Aliment Pharmacol Ther 2005; 22: 101–110. doi: 10.1111/j.1365-2036.2005.02535.x

The impact of major depressive disorder on the short- and long-term outcome of Crohn's disease treatment with infliximab

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Accepted for publication 4 May 2005

SUMMARY

Background: Major depressive disorder is the most common psychiatric diagnosis in Crohn's disease. In other chronic diseases, evidence suggests that depression influences the course of the disease. Strong evidence of such a mediating role of major depressive disorder in Crohn's disease has never been found.
Aim: To assess the relationship between major depressive disorder and outcome of treatment of luminal Crohn's disease with infliximab.
Methods: In this prospective study, 100 consecutive unselected patients underwent assessment of psychosocial, demographical disease-related biological and clinical parameters at baseline and at 4 weeks after infliximab. Major depressive disorder was diagnosed using the Patient Health Questionnaire. Subsequently, the patients were followed up clinically until the next flare or during 9 months.
Results: The Crohn's disease responded in 75% of the patients, and remission was achieved in 60%. The presence of major depressive disorder at baseline predicted a lower remission rate (OR = 0.166, 95% CI = 0.049–0.567, $P = 0.004$). At follow-up, 88% of the patients needed retreatment. At univariate regression analysis, major depressive disorder significantly decreased time to retreatment ($P = 0.001$). Multivariate Cox regression confirmed major depressive disorder as an independent determinant of active disease both at baseline and at re-evaluation (hazard ratio = 2.271, 95% CI: 1.36–3.79, $P = 0.002$).
Conclusion: Major depressive disorder is a risk factor for failure to achieve remission with infliximab and for earlier retreatment in patients with active luminal Crohn's disease. Assessment and management of major depressive disorder should be part of the clinical approach to patients with Crohn's disease.

INTRODUCTION

Crohn's disease (CD) is an idiopathic, multifactorial, inflammatory, gastrointestinal disease characterized by a chronic and relapsing course. Over the past 20 years, significant advances have been made in understanding the pathophysiology and the natural history of CD and also treatment has greatly improved. The specific contribution of psychosocial factors to the evolution of the disease remains unclear and controversial. The majority of the patients and their treating physicians attribute an important role to psychosocial factors in the clinical exacerbation of symptoms or even of disease activity.[1]

The presence of clinical depression may influence disease activity, aggravate disease symptoms, impact on the evolution of the disease or the response to therapy. The patient may experience enhanced morbidity, a poorer prognosis, and possibly even increased mortality.[2] Research into several chronic diseases over the past 5 years has yielded a growing body of evidence

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that psychological factors and depression in particular influence chronic disease in a complex manner.[3–5] In CD and ulcerative colitis (UC), the influence of stress and psychosocial factors has been investigated. A number of older studies yielded mixed results and sometimes measured only the subjective symptoms.[6–12] Four recent studies have substantiated the role of psychological distress in the exacerbation of 'objective' IBD activity. A cross-sectional study in UC showed a correlation between stressful life events, depression and disease activity.[13] The same group of investigators showed in a prospective study in 62 clinically remitted UC patients, that long-term perceived stress tripled the risk of exacerbation during the next 8 months. However, no clear association with depressive symptoms was found.[14] Bitton *et al.* followed 60 UC patients for 12 months and found that recent stressful events in the preceding month were associated with earlier time to relapse.[15] Finally, an 18-month prospective study in a mixed cohort of 60 clinically inactive CD and UC patients found that depressed mood and associated anxiety at baseline were independent risk factors for early clinical relapse and a higher frequency of relapses during the follow-up period.[16] However, it is possible that anxiety and depression in patients with IBD could be reactive to the disabling symptoms and to malnutrition.[17]

Depression is the most common psychiatric diagnosis in CD and previous studies provide evidence supporting an association between CD and major depressive disorder (MDD).[18] Factors which are strongly associated with major depression, such as ineffective coping strategies, pessimism, low perceived control and 'catastrophizing' thoughts, are assumed to predict poor outcome of IBD.[1]

Our hypothesis was that psychosocial factors might influence the short- and long-term outcome of treatment of active CD. As therapy needs to be very effective to evaluate the importance of predictive factors, we have chosen treatment with infliximab (Remicade®) as our experimental condition. The murine-human monoclonal chimeric antibody against tumour necrosis factor-α (TNF-α) has proven to be effective in severe, refractory luminal and fistulizing CD.[19–21] The primary objective of this prospective study was to assess if the presence of MDD at the time of treatment with infliximab had an impact on the short-term effectiveness and the duration of response to infliximab. Moreover, we studied whether the usefulness of the instruments we use in drug trials in CD, i.e. the CDAI is influenced by the presence of MDD. As a secondary objective, we assessed the impact of other psychosocial factors, such as anxiety, perceived social support, sleep and alexithymia.

MATERIAL AND METHODS

Patients

Between January 2003 and July 2003, all consecutive out-patients at the Inflammatory Bowel Disease day clinic at the University Hospital Gasthuisberg (Leuven, Belgium) were asked to participate in the study. Only patients with refractory, active luminal disease treated with infliximab (5 or 10 mg/kg) were included. Patients had active CD (defined as CD Activity Index >150). Only patients previously diagnosed with CD on the basis of clinical, standard radiological or endoscopic criteria, supplemented with the typical histological appearance in a mucosal biopsy or resection specimen,[22] could enter the study. Patients younger than 18 years were excluded, as were patients who suffered from a short bowel syndrome, patients with stomas or if they participated in a clinical trial. The institutional Ethical Committee approved the study and written informed consent was obtained from all participants at inclusion.

Measurement of disease-related characteristics

Relevant demographic data were recorded. Clinical disease activity, assessed with the CD Activity Index (CDAI,[23]) and C-reactive protein (CRP) were assessed. Concomitant drug treatment was recorded. Established predictors of relapse of disease activity in CD such as smoking and use of non-steroidal anti-inflammatory drugs (NSAID),[24] as well as the predictors of short- and long-term response to infliximab such as concomitant use of immunosuppressive therapy, age and location of disease were recorded.[25–28] The phenotype of the CD patients was described using the Vienna classification.[29] Age at diagnosis, disease duration, surgical history, time since previous treatment for a flare and the number of treatments for CD during the previous 12 months were recorded as well.

Measurement of psychosocial variables

Major depressive disorder. The presence of MDD was assessed by the self-administered Patient Health Questionnaire 9-items (PHQ-9). The PHQ-9 is the depression

module of the PRIME-MD Patient Health Questionnaire and was validated in primary care patients[30] and in gastroenterological patients.[31] Applying a diagnostic algorithm allows to diagnose MDD, a categorical psychiatric diagnosis according to the Diagnostical and Statistical Manual 4th Edition (DSM-IV).[32] A summed score of all items provides a measure of severity of depression.[30]

Anxiety. The seven-item anxiety subscale of the Hospital Anxiety and Depression Scale (HADS)[33] was used to measure the intensity of anxiety symptoms. A higher summed score of the recoded items represents a higher intensity of anxiety symptoms (range 0–21). The HADS has been used in IBD populations[6] and has good reliability and validity.

Sleep. The number of hours of actual sleep per night over the past month was recorded. A Visual Analogue Scale of 100 mm measured the subjective quality of sleep. Furthermore, the patients were asked if they had sleep difficulties and a number of possible reasons for the sleep disorder were presented.

Alexithymia. In individuals with an alexithymic personality, stress finds outlet in bodily symptoms because of a deficit in mental representation of emotions.[34] It has been shown that alexithymia is higher in patients with IBD[35] and has an influence on the subjective health status of patients with IBD.[36] The Toronto Alexithymia Scale 20 items (TAS-20) is a widely used alexithymia measure. Patients were instructed to indicate on a five-point likert scale to what extend they agreed or disagreed with 20 presented sentences. The TAS-20 has been shown to be a psychometrically sound measure of the alexithymia construct.[37]

Social support. Social support was measured with the Social Support List – Interactions (SSL-I).[38] Patients were instructed to indicate on a scale from 1 (seldom or never) to 4 (very often) how often each event happens to them. A first subscale of 34 items assessed the perceived positive interactions and a second subscale of seven items measured perceived negative interactions. A high score on the first subscale indicates a lot of perceived social support and a high score on the second subscale indicates a lot of negative interactions. The validity of the SSL-I has been demonstrated.[38]

Study protocol

At baseline, the clinical disease activity was assessed by physicians who were blinded for the psychological state of the patient and laboratory parameters were measured. Consequently, a single treatment with infliximab was given intravenously. Patients received self-report questionnaires assessing the psychosocial factors, which they completed just prior to the infliximab infusion. Four weeks after the infliximab infusion, the patients were re-evaluated to assess the clinical and biological effects of the treatment and the same disease-related parameters were obtained. The number of patients who responded partially defined as a drop in CDAI score of ≥70, and who completely responded (remission), defined as a CDAI score <150, was recorded. Patients also completed questionnaires re-assessing relevant psychosocial factors (state variables: MDD, anxiety and sleep). After the initial treatment infusion and the assessment at 4 weeks the patients were prospectively followed for 9 months or until any treatment for a relapse of disease activity was needed. Repeated infliximab treatment was carried out only on relapse of disease activity (episodic retreatment strategy). Retreatment with infliximab or any initiation other therapy for active CD or admission to the hospital was considered as a relapse of disease activity.

Statistical analyses

For all statistical analyses, the Statistical Package for Social Sciences, version 12.0 for Windows (SPSS 2003, version 12.0, SPSS Inc., Chicago, USA) was used. Descriptive statistics of all relevant variables for the total group was calculated. Comparisons between groups were performed with Student's *t*-tests, Mann–Whitney *U*-tests, Fischer's exact tests, chi-squared tests and McNemar's tests, as appropriate. The Pearson's r and the Spearman's ρ were used to estimate univariate correlations.

The determinants of the effectiveness (response and remission) of the infliximab treatment were assessed with forward stepwise logistic regression analyses. The C-statistic for the model was calculated. A higher C-statistic indicates that the logistic regression model assigns a higher probability of the correct classification of a case.

The associations between the demographic, disease-related and psychosocial variables and the time until the

next treatment were analysed in a univariate fashion by Cox regression analysis. Subsequently, multivariate Cox regression analysis was used to identify the independent determinants of time until retreatment. Significant and moderate ($P < 0.10$) univariate determinants were entered into the model. Kaplan–Meier curves showing the retreatment-free cumulative survival of the patients with and without MDD at baseline were calculated. The curves were compared by Log Rank tests.

The level of statistical significance was set at $P < 0.05$ and all *P*-values are two-sided.

RESULTS

A total of 109 consecutive CD patients were eligible to enter the study of whom nine patients refused to participate after reading the informed consent. There was no significant difference between the participating ($n = 100$) and non-participating patients for any of the baseline parameters. Table 1 shows the relevant socio-demographic, disease-related and psychosocial data of all participating patients at baseline. Sixteen patients had never been treated with infliximab (infliximab naïve), while 84 patients had already received episodic infliximab previously.

All patients ($n = 100$) were clinically re-assessed at 4 weeks after therapy with infliximab. Seventy-eight patients (78%) had responded to treatment and 60% achieved remission. The overall CDAI score and CRP had improved significantly (drop in mean CDAI from 261 ± 100 to139 ± 96, $P < 0.001$ and drop in median CRP from 9.2 mg/L, IQR = 4.1–24.2 mg/L to 3.3 mg/L, IQR = 0–8.3 mg/L, $P < 0.001$).

Eighty-eight patients (88%) required retreatment with infliximab or other rescue treatment for relapse of disease activity within 9 months. One of the 12 patients was lost to follow-up after 7 months before any retreatment. Eighty-two patients who relapsed (93%) received repeat infliximab infusion, six patients (7%) received other medications. The median number of days until retreatment for the total group was 68 days (IQR: 48–112 days).

Patients who needed retreatment had received more treatments for active CD during the previous year, in comparison to the non-retreated group (respectively median three treatments, (IQR = 2–5) treatments vs. median 1 treatment, (IQR = 0–2 treatments, $P < 0.001$). The median number of days since the previous treatment for active CD was also lower (not

Table 1. Baseline description of the demographics, the disease characteristics, the psychosocial variables and the medication use for the total group

	Total group ($n = 100$)
Demographics	
% Men (*n*)/%Women (*n*)	41% (41)/ 59% (59)
Age, mean years (s.d.)	34 (11)
Family status	
% Married – stable relationship (*n*)	61% (61)
% Living with family (*n*)	27% (27)
% Single [also divorced, widow(er)] (*n*)	12% (12)
% Smokers (*n*)	39% (39)
% Member patient association (*n*)	25% (25)
General course of the disease	
Age of diagnosis, mean years (s.d.)	23 (8)
Duration of the disease, median years (IQR)	10 (5–16)
% Previous abdominal surgery (*n*)	38% (38)
Vienna classification	
% Diagnosis <40 years old (*n*)	95% (95)
Localization:	
% Terminal ileum (*n*)	8% (8)
% Colon (*n*)	32% (32)
% Terminal ileum + colon (*n*)	51% (51)
% Upper GI involvement (*n*)	9% (9)
Type of disease:	
% Inflammatory type (*n*)	55% (55)
% Penetrating type (*n*)	45% (45)
Treatments within the last year	
Any treatment for flare, median (IQR)	3 (2–5)
Disease activity at inclusion	
CDAI, mean (s.d.)	261 (100)
CRP, median mg/L (IQR)	9.2 (4.1–24.2)
Psychosocial measures	
Depression intensity: PHQ-9 summed score (s.d.)	8.7 (5.7)
Anxiety intensity: HADS anxiety (s.d.)	7.4 (4.4)
Alexithymia: TAS total score (s.d.)	52.1 (12.7)
Social support	
SSL positive interaction (s.d.)	78.0 (16.9)
SSL negative interaction (s.d.)	10.7 (3.6)
Sleep	
Hours of sleep (IQR)	7 (6–8)
Sleep quality (s.d.)	48.6 (25.4)
Pharmacological therapy	
% 5-Aminosalycilates (*n*)	9% (9)
% Corticosteroids (*n*)	9% (9)
% Immunosuppressants (*n*)	81% (81)
% Pain medication (*n*)	29% (29)
% Antibiotics (*n*)	4% (4)
% Vitamin supplements (*n*)	51% (51)
% Antidepressants (*n*)	17% (17)
% Sedatives (*n*)	12% (12)
% Hypnotics (*n*)	10% (10)
% Alternative treatments (*n*)	9% (9)

statistically significant) in the retreatment group (97 days; 95%CI: 88 to 106 days vs. 161 days; 95% CI: 86 to 236 days; Log Rank statistic = 3.3; $P = 0.07$). At baseline, the disease activity was significantly higher in patients who required retreatment (CDAI score ± s.d. = 267 ± 103), compared with patients who did not need retreatment (CDAI score ± s.d. = 219 ± 53, $P = 0.02$). This difference was not present at 4 weeks.

Sixteen patients (16%) were infliximab naïve at the time of inclusion. In comparison with the patients who had already received infliximab in the past, infliximab-naïve patients had received significantly fewer treatments for active CD in the previous year ($P < 0.001$) and there had been a longer time since the previous treatment for active CD ($P = 0.002$). However, the time until retreatment ($P = 0.27$) and all other baseline and prospective variables did not differ significantly. The response at 4 weeks was similar in both groups.

Major depressive disorder

Twenty-four patients (24%) were diagnosed with MDD at baseline and the mean summed depression scores were significantly higher (16.8 ± 3.7) in these patients than in non-depressed patients (6.2 ± 3.2, $P < 0.001$). The demographics and the disease-related variables indicative of the disease course (in general and during the previous year) did not differ significantly between patients with and without MDD. Furthermore, the median number of days since the previous treatment for a flare of CD was not significantly different between patients with MDD (99 days; 95% CI: 85–117 days) and the patients without MDD (98 days; 95% CI: 69–127 days; Log Rank statistic <0.01; $P = 0.97$).

Compared with non-depressed patients, significantly larger proportions of patients with MDD were treated with pain medication (25%, $n = 11$ vs. 44%, $n = 18$, $P = 0.04$), with vitamin supplements (43%, $n = 33$ vs. 75%, $n = 18$, $P = 0.007$), with antidepressants (5%, $n = 4$ vs. 29%, $n = 7$, $P = 0.001$), with hypnotics (7%, $n = 5$ vs. 21%, $n = 5$, $P = 0.07$) and with alternative therapies (4%, $n = 3$ vs. 25%, $n = 6$). The proportion of depressed patients at baseline did not differ between infliximab-naïve and patients treated previously with infliximab ($P = 0.76$).

At 4 weeks, 15 (63%) out of 24 patients still met the diagnostic criteria of MDD and one additional patient was diagnosed with MDD, resulting in a significantly smaller proportion of depressed patients (16%) compared with baseline (24%, $P = 0.021$). The demographics and the disease-related variables did not differ significantly between patients still depressed at 4 weeks and non-depressed patients.

Evolution of clinical disease activity and MDD

The CDAI score in the 75 non-depressed patients (no MDD at baseline, nor at re-evaluation) improved significantly (243 ± 91 to 126 ± 86, $P < 0.001$). There was a significant positive relationship between the mean change in depression score and the mean change in CDAI in the non-depressed patients ($r = 0.35$, $P = 0.002$). At baseline, patients with MDD had significantly higher mean CDAI scores ($n = 24$; 322 ± 104) compared with non-depressed patients ($P < 0.001$). In the 15 patients with MDD at both measuring points, the CDAI score was still significantly higher at the 4 weeks re-assessment ($P < 0.001$), but it had also improved significantly (319 ± 104 to 223 ± 98; $P = 0.009$). The mean change of the CDAI score in these patients (Δ CDAI = 96 ± 120) did not differ from the change in non-depressed patients ($P = 0.49$). There was no relationship however between the mean change in depression score and the mean change in CDAI score in patients with MDD ($r = -0.17$, $P = 0.53$).

The CDAI score decreased significantly in the nine patients who were depressed only at baseline (325 ± 111 to 119 ± 111; $P < 0.001$), and this improvement was significantly more pronounced than in non-depressed patients ($P = 0.01$) and than in patients with MDD at both measuring points ($P = 0.01$). The median CRP at baseline was significantly higher in this group (46.1 mg/L; IQR = 16.5–68.8 mg/L) in comparison with the non-depressed patients (8 mg/L; IQR = 4–21 mg/L, $P = 0.003$) and the patients with MDD at both timepoints (10.6 mg/L; IQR = 3.5–26.5 mg/L, $P = 0.015$). There was no significant difference in CRP levels between the two latter groups at baseline ($P = 0.68$). There was no difference in CRP between the three groups at re-evaluation. The mean change in depression score in the patients who were only depressed at baseline was significant (14.4 ± 2.7 to 6.8 ± 2.7; $P = 0.007$).

Of note was the significant correlation between the depression score and well-being, one of the subjective items of the CDAI, in the total group ($n = 100$, $r = 0.44$, $P < 0.001$ at baseline and $r = 0.58$, $P < 0.001$ at re-evaluation). The correlation between the

depression score and the CDAI score without well-being (adjusted CDAI) was significant for the non-depressed patients at baseline and at re-evaluation (respectively $r = 0.23$, $P = 0.048$ and $r = 0.37$, $P = 0.003$). However, in MDD patients, there was no correlation between the adjusted CDAI and the depression score at baseline ($n = 24$, $r = 0.19$, $P = 0.38$) and at re-evaluation ($n = 16$, $r = -0.02$, $P = 0.95$).

Influence of MDD on short-term therapy outcome

Univariate analysis demonstrated that MDD and the other psychological variables had no effect on response to infliximab. They were not entered in the predicting model. Forward, stepwise logistic regression identified six variables as independent determinants of failure to respond to infliximab (C-statistic = 0.85, Nagelkerke $r = 0.38$, $P < 0.001$): the number of treatments for a flare in the previous year ($P = 0.011$), the number of days since the previous treatment ($P = 0.039$), previous abdominal surgery ($P = 0.006$), a diagnosis of CD after the age of 18 years ($P = 0.011$) and membership of a patient association ($P = 0.042$).

Significantly fewer patients with MDD at baseline however achieved remission (29%) in comparison with non-depressed patients (70%, $P < 0.001$). Additionally, patients with possible anxiety were also significantly less likely to achieve remission ($P < 0.001$). A stepwise regression analysis with remission as dependent variable, adjusted for the baseline CDAI score ($P = 0.006$) and other significant biological variables (Nagelkerke $R^2 = 0.40$, $P < 0.001$), yielded MDD as an independent determinant of failure to achieve remission (OR = 0.166, 95% CI = 0.049–0.567, $P = 0.004$). Other negatively correlated determinants of remission were previous surgery ($P = 0.003$) and female gender ($P = 0.034$). The C-statistic for this model was 0.82, indicating that 82% of all possible pairs of cases in which one case was in remission and the other was not, the logistic regression model assigns a higher probability of remission to the case in remission.

Influence of MDD on long-term outcome of therapy

All patients with MDD at baseline needed retreatment in contrast with 73% of patients without MDD (Fischer's exact test: $P = 0.04$).

Table 2 presents the results of the univariate Cox regression analyses for the significant ($P < 0.05$) and

Table 2. Significant and moderate determinants in univariate Cox regression analyses

	Relative hazard	95% CI	*P*-value
MDD (reference: no depression)	2.405	1.48–3.90	<0.001
Other Psychosocial variables			
Antidepressant (reference: no antidepressant)	1.657	0.98–3.68	0.058
HADS Anxiety subscale (reference: no anxiety)			0.025
Possible anxiety disorder (HADA >7)	1.361	0.80–2.33	0.26
Probable anxiety disorder (HADA >10)	2.038	1.22–3.42	0.007
SSL-I negative interaction	1.090 per 1 point ↑ on scale	1.03–1.16	0.006
Demographic and disease related variables			
Age (reference: quartile 4 = 42–59 years)			0.08
Age quartile 1 (18–25 years)	1.321	0.733–2.38	0.35
Age quartile 2 (26–33 years)	2.054	1.12–3.76	0.02
Age quartile 3 (34–41 years)	1.068	0.58–1.97	0.83
Member of patient association (reference: non-member)	1.521	0.94–2.45	0.09
Age of diagnosis (reference: quartile 4 = 28–55 years)			0.002
Age quartile 1 (6–17 years)	2.415	1.31–4.45	0.005
Age quartile 2 (18–22 years)	2.963	1.61–5.47	0.001
Age quartile 3 (23–27 years)	2.269	1.15–4.47	0.02
Colonic localization (reference other localizations)	1.491	0.95–2.33	0.08
Any treatment for flare within the previous year	1.378 per treatment	1.23–1.55	<0.001
Number of days since the previous treatment	0.996 per day	0.994–0.999	0.003
CDAI	1.002 per 1 point ↑ on CDAI	1.00–1.01	0.03
CDAI at re-evaluation	1.003 per 1 point ↑ on CDAI	1.00–1.01	0.008
Response at re-evaluation (reference: no response)	0.554	0.34–0.92	0.02

Table 3. Multivariate Cox regression with time to retreatment as dependent variable and baseline variables as predictors

Variables	Relative hazard	95% CI	*P*-value
MDD (reference: no depression)	2.271	1.36–3.79	0.002
Antidepressant (reference: no antidepressant)	2.332	1.16–4.67	0.017
Age of diagnosis (reference: quartile 4 = 28–55 years)			0.003
Age quartile 1 (6–17 years)	2.122	1.12–4.02	0.021
Age quartile 2 (18–22 years)	3.062	1.61–5.82	0.001
Age quartile 3 (23–27 years)	2.89	1.44–5.79	0.003
Any treatment for flare within the previous year	1.332 per treatment	1.17–1.51	<0.001
Crohn's colitis (reference: other localizations)	1.825	1.14–2.94	0.013

moderate (<0.10) psychosocial, demographic and disease-related and variables. There was a significant association between MDD and the time to retreatment. Also for anxiety, negative interaction in social support and sleep associations with time to retreatment were found. Also variables reflecting the course of the disease were moderately ($P < 0.10$) to significantly ($P < 0.05$) related to the time until the next treatment. Higher disease activity at baseline and even more at 4 weeks increased the risk of earlier retreatment, whereas a response to infliximab decreased this risk. All other variables did not show a statistically significant association with time until the next treatment for disease activity.

Major depressive disorder and the use of antidepressants were identified by a multivariate Cox regression analysis as independent, significant predictors of time to retreatment (Table 3). Additionally, variables reflecting the course of the disease were also identified as predictors. A Kaplan–Meier survival curve demonstrates the significant difference in time until the next retreatment between patients with MDD and without MDD (Figure 1). Substituting the baseline measurements by the measurements at re-evaluation (PHQ, HADS and CDAI at re-evaluation) and adding response to the infliximab treatment to the model did not yield different determinants. Moreover, the 16 patients with MDD at re-evaluation had a relative risk of 3.218 (95% CI = 1.712–6.051, $P < 0.001$) for earlier relapse, whereas *post hoc* analysis showed that the risk at earlier relapse was not significantly increased in the nine patients who only fulfilled the diagnostic criteria for MDD at baseline (RR = 1.282, 95% CI = 0.641–2.565, $P = 0.48$).

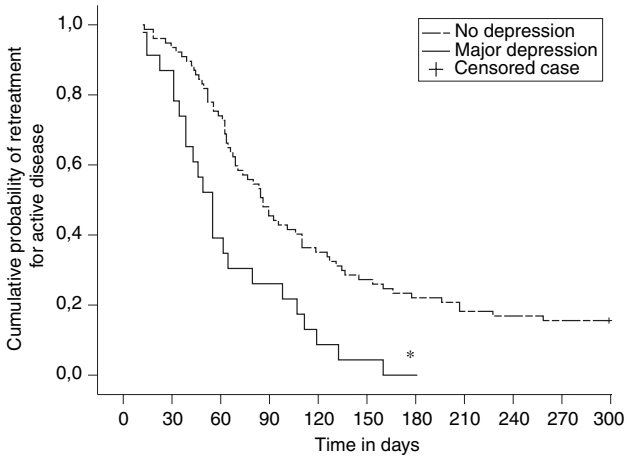

Figure 1. Patients with MDD needed retreatment for disease activity significantly earlier than patients without MDD. *Log Rank statistic = 11.62; $P = 0.0007$.

DISCUSSION

The principal finding of this study is that MDD is a predictor of failure to reach remission after infliximab treatment for active luminal CD and of an earlier need for retreatment. Major depressive disorder is a highly relevant comorbid condition to patients with CD, given that this disorder is the most common psychological disorder in CD. Studies in IBD and other chronic medical diseases, which assessed MDD as a separate categorical diagnosis, found prevalence rates of 6–14%.[6, 39, 40] At baseline, the prevalence of depression in our cohort was higher, which could be explained by the fact that only patients with active CD were included. At re-assessment after treatment, the proportion of patients with MDD

was comparable with that previously reported,[6, 39] suggesting that if MDD was diagnosed at baseline, but not at re-evaluation, this reflected a psychological reaction to the disease activity in a subgroup of patients. The higher CRP at baseline and the significantly larger improvement of disease activity in this subgroup of patients supports the hypothesis that these patients were indeed objectively more seriously ill. However, the severity of objective disease activity does not provide sufficient explanation for the presence of MDD in the 15 patients who still fulfilled the diagnostic criteria of MDD after treatment, as in these patients the disease activity had also improved significantly. Improvement of the disease activity had little effect on the depressed mood in the these patients.

Major depressive disorder and other psychosocial variables were not predictive of short-term response to infliximab. Predominantly variables reflecting a severe or refractory course of CD were associated to a failure of short-term response to infliximab treatment, as already found in previous studies.[25–28] Conversely, MDD was an independent determinant in the disease activity-adjusted prediction of short-term remission, as was female gender. In the present study, MDD and antidepressant therapy were also significant risk factors influencing the long-term outcome of CD after infliximab. It has been shown that depressed mood contributes to poorer well-being, lower pain thresholds and more reported symptoms, which might explain the higher CDAI scores at baseline and at re-evaluation in depressed patients.[41, 42] Furthermore, female gender influences symptom reporting, whether or not there is a psychiatric comorbidity.[43]

Of all assessed psychosocial variables, MDD was the only variable which was an independent determinant of unfavorable short-term (remission) and long-term outcome after infliximab. Besides the greater disease severity in patients with MDD, the presence of MDD might also bias the short-term outcome after treatment by its influence on the disease activity score, the CDAI. The high weight resulting from subjective well-being is a recognized limitation in the CDAI.[44] This is illustrated in the present study by the significant relationship between the depression score and subscore of well-being on the one hand, and by the lack of relationship between the depression score in MDD patients and the adjusted CDAI score on the other hand. Thus, the presence of MDD clearly influences the CDAI score. As a consequence remission may not have been achieved, due to a higher baseline and follow-up CDAI score through the subjective item of well-being, whereas response on the CDAI score which decreases proportionally in comparison with non-depressed patients was not affected. Conversely, MDD seems to have a true effect on the long-term outcome of CD after infliximab treatment. Our results show that depression in the subgroup of 15 patients with MDD at both measuring points was unrelated to the disease course and overall severity prior to inclusion in the study. Yet, the relative risk at early retreatment was three times higher for patients with MDD after treatment with infliximab.

The presence of MDD may worsen the disease. Major depressive disorder may have a direct influence on immune deregulation associated with CD. Several studies have shown that MDD is associated with enhanced production of cytokines, such as IL-6 and TNF-α, and successful pharmacological treatment of MDD decreases the elevated cytokine levels.[45–47] Major depressive disorder might also have an indirect influence through adverse health behaviours, such as smoking and inappropriate diet, or through non-compliance to self-care regimens. A recent meta-analysis has indicated that depression is one of the main reasons of non-compliance to treatment in patients with chronic diseases.[48] Additionally, IBD patients with a comorbid psychiatric disorder present with significantly more medically unexplained symptoms and have an altered perception of disease severity.[39] Furthermore, depressed patients with chronic medical illness consult their physician more frequently.[2] These factors might ultimately lead to earlier consultation and retreatment in CD patients with MDD.

Our findings support the need for an active identification and management of MDD in CD patients in stead of merely attributing depressed mood to the severity of the disease. This certainly applies to patients who still show signs of depression after an adequate treatment for active CD. This might also be the right time to screen for MDD, which is a clearly defined and well-treatable psychiatric disorder. Recent evidence has indicated that psychological support improves compliance to gluten-free diet in patients with celiac disease.[49] In diabetic patients, psychological therapies result in a reduction of psychological distress and in significantly better glycemic control[50] Furthermore, it may be important to detect MDD in patients under consideration for pivotal drug studies as patients with concomitant MDD may not be good candidates to take part in these studies. Active screening for MDD in studies and during treatment for

CD can be done with the PHQ. This is a very short (nine items) and reliable self-report questionnaire, which yields a categorical diagnosis of MDD and a severity score of depression and which has been validated in medical and gastroenterological patients.[30, 31] In this way, awareness in gastroenterologists and patients could be increased. Psycho-education of CD patients concerning psychological distress and disorders should be standard practice. Efficacious, safe medication and psychotherapy for MDD are also available. Ideally, follow-up of CD patients with MDD should be done in collaboration with a liaison psychologist or psychiatrist. Future research is needed to identify subgroups of patients at risk of developing MDD or other psychiatric disorders and to examine if interventions such as prevention strategies, psychopharmacotherapy, or psychotherapy have an effect on the outcome after treatment.

In conclusion, our results show that MDD influences the short- (remission) and long-term outcome after treatment with infliximab in CD patients. Persistent MDD after adequate treatment of CD is a risk factor for early retreatment. As there is no cure for CD, it is important to optimize the available therapy and ultimately maximize the time of remission. Therefore, adequate management of depression in the CD patient is necessary.

ACKNOWLEDGEMENTS

This study was funded by the Fund of Scientific Research – Flanders (Belgium).

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