 and 4 wk. Analysing infliximab naïve patients separately did not change the outcomes.

Quality of life

Quality of life was significantly increased 4 wk after the last infliximab infusion compared to the baseline values. Table 3 shows the average of the total IBDQ score and the subscale systemic symptoms.

Depression scale

Placebo infusion did not interfere with feelings of mental depression or reduced psychological well-being. A significant effect of infliximab infusion on feelings of depression was found 4 wk after the last infusion (Table 3).

Clinical disease activity

CDAI: At baseline, the mean CDAI score (± SEM) was 222.3 (± 25.7). After the infliximab infusion and placebo infusion, CDAI scores showed a significant decrease (Table 2).

Table 3 Effect of infliximab on IBDQ and CES-D scores, and IL-18, CRP mean ± SEM

	Placebo infusion		Infliximab infusion		
Parameters	Baseline	d 14	Baseline	d 14	d 28
Total IBDQ (range 32-224)	138.6 ± 9.4				179.4 ± 6.7[a]
Systemic symptoms (range 5-35)	19.9 ± 5.9				25.1 ± 1.6[b]
CES-D (range 0-60)	20.4 ± 9.4	17.0 ± 2.9	17.0 ± 2.9	14.0 ±2.4	11.3 ± 2.2[b]
IL-18 (ng/L)	37.1 ± 6.4	37.3 ± 6.5	37.3 ± 6.5	27.4 ± 5.2[c]	26.6 ± 3.8[e]
CRP (mg/L)	21.4 ± 6.2	21.9 ± 6.3	21.9 ± 6.3	9.1 ± 1.4[d]	8.7 ± 0.8[e]

[a]$P \leqslant 0.005$; [b]$P \leqslant 0.01$ between baseline (before infliximab infusion) and 4 wk after infliximab infusion; [c]$P \leqslant 0.005$; [e]$P \leqslant 0.05$ between baseline and 2 or 4 wk after infliximab infusion. IBDQ: Inflammatory Bowel Disease Questionnaire; CES-D: Center for Epidemiological Studies Depression scale; IL-18: Interleukin 18; CRP: C-reactive protein.

If clinical response is defined as a reduction of 70 or more points of the CDAI score, 50% of the patients clinically responded after infliximab infusion, compared to 20% after placebo infusion. Excluding the patients with fistulising disease ($n = 2$), the same results were obtained, with a more explicit, although not significant, difference in CDAI score decrease after both infusions.

PCDAI: No significant decrease in the PCDAI score in the five patients with fistulising disease was measured at the end of the study, compared to the baseline values. No differences were found in the effect of the two infusions.

Cytokine, biochemical and haematological tests

IL-18: All patients had detectable levels of IL-18. A significant decrease was found 2 wk after infliximab infusion, which still existed 4 wk after the last infliximab infusion. Placebo infusion did not influence the levels of IL-18 expression (Table 3).

IL-6, IL-10, TNF-α: These cytokines were detected in half of the patients or less, at different measure points. The circulating levels of IL-6, IL-10 and TNF-α were not affected by infliximab or placebo.

Hemoglobin, CRP: No differences in levels of hemoglobin were found after both infusions. At baseline, 6 patients had a CRP above 7 mg/L. A significant decrease in CRP was found 2 wk after Infliximab infusion, which still existed 4 wk after infusion. Placebo infusion did not influence the CRP level (Table 3).

Partial correlation

The general fatigue score was positively related to the total CES-D score ($r = 0.781$; $P < 0.001$), as was the decrease in general fatigue levels to the decrease in CDAI score ($r = 0.642$; $P < 0.001$). The total IBDQ score, and the subscale systemic symptoms were both inversely correlated to the fatigue scores ($r = 0.765$, and $r = 0.791$; both $P < 0.001$). No significant correlations were found between fatigue scores and CRP and haemoglobin, or with any of the tested cytokines.

DISCUSSION

The present study is the first placebo-controlled study that was conducted to examine the effect of infliximab

on fatigue in CD patients, and the role of cytokines in this respect. Our results show that fatigue is significantly reduced by administration of infliximab, although it is important to bear in mind that complaints like fatigue are susceptible to a placebo effect, as was clearly demonstrated in the present study. Furthermore, infliximab reduces depression scores, and improves the quality of life.

This particular study design enabled us to use patients as their own controls, restricting the sample size. A cross-over design was not thought to be appropriate since we anticipated a long lasting carry-over effect of infliximab.

Although the number of subjects studied was relatively small, we believe that this study truly reflects the influence of infliximab on fatigue in patients with active CD. In daily practice, patients frequently experience a rapid reduction of fatigue after treatment with infliximab. In the present study, fatigue scores rapidly decreased after infusion with placebo, but returned to baseline values within 14 d. In contrast, the decrease of fatigue scores after infliximab infusion persisted until the end of the study, suggesting a real pharmacological effect of infliximab.

The effect of infliximab on fatigue has been described previously[16,17,31], but this has never been studied in a placebo-controlled study, using dedicated and validated instruments. Lichtenstein *et al*[16] reported a significant increase in the subscale systemic symptoms of IBDQ in infliximab-treated CD patients. The IBDQ, however, is not designed to study fatigue. As mentioned before, the subscale "systemic symptoms" contains only two questions evaluating fatigue/energy loss. Persoons *et al* reported a significant improvement of fatigue levels in CD patients after treatment with infliximab within two weeks. In this uncontrolled study, a dedicated instrument designed to measure multiple fatigue dimensions was used[17].

We also demonstrated a beneficial effect of infliximab on feelings of mental depression or psychological well-being, as did Persoons *et al* recently[32]. Fatigue is known to be related to negative emotions, in particular depression[17,22], which was confirmed in the present study by a positive relation between fatigue and feelings of depression. The impact of fatigue on the quality of life was demonstrated by the inverse correlation between both questionnaires.

A clinical response was found after infliximab infusion as well as after placebo infusion, indicating the presence of a placebo effect. This is in line with the findings of Targan *et al* who demonstrated a clinical response in patients treated with infliximab (50%-81%), as well as in the placebo group (17%)[13]. Su *et al*[33] reported in their meta-analysis place rates of remission up to 50%.

Studies of human and experimental models indicate that IL-18 plays an important role in CD[6,7,11]. IL-18 is up-regulated in colonic specimens of CD patients, especially in the mucosal samples taken from areas with disease activity[7]. In the present study, IL-18 was expressed in all patients, showing a significant decrease of IL-18 levels after infliximab infusion. Simultaneously with the decrease in IL-18 levels, a decrease in fatigue scores was detected after infliximab infusion, suggesting a relation between both parameters. However, this could not be demonstrated statistically.

In conclusion, we confirmed the impact of fatigue on the quality of life, and psychological well-being. Furthermore, we have shown that the reported rapid reduction of fatigue after treatment with infliximab in daily practice is subjective to a placebo effect. The effect of infliximab on fatigue, however, persists while the placebo effect extinguishes after a short period of time. This implicates that infliximab can interfere with the pathogenesis of fatigue in CD patients. An evident role of cytokines in the generation of fatigue could not be substantiated.

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