

## Concise Report

# Depression in RA patients treated with anti-TNF is common and under-recognized in the rheumatology clinic

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**Objectives.** Depression is common in RA and may be influenced by both disease activity and severity. The aims of this study were to investigate the prevalence of depression in RA patients starting anti-TNF therapy, to investigate how mood alters after exposure to anti-TNF and to determine whether depression is recognized and appropriately managed in the clinic.

**Methods.** Patients starting anti-TNF therapy were assessed for depression using the Hospital Anxiety and Depression Scale (HADS-D), and classified as depressed with an HADS-D of  $\geq 8$ . Change in mood was assessed at 6 weeks, 4 months and 12 months. Disease activity data were recorded at baseline, 3 and 12 months. Patients who remained persistently depressed at 4 months had their clinical case notes reviewed to determine whether their low mood had been recognized or treated.

**Results.** Depression was common in this cohort. Depressed patients had higher disease activity scores (DAS28) at all time points, and patients with persistent depression had smaller reductions in DAS28 [median (interquartile range or IQR) change DAS28 1.71 (0–2.6) vs 2.2 (1.5–3.2);  $P=0.005$ ]. Only 57% (13/23) patients with persistent depression at 4 months had their depression recognized or managed within the rheumatology clinic.

**Conclusions.** Depression is common but under-recognized in RA patients starting on anti-TNF therapy. Patients with persistent depression tended to respond less well to anti-TNF, with smaller reductions in DAS28. Given that a significant reduction in DAS28 is a requirement for continuing therapy, recognition and appropriate management of depression may improve TNF effectiveness.

**KEY WORDS:** Rheumatoid arthritis, Depression, Anti-TNF.

## Introduction

RA and depression commonly co-exist with conservative estimates of the prevalence of depression in RA between 13 and 20% [1–3]. Prevalence of depression in RA is related to several factors including pain, physical disability [4] and comorbidity [5], and is highest among those with the most severe disease. Data from the UK biologics registry suggested that 19% of those commencing anti-TNF therapy had a diagnosis of depression at some time in their disease course [6].

Importantly, depression may influence both reporting of symptoms and response to medication. Studies show that the HAQ score, the most frequently used measure of physical disability, is strongly influenced by depression [7] and pain reporting is similarly influenced [2]. Comorbid depression increases both work disability [8] and mortality in RA [9]. In addition, depression may influence response to treatment both in RA [10] and in FM [11].

Thus, comorbid depression is common and negatively influences disease course and treatment outcome. This study was undertaken to investigate whether depression was recognized and appropriately treated within the routine rheumatology clinic in a cohort of patients with severe RA starting on anti-TNF therapy.

## Patients and methods

### Subjects

Patients were recruited from the anti-TNF clinic at the Staffordshire Rheumatology Centre, a large secondary

care centre. All patients starting anti-TNF therapy for RA between 2002 and 2006, satisfying ARA criteria for RA [12], were eligible to be included in the study. Patients were assessed for depression using the Hospital Anxiety and Depression Scale (HADS) [13]. Patients were classified as having probable depression if they had an HADS depression score (HADS-D) of  $\geq 8$ , and severe depression if they had an HADS-D of  $\geq 11$ . Change in mood using the HAD was assessed at 6 weeks, 4 and 12 months. Patients were classified as persistently depressed if they had an HADS-D score of  $\geq 8$  at baseline and on a second occasion in the first 4 months. Data on disease activity, including components of the disease activity score (DAS28) [14], were recorded at baseline, 3 and 12 months. Patients who were withdrawn from anti-TNF for any reason during the study were excluded from further follow-up. Patient's written consent was obtained according to the Declaration of Helsinki, and the study was approved by the North Staffordshire local research ethics committee.

To determine whether depression was recognized and appropriately managed within the routine rheumatology clinic, patients who remained persistently depressed at 4 months had their clinical case notes reviewed to determine whether their low mood had been recognized and/or managed with either anti-depressant therapy or onward referral. This cut-off of 4 months for persistent depression was deliberately chosen as we hypothesized that if anti-TNF therapy is effective and leads to an improvement in disease activity and pain, there may be an associated improvement in mood and, therefore, we did not wish to be prematurely treating patients with low mood who may have improved without additional management.

### Statistical analysis

Differences in the clinical variables between depressed and non-depressed patients were investigated using the Wilcoxon–Mann–Whitney test for continuous variables. Data are presented as median [interquartile range (IQR)] unless otherwise stated. All analyses were performed using STATA 8.

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Submitted 13 October 2008; revised version accepted 26 May 2009.

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## Results

### *Patient characteristics and prevalence of depression*

Of 160 potentially eligible patients, 159 were eligible for the study. This was a typical cohort of anti-TNF patients with severe long-standing RA, mean  $\pm$  (s.d.) disease duration of 13.6 (8.7) years. Within the cohort, 72% were female, with a mean  $\pm$  (s.d.) age of 56.4 (12.18) years, and 76% of the patients were RF positive. Depression occurred frequently in this cohort, with 76/160 (47.5%) classified as depressed at baseline. The proportion of patients continuing on anti-TNF therapy was 156/159 (98%) at 6 weeks, 138/159 (87%) at 4 months and 122/159 (77%) at 12 months. The percentage of patients completing the HAD was 114/156 (73%) at 6 weeks, 106/138 (77%) at 4 months and 82/122 (67%) at 12 months. The proportion of patients continuing anti-TNF but remained depressed fell to 24% at 6 weeks, 19% at 4 months and 15% at 12 months. The development of new depression following anti-TNF exposure was uncommon; only five patients were subsequently classified as depressed over the next 12 months.

### *Effect of persistent depression on disease activity*

Subjects who were classified as depressed at baseline had higher DAS28 scores than those who were not depressed at baseline at all time points (Table 1), although this difference was no longer statistically significant at 12 months. Evaluating the DAS28 scores at 3 months of those remaining on anti-TNF ( $n=138$ ), in those subjects with persistent depression, the reduction in DAS28 at 3 months was lower than in those without persistent depression [median (IQR) change DAS28 1.71 (0–2.6) vs 2.2 (1.5–3.2);  $P=0.005$ ], indicating that the anti-TNF therapy had a less beneficial impact on their disease activity measures. This difference was due to effects on both objective measures of inflammation [swollen joint count (SJC) persistent depressed vs non-depressed, 7 vs 4;  $P=0.006$ ] and more subjective measures (or potentially influenced by mood) such as the tender joint count (TJC) (persistent depressed vs non-depressed, 9 vs 5;  $P=0.001$ ), and was despite having similar disease activity at baseline. These results are summarized in Table 2.

### *Management of persistent depression in the routine clinic*

Of the 23 patients with persistent depression at 4 months, depression had been recognized and treatment initiated before the start of anti-TNF in nine (39%) patients. Further, four (17%) patients received treatment for depression following anti-TNF initiation. However, 10/23 (43%) patients did not have their depression recognized or treated during the follow-up. Three (30%) of these patients with unrecognized depression had an HADS-D score of  $\geq 11$  at baseline, suggesting severe depression. The majority of those patients receiving treatment for depression was prescribed anti-depressants although 6/23 (26%) were also referred to a liaison psychiatry clinic for further assessment.

## Discussion

Co-existent depression is common in RA and is more frequent with both worsening disease activity and severity. As expected,

in this cohort of patients with severe disease starting anti-TNF treatment, co-existent depression was common. The prevalence of depression in our cohort was higher than that reported by Hyrich *et al.* [6]. Only a small proportion of non-depressed patients at baseline subsequently developed depression following exposure to anti-TNF therapies. This suggests that anti-TNF does not have significant adverse effects on mood in RA.

Patients who were classified as depressed had higher DAS28 scores than those not depressed, although it is of note that both objective measures (such as SJC) and potentially subjective measures (such as TJC) were higher in depressed patients. In addition, patients who exhibited persistent depression had poorer responses to anti-TNF therapy at 3 months, with smaller reductions in DAS28 score. Given that an adequate reduction in DAS28 is a pre-requisite for continuing with anti-TNF therapy, this suggests that depressed patients, particularly those whose depression is persistent, may be more at risk of having their treatment deemed ineffective than those not depressed.

Depression was generally poorly recognized within the routine rheumatology clinic with 10/23 (43%) of those patients with persistent depression not having their depression recognized or treated. This is despite frequent outpatient attendances by all patients as they were started on new therapeutic regimes. Given that depression is eminently treatable, with studies suggesting that 70% of the patients respond to first-line treatment with anti-depressants [15, 16], these results are disappointing and represent a missed opportunity to improve care for these patients. However, given that studies suggest only 30–50% of the general population with depression receive appropriate intervention [17], and we studied patients with severe and active RA for whom the focus of the consultation would not have been mood disturbance, our results are perhaps not surprising. We included all patients with an HAD-D of  $\geq 8$  in the analysis, including those who had treatment initiated for depression before commencing anti-TNF, as they had failed to respond adequately to anti-depressant therapy as indicated by an HAD-D of  $\geq 8$ .

There are a number of strengths and weaknesses that need to be considered when interpreting the results of this study. All RA patients starting anti-TNF therapy were included in the study and thus results should be generalizable to other large secondary care urban rheumatology centres. Data were collected during the time period that anti-TNF was introduced to the UK. This inevitably means that a severely affected group of historical non-responders to DMARDs are included within this cohort. These patients tend to have severe RA and may have higher levels of physical functional loss, disease activity and depression. This should not influence the overall findings of this study, but may have increased the levels of disease activity and depression described within the cohort.

Patients were characterized as depressed if they had an HAD-D score of  $\geq 8$ . Although a diagnosis of depression can only be made on the basis of a diagnostic interview, studies suggest that using an HAD-D cut-off of  $\geq 8$  to identify depression compares well with the gold standard of a diagnostic interview, with a sensitivity and specificity of around 0.8 [18]. In addition, patients completed the HAD questionnaires at different time points to their clinical reviews, disease activity and DAS28 assessments to attempt to reduce any direct effects of clinician contact on mood.

TABLE 1. Effect of baseline depression on the DAS28 and HAD-D score

	Baseline depressed, median (IQR)	Baseline not-depressed, median (IQR)	<i>P</i> -value	Mean $\pm$ s.d. change from baseline depressed	Mean $\pm$ s.d. change from baseline not-depressed	<i>P</i> -value
HADS-D baseline	11 (9–13)	5 (3–6)	0.0001			
HADS-D 6 weeks	8 (5–11)	3 (1–5)	0.0001	2.9 $\pm$ 3.75	1 $\pm$ 2.6	0.004
HADS-D 4 months	8 (4–11)	4 (1–5)	0.0001	3.2 $\pm$ 4.58	1.11 $\pm$ 2.8	0.01
HADS-D 12 months	8 (3–9)	2 (1–4)	0.0001	3.75 $\pm$ 3.95	1.49 $\pm$ 2.4	0.01
DAS28 baseline	7.2 (6.5–7.8)	6.7 (5.9–7.4)	0.005			
DAS28 3 months	5.0 (3.9–6.4)	4.5 (3.7–5.3)	0.02	1.93 $\pm$ 1.38	2.1 $\pm$ 1.2	0.32
DAS28 12 months	5.5 (4.8–6.3)	4.5 (3.1–5.6)	0.42	2 $\pm$ 1.37	1.95 $\pm$ 1.69	0.85

TABLE 2. Effect of persistent depression on disease activity

	Persistent depression	No persistent depression	P-value
Baseline			
28-TJC	18 (11–24)	17 (11–24)	0.76
28-SJC	13 (10–18)	11 (8–16)	0.1
ESR	52 (38–64)	46 (32–70)	0.35
CRP	59 (27–91)	45 (23–65)	0.16
PGA	72 (60–89)	77 (68–86)	0.5
DAS28	7.1 (6.43–7.82)	6.8 (6.06–7.58)	0.09
3 months			
28-TJC	9 (4–19)	5 (2–8)	0.001
28-SJC	7 (4–11)	4 (2–7)	0.006
ESR	39 (20–62)	27 (12–43)	0.08
CRP	22 (9–60)	12 (5–37)	0.045
PGA	35 (22–62)	29 (17–45)	0.3
DAS28	5.8 (4.4–6.7)	4.4 (3.5–5.3)	0.001
Change DAS28	1.7 (0–2.6)	2.2 (1.5–3.2)	0.005

Results are expressed as median (IQR).

Because treatment for depression was determined by the review of secondary care case notes, it is possible that some patients may have received treatment for depression, initiated in primary care, but not recorded in the secondary care. However, patients were specifically asked to report any change in medication at each clinic attendance, and subsequent under-reporting of anti-depressant initiation is unlikely to have significantly influenced our findings.

In summary, depression is common in patients starting anti-TNF therapy and tends to improve after anti-TNF exposure. However, depression is significantly under-recognized and treated within the rheumatology clinic. Given that depression is treatable and is associated with poorer responses to anti-TNF, recognition and appropriate management of depression may improve TNF effectiveness.

### Rheumatology key messages

- Persistent depression is poorly recognized and managed in routine rheumatology clinics.
- Patients with persistent depression have a poorer response to anti-TNF therapy.
- Appropriate management of depression may improve effectiveness of anti-TNF.

**Disclosure statement:** J.C.P. has received unrestricted educational grants from Wyeth and Roche for studies in RA and AS unrelated to this publication. All other authors have declared no conflicts of interest.

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