

Characterisation of depressive symptoms in rheumatoid arthritis patients treated with tocilizumab during routine daily care

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Abstract Objective

To assess whether tocilizumab treatment is associated with changes in depression symptoms in patients with rheumatoid arthritis (RA) during routine daily care.

Methods

We retrospectively analysed data from a German non-interventional study (ARATA) of adult, tocilizumab-naïve RA patients who initiated subcutaneous tocilizumab and were followed for 52 weeks. The Beck Depression Inventory II (BDI-II) was used to assess symptoms of depression and create baseline subgroups of no (BDI-II<14), mild (14–19), moderate (20–28), and severe (≥29) depression. Other key outcomes included Disease Activity Score-28 joints (DAS28), patient-reported outcomes (PROs), and adverse events. Mixed model repeated measures (MMRM) assessed the impact of DAS28 on BDI-II over time, and Pearson correlation analyses evaluated associations between changes from baseline.

Results

Of 474/1155 ARATA patients who completed the BDI-II at baseline, 47.7% had evidence of depression: 18.4% mild, 17.7% moderate, and 11.6% severe. 229 patients (48.3%) completed the BDI-II at both baseline and week 52. Two-thirds of patients with moderate or severe depression at baseline improved to a milder or no depression subgroup at week 52 (44/65 [67.7%]). Improvements in disease activity and PROs were observed in all subgroups, but patients with depression had lower response and higher adverse events rates. We observed an association between DAS28 and BDI-II over time in MMRM analyses, but the Pearson correlation for change from baseline was weak ($r=0.10$).

Conclusion

Depression is common in patients receiving routine care for RA. Improvements in depressive symptoms in RA during tocilizumab therapy appear to be distinct from changes in disease activity.

Key words

tocilizumab, depression, rheumatoid arthritis, disease activity, biologic agents

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Introduction

Symptoms of depression are common
 in patients with rheumatoid arthritis
 (RA) (1). In a recent study, more than
 half of RA patients reported mild or
 worse depression and 23% reported
 moderate or worse depression (2).
 Compared with matched cohorts with-
 out RA, RA patients have an approxi-
 mately 50% higher incidence of de-
 pression (3). Despite changes in man-
 agement, including the widespread use
 of anti-tumour necrosis factor (TNF)
 agents and treat-to-target strategies, the
 risk of depression in patients with RA
 remained fairly steady between 1989
 and 2012 (1). It has been hypothesised
 that higher rates of depression in RA
 may be related to the increased inflam-
 matory burden associated with this dis-
 ease (4).

Interleukin-6 (IL-6) levels are in-
 creased in patients with depression (5)
 and several lines of evidence impli-
 cate this cytokine in the pathogenesis
 of depression (6). In a study involving
 healthy volunteers, induction of sys-
 temic inflammation by endotoxin ad-
 ministration resulted in both depressive
 symptoms and increased IL-6 in the
 cerebrospinal fluid. IL-6 levels corre-
 lated with dysthymia scores at all time
 points (7). A meta-analysis of studies
 of peripheral cytokine levels in major
 depressive disorder found that treat-
 ment with antidepressants significantly
 reduced IL-6 levels (8).

Tocilizumab, a humanised monoclonal
 antibody that inhibits the IL-6 signaling
 pathway by binding to the IL-6 recep-
 tor, is approved for the treatment of RA
 throughout the world. Small studies (9)
 and meta-analyses (10) have suggested
 a decrease in depressive symptoms in
 RA patients treated with tocilizumab.
 The aim of the current study was to
 assess whether tocilizumab was asso-
 ciated with changes in symptoms of
 depression during routine daily care of
 patients with RA.

Patients and methods

Study design

This was a *post-hoc* analysis of data
 from a prospective, multicentre, non-
 interventional study of German pa-
 tients with RA (the ARATA study;

NCT02251860). Adult (≥ 18 years)
 tocilizumab-naïve patients with active
 RA based on clinician assessment who
 initiated tocilizumab therapy during
 routine clinical care were eligible for
 study enrolment. No other inclusion
 criteria were applied. All patients gave
 informed consent. The study was con-
 ducted in accordance with the Declara-
 tion of Helsinki and the International
 Conference on Harmonisation Good
 Clinical Practice Guidelines. Ethics
 approval was obtained from the Ethics
 Commission of the Medical Depart-
 ment of Goethe University, Frankfurt
 am Main, Germany and the Ethics
 Commission of the Medical Associa-
 tion of Rheinland-Pfalz, Mainz, Ger-
 many.

Data collection began at the baseline
 visit (week 0) before initiation of to-
 cilizumab treatment; the data reported
 here are based on the first 52 weeks fol-
 lowing study initiation (study visits at
 weeks 4, 12, 24, 36, and 52). Data were
 collected on an electronic case report
 form, patient diaries, and question-
 naires. The effectiveness set was de-
 fined as all eligible patients with docu-
 mented informed consent who received
 a first dose of subcutaneous (SC) toci-
 lizumab on or within four weeks after
 the baseline visit and had at least one
 post-baseline visit.

By German law, patients had the dis-
 cretion to choose which self-report
 questionnaires to complete. The evalu-
 ations reported here focus on patients
 who completed the Beck Depression
 Inventory II (BDI-II) questionnaire at
 baseline (BDI-II cohort).

Outcomes

Outcome data encompassed patient-
 reported mental health, additional pa-
 tient-reported outcomes (PROs), and
 measures of disease activity.

Mental health outcomes were assessed
 by the BDI-II and the State-Trait Anxi-
 ety Inventory (STAI) form X. The
 BDI-II is a self-report questionnaire
 for depression screening that has been
 validated in RA (11). It consists of 21
 items representing typical signs of de-
 pression scored on a scale ranging from
 0 (best) to 3 (worst) for a total score of
 0 to 63. For the analyses in this study,

BDI-II scores <14 were classified as “no depression,” scores of 14-19 were considered “mild depression,” 20 to 28 “moderate depression,” and ≥ 29 “severe depression” (12). BDI-II changes of ≥ -10 to ≤ 10 were considered no or minimal change, changes >10 were considered moderate to large deterioration, and changes < -10 were considered large to moderate improvement (13). Suicidal ideation was assessed by BDI-II question 9; any answer other than no (=0) was considered as “yes.” The study physician was informed by email about outcomes with BDI-II ≥ 14 or suicidal ideation.

The STAI is a patient-reported questionnaire with two 20-item subscales measuring how respondents feel “right now” (state anxiety; STAI-state) and their overall inclination for anxiety (trait anxiety; STAI-trait). Higher scores indicate greater anxiety (14).

PROs were used to assess global disease activity, pain, fatigue, sleep, and function. The patient global assessment of health (PGA), pain (last 7 days), fatigue (last 7 days), and sleep difficulties (last 4 weeks) were assessed on 100-point visual analogue scales (VAS) from 0 mm (best possible status) to 100 mm (worst possible status). The Health Assessment Questionnaire-Disability Index (HAQ-DI), a measure of functional ability, was assessed on a scale of 0 (best) to 3 (worst) (15). HAQ-DI ≤ 0.5 was considered functional remission.

We used the Disease Activity Score based on 28 joints (DAS28) and the Clinical Disease Activity Index (CDAI) as assessments of disease activity; higher scores indicate greater disease activity for both. DAS28 was calculated using erythrocyte sedimentation rate (ESR) as the acute phase reactant (DAS28-ESR). Remission was defined as < 2.6 (16) and an individual therapeutic response (DAS28- d_{crit}) was defined as a DAS28-ESR decrease ≥ 1.8 from baseline (17). For the CDAI (18), remission was defined as ≤ 2.8 (16). The physician global assessment of health (PhGA) was assessed by the clinician on a VAS from 0 (best) to 100 (worst) possible status.

Safety analyses were based on adverse event reports obtained at each visit.

Table I. Baseline characteristics of patients with completed BDI-II questionnaires by BDI-II subgroup.

Characteristic	No depression (BDI-II <14)	Mild depression (BDI-II 14-19)	Moderate depression (BDI-II 20-28)	Severe depression (BDI-II ≥ 29)
n*	248	87	84	55
Age, mean (SD)	56.0 (12.7)	55.3 (11.6)	54.6 (12.5)	55.4 (13.5)
Female sex, n (%)	175 (70.6)	67 (77.0)	69 (82.1)	48 (87.3)
RA disease duration, mean (SD) [n evaluated]	11.2 (8.8) [246]	10.3 (10.4) [85]	9.9 (8.8) [83]	9.8 (9.3) [54]
Disease activity measures, mean (SD)				
DAS28-ESR, mean (SD) [n evaluated]	4.9 (1.2) [207]	5.0 (1.2) [73]	4.9 (1.3) [68]	4.9 (1.3) [47]
CDAI, mean (SD) [n, evaluated]	23.9 (10.2) [244]	25.3 (10.6) [84]	24.7 (10.7) [75]	24.2 (9.2) [53]
PhGA, [†] mean (SD) [n evaluated]	57.3 (21.6) [245]	58.3 (21.6) [85]	58.7 (21.6) [80]	58.5 (21.0) [54]
Patient-reported outcomes				
BDI-II, mean (SD)	6.8 (4.4)	16.3 (1.6)	23.1 (2.6)	37.2 (8.9)
STAI-State, mean (SD) [n evaluated]	38.6 (9.6) [223]	44.1 (10.4) [78]	49.2 (9.3) [72]	56.7 (9.7) [46]
STAI-Trait, mean (SD) [n evaluated]	36.3 (8.5) [219]	43.9 (8.8) [79]	47.3 (9.0) [75]	57.2 (8.2) [48]
Use of antidepressants, [‡] n (%)	12 (4.8)	7 (8.0)	4 (4.8)	9 (16.4)
Suicidal ideation, n (%) [n evaluated]	5 (2.0) [248]	5 (5.7) [87]	11 (13.1) [84]	29 (52.7) [55]
PGA, [†] mean (SD) [n evaluated]	59.2 (23.5) [247]	62.7 (22.2) [86]	66.5 (17.8) [78]	69.9 (21.4) [54]
HAQ-DI, mean (SD) [n evaluated]	0.9 (0.7) [242]	1.3 (0.7) [87]	1.4 (0.6) [84]	1.6 (0.7) [54]
Fatigue, [†] mean (SD) [n evaluated]	45.1 (28.6) [192]	64.2 (25.8) [67]	65.1 (22.1) [63]	77.7 (18.0) [40]
Pain, [†] mean (SD) [n evaluated]	51.6 (27.8) [193]	61.2 (23.6) [66]	62.3 (24.8) [63]	71.6 (21.4) [40]
Sleep disturbance, [†] mean (SD) [n evaluated]	35.0 (30.0) [191]	50.7 (30.6) [66]	59.2 (28.7) [63]	67.2 (28.2) [40]
Prior therapy, n/N (%)				
sDMARD only	95/248 (38.3)	28/87 (32.2)	30/84 (35.7)	22/55 (40.0)
bDMARD only	74/248 (29.8)	20/87 (23.0)	17/84 (20.2)	9/55 (16.4)
sDMARD and bDMARD	78/248 (31.5)	39/87 (44.8)	36/84 (42.9)	24/55 (43.6)
No information	1/248 (0.4)	0	1/84 (1.2)	0
Therapy at baseline, n/N (%)				
SC TCZ therapy	248/248 (100)	87/87 (100)	84/84 (100)	55/55 (100)
TCZ + any sDMARD	91/248 (36.7)	36/87 (41.4)	22/84 (26.2)	16/55 (29.1)
TCZ without sDMARD	157/248 (63.3)	51/87 (58.6)	62/84 (73.8)	39/55 (70.9)
Systemic glucocorticoids	151/248 (60.9)	57/87 (65.5)	58/84 (69.0)	33/55 (60.0)
Mean glucocorticoid dose in mg/day (SD) [n evaluated]	6.1 (3.6) [151]	7.5 (5.1) [57]	7.8 (7.1) [58]	7.1 (3.9) [33]

*If not indicated otherwise, [†]Evaluated on a visual analogue scale from 0 (best) to 100 (worst)

[‡]Based on free text entry from patient self-report; antidepressant use was not included on the case report form and past medical records were not evaluated

BDI-II: Beck Depression Inventory II; CDAI: Clinical Disease Activity Index; DAS28: Disease Activity Score based on 28 joint count; ESR: erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire-Disability Index; PGA: patient global assessment; PhGA: physician global assessment; RA: rheumatoid arthritis; SC: subcutaneous; SD: standard deviation; sDMARD: synthetic disease-modifying antirheumatic drug (methotrexate [oral or parental], leflunomide, cyclosporine A, gold, azathioprine, tofacitinib, sulfasalazine); STAI: State-Trait Anxiety Index; TCZ: tocilizumab.

Statistical analyses

Statistical analyses were performed using SAS v. 9.4 (Cary, NC, USA). Descriptive statistics or frequencies were computed for all data as appropriate. Missing data were not imputed. Analy-

ses on change from baseline to week 52 were performed on patients in the BDI-II cohort with data for the given evaluation at both time points. Pearson correlation analyses with 95% confidence intervals (CIs) were used to ex-

plore association between change from baseline for specified pairs of variables; CIs that crossed zero indicated that no statistically significant correlation was observed. As this was an observational study, CIs should be considered descriptive. Mixed models repeated measures (MMRM) analyses were used to evaluate the association of DAS28-ESR and BDI-II over time, with DAS28-ESR and BDI-II scores as continuous variables and time as visits from baseline to week 52. An unstructured covariance matrix was used. *p*-values <0.05 were considered significant.

Results

Patient population

Patients were enrolled from 108 clinical centres throughout Germany between 23 May 2014 and 11 July 2018. The effectiveness set encompassed 1155 patients of whom 856 (74.1%) were female. The mean (standard deviation [SD]) age was 57.4 (12.3) years and the mean (SD) RA duration was 10.1 (9.1) years (Supplementary Table S1).

A total of 474 patients (41.0%) in the effectiveness cohort completed the BDI-II questionnaire at baseline (BDI-II cohort; Table I). Of these patients, 256 had BDI-II data at week 24 and 229 had BDI-II data at week 52 (Suppl. Fig. S1). Patients who completed the BDI-II had similar baseline characteristics to patients who did not complete this questionnaire (n=681; Suppl. Table S2), including DAS28-ESR (mean [SD] of 4.9 [1.2] for patients who completed the BDI-II vs. 4.9 [1.3] for those who did not) and PGA (62.3 [22.4] vs. 64.3 [20.8]).

Almost half (226/474; 47.7%) the patients in the BDI-II cohort had evidence of depression as indicated by BDI-II scores ≥ 14 . About 30% reported moderate (84; 17.7%) or severe (55; 11.6%) depression. Patients with more severe depression showed differences in baseline characteristics compared with patients with less severe depression (Table I). Disease activity scores were generally comparable across depression subgroups, but patients with severe depression reported reduced functional ability (HAQ-DI) and higher levels of anxiety, fatigue, pain, and sleep disturbance. PGA scores increased with increas-

Table II. Changes in measures of depression and disease activity outcomes over 52 weeks by baseline BDI-II subgroup.

Outcome	No depression (BDI-II <14)	Mild depression (BDI-II 14-19)	Moderate depression (BDI-II 20-28)	Severe depression (BDI-II ≥ 29)
n at baseline	248	87	84	55
Change from baseline to week 52, mean (SD)				
BDI-II	1.1 (7.3)	-4.6 (9.2)	-8.7 (9.3)	-10.8 (10.6)
[n evaluated]	[125]	[39]	[39]	[26]
STAI-State	-2.3 (9.3)	-4.1 (12.4)	-7.0 (12.7)	-4.6 (10.5)
[n evaluated]	[143]	[45]	[43]	[29]
STAI-Trait	-1.7 (8.1)	-1.7 (9.2)	-4.3 (10.0)	-7.1 (6.9)
[n evaluated]	[138]	[46]	[46]	[30]
DAS28-ESR	-2.4 (1.7)	-2.4 (1.6)	-2.2 (2.1)	-2.1 (1.6)
[n evaluated]	[138]	[47]	[46]	[29]
CDAI	-16.0 (12.6)	-17.2 (11.4)	-15.6 (14.2)	-12.9 (9.7)
[n evaluated]	[204]	[64]	[56]	[37]
HAQ-DI	-0.1 (0.6)	-0.3 (0.5)	-0.4 (0.7)	-0.3 (0.5)
[n evaluated]	[177]	[61]	[55]	[36]
PGA	-32.6 (30.8)	-38.1 (25.6)	-34.0 (33.2)	-33.1 (29.0)
[n evaluated]	[208]	[65]	[59]	[38]
PhGA	-37.6 (28.6)	-39.3 (26.7)	-36.6 (30.1)	-30.9 (29.7)
[n evaluated]	[206]	[64]	[61]	[38]
Fatigue	-8.6 (32.3)	-14.4 (31.5)	-18.1 (32.6)	-18.3 (26.8)
[n evaluated]	[135]	[47]	[44]	[26]
Pain	-16.6 (33.5)	-23.6 (29.6)	-26.2 (34.6)	-34.7 (29.5)
[n evaluated]	[138]	[47]	[43]	[26]
Sleep disturbance,	-3.7 (33.7)	-11.1 (26.0)	-21.5 (27.3)	-9.7 (26.7)
[n evaluated]	[136]	[45]	[44]	[26]
Week 52 response and remission rates, n/N (%)				
DAS28-ESR-d _{crit} (decrease ≥ 1.8)	92/138 (66.7)	32/47 (68.1)	27/46 (58.7)	15/29 (51.7)
DAS28-ESR remission (<2.6)	98/153 (64.1)	29/48 (60.4)	30/53 (56.6)	13/29 (44.8)
CDAI remission (<2.8)	68/207 (32.9)	18/64 (28.1)	19/63 (30.2)	5/38 (13.2)
HAQ-DI remission (≤ 0.5)	89/211 (42.2)	17/67 (25.4)	21/66 (31.8)	4/39 (10.3)
Week 52 therapy, n/N (%)				
SC TCZ therapy	189/230 (82.2)	51/73 (69.9)	52/71 (73.2)	29/46 (63.0)
TCZ + any sDMARD	62/230 (27.0)	22/73 (30.1)	16/71 (22.5)	5/46 (10.9)
TCZ without sDMARD	127/230 (55.2)	29/73 (39.7)	36/71 (50.7)	24/46 (52.2)
IV TCZ therapy	7/230 (3.0)	2/73 (2.7)	1/71 (1.4)	4/46 (8.7)
Other biologic therapy	22/230 (9.6)	10/73 (13.7)	11/71 (15.5)	5/46 (10.9)
sDMARD alone	7/230 (3.0)	5/73 (6.8)	1/71 (1.4)	7/46 (15.2)
Systemic glucocorticoids	103/230 (44.8)	34/73 (46.6)	31/71 (43.7)	18/46 (39.1)
Mean glucocorticoid dose				
in mg/day (SD)	5.3 (3.8)	6.0 (4.4)	6.6 (4.9)	5.3 (2.4)
[n evaluated]	[103]	[34]	[31]	[18]

BDI-II: Beck Depression Inventory II; CDAI: Clinical Disease Activity Index; DAS28: Disease Activity Score based on 28 joint count; d_{crit}: critical difference for change in DAS28; ESR: erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire-Disability Index; IV: intravenous; PGA: patient global assessment; PhGA: physician global assessment; SC: subcutaneous; SD: standard deviation; sDMARD: synthetic disease-modifying antirheumatic drug (methotrexate [oral or parental], leflunomide, cyclosporine A, gold, azathioprine, tofacitinib, sulfasalazine); STAI: State-Trait Anxiety Index; TCZ: tocilizumab.

ing depression, but PhGA scores were similar. Patients with severe depression were more likely to be female than patients with no depression (87.3% vs. 70.6%). A greater proportion of patients with severe depression used antidepressants, and over half (29/55; 52.7%) reported suicidal ideation (Table I). Statistical analyses of these differences were not considered appropriate due to the influence of confounding factors.

Comorbidities were common in the BDI-II patient cohort (Suppl. Table S2). Depression was identified as a baseline comorbidity based on review of medical records in 35/472 (7.4%) of patients (no comorbidity data were available for 2 patients). Almost half of patients with severe depression reported arterial hypertension (27/55 [49.1%]) compared with 32.5% to 38.1% in subgroups with no or milder depression. Hepatic disease

and fibromyalgia were also more common in patients with severe depression.

Changes in symptoms of depression

The majority of patients with baseline BDI-II data remained in the study throughout the 52-week period (414/474 [87.3%]) (Suppl. Fig. S1). Of the patients remaining in the BDI-II cohort, 48 (11.6%) had switched to another biologic disease-modifying anti-rheumatic drug (DMARD) at week 52, 20 (4.8%) were on a synthetic DMARD alone, and 14 (3.4%) were treated with intravenous (IV) tocilizumab. Compared with patients with no or mild depression, higher proportions of patients with severe depression switched to IV tocilizumab or to a synthetic DMARD alone (Table II). A total of 229 of the 474 patients (48.3%) in the BDI-II cohort completed the BDI-II at both baseline and week 52. In this subgroup of patients with data at both time points, increases were observed in the proportion of patients with no depression and mild depression, while decreases occurred in the proportions of patients with moderate or severe depression (Fig. 1). Of the 39 patients with moderate depression at baseline, almost three-quarters improved to no depression (18/39 [46.2%]) or mild depression (11/39 [28.2%]) at week 52; moderate depression remained unchanged in 8 patients (20.5%) and worsened to severe depression in 2 (5.1%). The 26 patients with severe depression at baseline were somewhat more resistant to improvements in symptoms, with 11 (42.3%) continuing to report severe depression, but the majority showed improvements in depressive symptoms. Overall, 44/65 (67.7%) patients with moderate or severe depression at baseline improved to a milder or no depression subgroup at week 52.

Shifts in BDI-II categories over 52 weeks were accompanied by decreases (improvements) in mean BDI-II scores from baseline in subgroups with baseline depression (Table II). Despite these improvements, patients with more severe depression at baseline continued to report higher mean BDI-II values at week 52 (mean [SD] of 27.0 [12.9] for patients with severe depression compared with 7.6 [7.2] for patients with no depression; Suppl. Table S3).

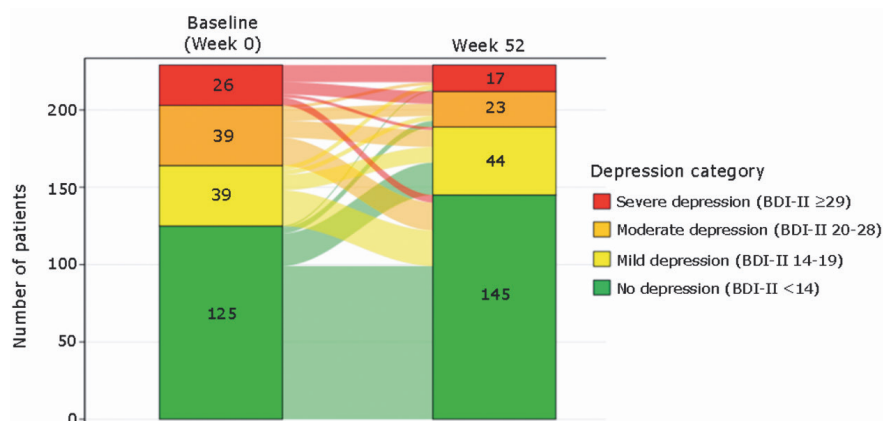


Fig. 1. Change in the number of patients in each BDI-II category between baseline and 52 weeks. BDI-II: Beck Depression Inventory II.

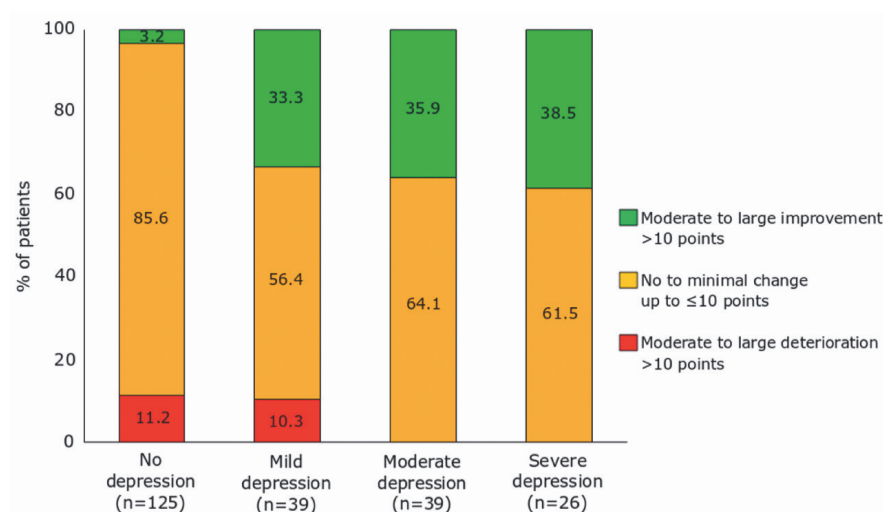


Fig. 2. Change (improvement or deterioration) in BDI-II scores over 52 weeks by BDI-II subgroup at baseline. BDI-II: Beck Depression Inventory II.

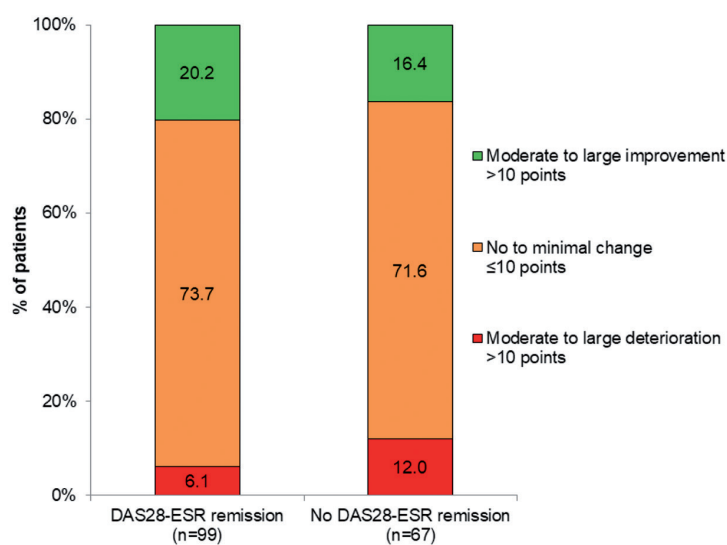


Fig. 3. Change in BDI-II scores between baseline and week 52 in patients with or without DAS28-ESR remission at week 52. Analysis was conducted in patients with both DAS28-ESR and BDI-II data at week 52. BDI-II: Beck Depression Inventory II; DAS28: Disease Activity Score based on 28 joints; ESR: erythrocyte sedimentation rate.

Table III. Pearson correlation coefficients (r values) for change from baseline to week 52.

Variable	BDI-II	Pain	Fatigue	Sleep difficulty	PGA	PhGA	STAI-State	STAI-Trait
BDI-II	1.0 (NA)	0.36 (0.23–0.48)	0.27 (0.13–0.40)	0.31 (0.17–0.44)	0.28 (0.15–0.40)	0.13 (0.00–0.26)	0.44 (0.32–0.55)	0.53 (0.42–0.62)
n	474	181	181	180	220	219	195	196
DAS28-ESR	0.10 (-0.06–0.25)	0.45 (0.36–0.53)	0.30 (0.20–0.39)	0.29 (0.19–0.38)	ND	ND	ND	ND
n	153	370	365	365				
CDAI	0.05 (-0.08–0.18)	0.35 (0.27–0.42)	0.25 (0.17–0.33)	0.22 (0.14–0.30)	ND	ND	ND	ND
n	215	529	523	521				

Variable data are presented as r values (95% CI).

BDI-II: Beck Depression Inventory II; CDAI: Clinical Disease Activity Index; CI: confidence interval; DAS28: Disease Activity Score based on 28 joint count; NA: not applicable; ND: not determined; PhGA: physician global assessment; PGA, patient global assessment.

We also evaluated the magnitude of changes in BDI-II scores over 52 weeks in patients with BDI-II data at baseline and week 52. About one-third of patients in the mild to severe depression subgroups had moderate to large improvements (decreases >10 points) in BDI-II scores and none experienced a moderate to large deterioration (increases >10 points) (Fig. 2).

Changes in additional outcomes over 52 weeks

Improvements in disease activity and PROs were observed in patients during the 52-week observation period (Table II; Suppl. Table S3). Patients with severe depression reported greater improvements in pain and fatigue than patients with no or milder depression (Table II). Changes in disease activity were generally comparable among the different depression subgroups, but the frequency of individual therapeutic responses (DAS28-ESR- d_{crit}) and remission rates decreased with more severe baseline depression. For instance, the DAS28-ESR- d_{crit} response rate was 66.7% in the no depression subgroup compared with 51.7% in the severe depression subgroup, and CDAI remission rates were 32.9% and 13.2% for the no and severe depression subgroups, respectively.

Association between disease activity assessments, PROs, and BDI-II

At week 52, 166 patients had both DAS28-ESR and BDI-II data available. We analysed changes in BDI-II scores between baseline and week 52 in subgroups of these patients who did (n=99) or did not (n=67) achieve DAS28-ESR remission at week 52 (Fig. 3). The subgroup that did not

Table IV. Adverse events by baseline BDI-II subgroup.

Adverse event	No depression (BDI-II <14) (n=248)	Mild depression (BDI-II 14–19) (n=87)	Moderate depression (BDI-II 20–28) (n=84)	Severe depression (BDI-II ≥29) (n=55)
AEs	102 (41.1%) [237]	48 (55.2%) [114]	47 (56.0%) [123]	30 (54.5%) [55]
SAEs	21 (8.5%) [41]	14 (16.1%) [19]	9 (10.7%) [9]	5 (9.1%) [8]
SAEs related to TCZ SC	7 (2.8%) [7]	5 (5.7%) [5]	3 (3.6%) [3]	0 (0.0%) [0]
Severe infections	4 (1.6%) [9]	1 (1.1%) [1]	0 (0.0%) [0]	1 (1.8%) [2]
AEs leading to therapy discontinuation	28 (11.3%) [36]	13 (14.9%) [14]	17 (20.2%) [21]	14 (25.5%) [15]

Data are presented as number of patients (%) [number of events].

AE: adverse event, BDI-II: Beck Depression Inventory II; SAE: serious adverse event; SC: subcutaneous; TCZ: tocilizumab.

achieve remission had approximately twice as many patients with a moderate to large deterioration in BDI-II subscores as the subgroup that achieved remission (12.0% vs. 6.1%), but patient numbers were small. In MMRM analyses (Suppl. Table S4), an association between DAS28-ESR and BDI-II was observed over time ($p=0.016$); higher values of DAS28-ESR (greater disease activity) corresponded to higher values of BDI-II (more severe depression). In contrast, BDI-II did not affect DAS28-ESR values over time ($p=0.355$).

In correlation analyses of change from baseline to week 52, BDI-II changes showed negligible correlations with changes in DAS28-ESR and CDAI ($r=0.10$ [95% CI -0.06–0.25] and 0.05 [95% CI -0.08–0.18], respectively; Table III), while changes in pain, fatigue, and sleep difficulty showed higher correlations with changes in disease activity measures ($r=0.22$ to 0.45; lower 95% CIs > 0). Changes in BDI-II showed

moderate correlations with PROs (pain, fatigue, sleep difficulty, STAI-State, STAI-Trait, and PGA), but not with PhGA (Table III). With the exception of PGA ($r=0.28$), BDI-II changes had minimal correlations with individual components of DAS28-ESR or CDAI (Suppl. Table S5 and Table III).

Safety evaluations

Patients with any severity of depression had more adverse events (125/226; 55.3%) than patients with no depression (102/248; 41.1%) and a higher frequency of serious adverse events (28/226 [12.4%] vs. 21/248 [8.5%]) (Table IV). However, the occurrence of adverse events did not correspond to severity of depression: the highest rate of serious adverse events was observed in patients with mild depression. In contrast, therapy discontinuation rates due to adverse events increased with higher levels of depression (from 11.3% in patients with no depression to 25.5% for

severe depression) (Table IV). Adverse event rates were generally comparable in the BDI-II cohort compared with patients who did not complete the BDI-II (Suppl. Table S6).

Discussion

Depression is a common comorbidity in patients with RA and has the potential to influence outcomes and management. Patients with concomitant RA and depression have reduced quality of life (19), less improvement during biologic therapy (20), and a 35% higher mortality risk than RA patients without depression (21). The effects of depression extend to economic outcomes and health utilisation. RA patients with depression are more likely to apply for work disability; depression is a stronger predictor of early retirement for German patients with RA than age, functional disability, or disease activity (22). In a US study, concomitant depression was associated with more physician visits, emergency room visits, hospitalisations, and hospital days, resulting in an incremental adjusted annual cost of \$8488 (23).

The association between RA and depression is not well understood and may be bidirectional. Depression can both cause and be exacerbated by increased inflammation (24). Although some studies have found that depression is associated with increased RA disease activity (19, 25), others have been unable to identify a direct association between disease activity and depressive symptoms after controlling for other factors (26-29). However, associations between depressive symptoms and PROs, including PGA and illness perceptions, have been consistently observed (26, 28, 29). Other influences, including personality type and socioeconomic factors, may also affect the impact of depressive symptoms in RA (27, 30). Interpretation of studies of depression in RA is complicated by the fact that there are several different depression scales in use and some analyses combine patients with depression with those with anxiety (25, 26, 31, 32).

Minimal data are available concerning effective interventions for depression in RA. A recent meta-analysis identified only eight randomised trials of depression interventions in RA, and none

had a high strength of evidence (33). Pharmacologic antidepressants appear to have some effect in reducing depressive symptoms in this patient population (33), but additional options are needed. Given the potential connection between inflammation and depression (4), the impact of anti-inflammatory therapies on depression has been the subject of much speculation. However, the antidepressive effect of non-steroidal anti-inflammatory drugs remains unclear (34), while systemic glucocorticoids are associated with initial euphoria but can induce depressive symptoms during long-term use (35). In a recent study of 9000 patients treated with systemic or local (primarily inhaled/nasal) corticosteroids, regular corticosteroid use was associated with a 26% increase in risk of depressive symptoms or dysthymia (36). Accordingly, anti-inflammatory effects do not appear to be sufficient for improvements in depression, although they may make some contribution. The possible utility of TNF inhibitors and other immunomodulators in treating depression is suggested by some studies (10, 37, 38). However, infliximab did not result in overall improvement in treatment-resistant depression in non-RA patients, although it was associated with improved depressive symptoms in the subgroup of patients with high baseline levels of inflammation (39), suggesting that effects on depression are mediated in part through anti-inflammatory activity. IL-6 is another potential target for anti-depressant therapies (38, 40), but a randomised study of sirukumab in major depressive disorder did not observe significant improvements in depressive symptoms in sirukumab-treated patients compared with placebo (41). Pilot studies to examine the effect of tocilizumab in patients with depression have been initiated (42, 43). Tocilizumab could potentially impact depressive symptoms through inhibition of IL-6, anti-inflammatory effects, as yet undetermined mechanisms of action, or a combination of some or all of these activities.

The objective of the current *post-hoc* analysis was to assess changes in symptoms of depression in tocilizumab-treated patients with RA during routine daily care. We found that depressive

symptoms were common: almost half the patients (48%) who completed the BDI-II at baseline had some evidence of depression and 29% reported moderate or severe depression. The prevalence of depression documented here is higher than the 28% based on BDI-II scores in a recent cross-sectional study of RA patients in Germany (2). In both studies, the reported rate of depression during baseline comorbidity assessments was approximately 7.5%, suggesting that underdiagnosis and underrecognition of depression is widespread. Other studies have similarly noted underdiagnosis and undertreatment of depression in the RA patient population (44-46).

We found that baseline depression was associated with higher (poorer) PGA, HAQ-DI, fatigue, anxiety, and pain scores, but similar disease activity scores. This finding indicates that patients with similar disease activity levels can experience a wide range of levels of depression. PhGA scores were also similar across the depression subgroups. The discrepancy between PhGA and PROs suggests that depressive patients may have a different perception of their disease severity compared with the clinician's assessment and objective measures of disease activity. Studies of discordance between PGA and PhGA have found that depressive symptoms are associated with worse patient ratings compared with physician ratings (47, 48).

Depressive symptoms improved substantially in the 52 weeks following initiation of tocilizumab therapy. Two-thirds of patients with moderate or severe depression improved to a milder depression or no depression subgroup, and about one-third showed moderate to large improvements (>10 points) in BDI-II scores.

All of the subgroups showed improvements in disease activity, but response and remission rates varied markedly: patients with no or milder depression tended to achieve higher rates of response and remission than patients with severe depression, regardless of the assessment used to evaluate outcomes. Other studies have also observed lower remission rates in RA patients with depression or depression/anxiety (20, 25, 32, 49). These reduced response rates

may be driven by underlying disease severity or by patient illness perceptions. Improvements in depressive symptoms were also accompanied by improvements in PROs. Changes in pain corresponded closely to depression subgroups, with the greatest improvements observed in patients with severe depression and the least improvement in the no depression subgroup. This association mirrors baseline pain scores, which were higher in the severe depression subgroup. However, patterns of improvements in sleep disturbance, which also had the highest baseline levels in the severe depression subgroup, did not correspond to depression subgroups; the largest improvements were seen in patients with moderate or mild depression, despite previous findings that sleep quality is linked to pain and depression in patients with RA (50, 51). These varying patterns highlight the complex interplay among PROs.

In analyses of the association between change in disease activity and depressive symptoms over time, we observed that whereas DAS28-ESR had a significant positive effect on BDI-II, BDI-II did not show an effect on DAS28-ESR. These analyses suggest that greater disease activity is associated with more severe depression, but depressive symptoms do not have a corresponding influence on disease activity. Correlation analyses found negligible correlations between changes from baseline in BDI-II and changes in disease activity measures, providing further support for a lack of association between depression symptoms and disease activity. BDI-II changes showed higher correlations with other PROs, particularly STAI assessments (anxiety), but not with PhGA, again suggesting that depressive symptoms have a greater influence on the patient's perception of disease activity than on the physician's assessment. Although these insights into possible associations between depression and disease activity are tantalising, it should be noted that this study was not designed to investigate these associations and our analyses should be considered exploratory.

Patients with depression had more adverse events than patients without de-

pression, and therapy discontinuation rates due to adverse events increased with severity of depression. Other therapeutic areas, ranging from diabetes (52) to epilepsy (53), have reported similar observations concerning the impact of depression on adverse event reports, but to the best of our knowledge this is the first report of this association in RA. Further studies will be required to evaluate whether this effect is related to underlying disease severity, physiologic changes related to depression, psychobehavioural characteristics, or some combination of these factors.

Limitations of this study include challenges faced by all observational studies, including the lack of a comparator group. Although the subgroups were well-balanced with respect to age and disease activity, residual confounding is possible due to unidentified variables. Patient numbers were reduced because not all patients chose to complete the BDI-II questionnaire. Because patients were allowed to choose which PROs to complete, bias may potentially have been introduced by patient self-selection, although baseline characteristics of the two groups were comparable. Not all patients remained on tocilizumab for 52 weeks, but we believe it is unlikely that the small number who discontinued the study or stopped tocilizumab treatment significantly changed the results.

In conclusion, our data document a high burden of depression in patients receiving routine clinical care for RA and clinically significant changes in symptoms of depression during the 52 weeks following initiation of tocilizumab therapy in tocilizumab-naïve patients with RA. Additional studies will be required to evaluate whether the impact of tocilizumab on depression is associated with or independent of improvement in disease activity, as well as to compare the effect of tocilizumab on depressive symptoms with other synthetic or biologic DMARDs used to treat RA. It will also be interesting to see if the potential association between tocilizumab and depressive symptoms is retained in treatment-naïve patients with RA. The effects of antirheumatic drugs on depression are highly relevant due to the increased prevalence and substantial

burden of depression in patients with RA. We encourage rheumatologists and other clinicians who treat RA to consider the risk of depression during routine daily care and provide resources to assist in the management of depressive symptoms if appropriate.

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