Improvements in patient-reported outcomes, symptoms of depression and anxiety, and their association with clinical remission among patients with moderate-to-severe active early rheumatoid arthritis

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Abstract

Objectives. To assess the association between clinical remission in RA and patient-reported outcomes (PROs), including depression/anxiety symptoms, in adults with moderate-to-severe active early RA.

Methods. Patients from the COMbination of Methotrexate and ETanercept in Active Early Rheumatoid Arthritis (COMET) trial (104 weeks) with measures on the Hospital Anxiety and Depression Scale at baseline and subsequent visits (n = 389) were included. PROs investigated were the HAQ disability index, pain and fatigue visual analogue scales (VASs), EuroQoL health status VAS and the Medical Outcomes Short Form-36 physical and mental component summaries. The impact of clinical remission as measured by 28-joint DAS (DAS-28) on depression/anxiety symptoms at Week 104 was assessed using logistic regression. Least square means for PRO improvements from baseline were estimated by analysis of covariance. Missing data were imputed using the last observation carried forward method.

Results. When depression/anxiety symptoms were absent at baseline, significantly more patients achieved clinical remission, low disease activity and normal functioning at Week 104. Reciprocally, patients who achieved clinical remission were less likely to maintain symptoms of depression or anxiety compared with non-remitters [depression odds ratio (OR): 0.35, \(P = 0.0233\); anxiety OR: 0.48, \(P = 0.0371\)]. Fatigue and pain had a significant impact on changes in depression status, but did not influence anxiety status. Finally, clinical remission was significantly associated with improvements in all PRO measures (\(P < 0.001\)); conversely, depression/anxiety symptoms reduced PRO improvements.

Conclusions. Among moderate-to-severe active early RA patients, clinical remission reduces symptoms of depression/anxiety, and independently improves PROs, thereby suppressing the negative impact of depression/anxiety on these measures.

Key words: Rheumatoid arthritis, Remission, Depression, Anxiety, Patient-reported outcomes.

Introduction

RA is associated with considerable comorbidity, which interferes with normal functioning and well-being and contributes to a decline in quality of life [1]. Patients with RA commonly suffer from pain and fatigue, and progress to physical disability as a result of joint destruction. Depression and anxiety are often reported by RA patients, with a prevalence of up to 43 and 89% for depression and anxiety, respectively [2–4]. Anxiety is believed to occur more frequently among RA patients suffering from
depression compared with non-depressive RA patients [5]. It has been noted that depression in RA patients can arise from complex interactions between clinical, demographic and psychological factors [3].

Serious consequences are attributed to depression. It has been noted that concomitant depression and RA can disproportionately worsen several outcomes [6]. In the worst case, it may lead to suicide, and it is an independent risk factor for mortality [2]. More insidiously, patients with depression are often less compliant with treatment and may underestimate its effectiveness. In addition, depression and anxiety may also affect patient perception and attitude towards possible treatment side effects. Health resource utilization is increased among RA patients suffering from depression, resulting in increased medical expenditure [7]. Depression may also interfere with work productivity and increase sick leave.

The relationship between depression or anxiety, and pain, fatigue and disability, seems to be bidirectional. While it has been shown that fatigue, pain and physical disability predicted depression [3, 8], depression was considered to be a strong predictor of pain among patients with early inflammatory arthritis [9]. Anxiety was strongly associated with the course of pain for patients with recent onset RA [10].

RA therapies have been shown to improve patient’s quality of life by reducing the burden of fatigue, pain and disability among patients with early and established RA [11–13]. Specifically, patient-reported outcomes (PROs) including depression and anxiety have been shown to improve for RA patients achieving remission [11–13]. As many patients achieve clinical remission and low disease activity, particularly in phases of early RA, their symptoms of depression and anxiety may also improve at the same time. It is not clear whether improvement in these symptoms can be attributed at least in part to achieving clinical remission. Furthermore, whether the impact of clinical remission on PROs is different in the presence of depression and anxiety needs further investigation. Lastly, the effects of depression and anxiety on PROs such as fatigue, pain and disability, have not been compared in the presence or absence of RA remission.

The objective of this study was to assess the impact of clinical remission on symptoms of depression and anxiety in patients with moderate-to-severe active early RA, and to explore the effect of remission on PROs in the presence of depression and anxiety symptoms.

Patients and methods

Study design and outcomes

The COmbination of Methotrexate and ETanercept in Active Early Rheumatoid Arthritis (COMET) study was a 24-month, randomized, double-blind, two-period trial to assess the efficacy and safety of a combination of etanercept 50 mg plus MTX compared with MTX alone in outpatients with moderate-to-severe active early RA [14, 15]. PRO measures were collected during the trial as secondary endpoints. This article reports COMET 2-year PRO data that were pooled across treatment arms. Given that this analysis is focused around depression and anxiety, only patients who had reported measures of Hospital Anxiety and Depression Scale (HADS) in the baseline and subsequent visits were included (n = 389). Informed consent was obtained from all participants and approval from the Institutional Review Board was obtained at all enrolment sites.

Clinical remission at the end of the second year (Week 104) was defined as the proportion of patients achieving 28-joint DAS (DAS-28) remission (DAS-28 < 2.6). PRO measures were collected, among other time points, at study entry (baseline) and at Week 104, and included: the HAQ Disability Index [HAQ-DI; range 0 (no difficulty) to 3 (unable to do)] [16], pain visual analogue scale [VAS; range 0–100 (maximum pain imaginable)], fatigue VAS [range 0–100 (maximum fatigue imaginable)], EuroQoL health status (EQ-5D) VAS [range 0–100 (best imaginable health state)] [17] and the Medical Outcomes Short Form-36 [SF-36 physical component summary (PCS) and mental component summary (MCS); range 0 (worst) to 100 (best)] [18]. SF-36 scores were normalized using a general US population mean of 50. The HADS, a self-administered questionnaire with two subscales of seven items each [range 0–21 (greatest dysfunction)], was used to assess anxiety and depression status [19]. A HADS score ≥ 8 is indicative of the presence of symptoms of mild, moderate or severe depression or anxiety [19].

Patients

Patients (n = 389) were adults with disease duration ranging from 3 months to 2 years, who had active RA at study randomization, indicated by a DAS-28 of ≥ 3.2 and either ESR ≥ 28 mm/h or CRP levels ≥ 20 mg/l. Patients previously exposed to MTX or anti-TNF-α therapies were excluded.

Data analyses

The COMET 2-year data were pooled across treatment arms for the modified intention-to-treat population, which included all enrolled patients who received at least one dose of study treatment and completed at least the first study year.

Two separate sets of analysis were performed for symptoms of depression and anxiety. First, the impact of clinical remission on depression status at Week 104 was assessed using logistic regression analyses for patients with or without depression at baseline. Age, gender, disease duration and Week 104 clinical remission status were used as independent variables. Change from baseline of pain and fatigue scores were also included as independent variables, since the effect of remission could very well be confounded by improvement in pain and fatigue. Similar analyses were performed for anxiety status. Secondly, least square means for improvement in PRO measures from baseline to Week 104 were estimated by analysis of covariance, controlling for age, sex, disease duration, baseline depression symptoms, DAS-28...
remission at Week 104, interaction of baseline depression and DAS-28 remission and baseline PRO score. A similar analysis was done for anxiety. When Week 104 values were not available, the last observation carried forward (LOCF) method was used to impute missing data [20].

Results

Patient characteristics by baseline depression and anxiety status

Of the 389 study patients, 158 (41%) suffered from depression symptoms compared with 231 (59%) who did not have depression at baseline (Table 1). Patients stratified by their depression status had comparable baseline demographics. However, patients with baseline depression had significantly worse baseline PROs (HAQ, pain, fatigue and EQ-5D), and worse measures of inflammation and disease activity (CRP, ESR and DAS-28) compared with those who did not have depression at baseline.

For the same overall cohort, 177 (46%) patients were found to have anxiety symptoms at baseline (Table 1). More females than males had anxiety at baseline, and anxious patients were slightly younger than patients without baseline anxiety. With the exception of SF-36 PCS, PRO measures were worse at baseline when patients had anxiety. Similarly, disease activity was worse (DAS-28 higher) for patients with anxiety at baseline compared with those without. Unlike depression, however, anxiety symptoms at baseline did not correlate with inflammation markers (CRP and ESR).

Clinical outcomes and PROs at Week 104 by baseline depression and anxiety status

As shown in Table 2, the proportion of patients with clinical remission and low disease activity at Week 104 was significantly higher for those without baseline depression or anxiety symptoms vs those who suffered from depression or anxiety at baseline. Similar outcomes were also

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Status at baseline</th>
<th>Status at baseline</th>
<th>Status at baseline</th>
<th>Status at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No depression (C1)</td>
<td>Depression (C2)</td>
<td>P-value (C1 vs C2)</td>
<td>No anxiety (C3)</td>
</tr>
<tr>
<td>n (%)</td>
<td>231 (59)</td>
<td>158 (41)</td>
<td>-</td>
<td>212 (54)</td>
</tr>
<tr>
<td>Age, years</td>
<td>52.84</td>
<td>50.06</td>
<td>0.051</td>
<td>53.60</td>
</tr>
<tr>
<td>Female, %</td>
<td>70.6</td>
<td>76.6</td>
<td>0.189</td>
<td>67.5</td>
</tr>
<tr>
<td>Disease duration, months</td>
<td>8.60</td>
<td>9.01</td>
<td>0.490</td>
<td>8.50</td>
</tr>
<tr>
<td>HAQ-DIa</td>
<td>1.49</td>
<td>1.92</td>
<td>&lt;0.001</td>
<td>1.56</td>
</tr>
<tr>
<td>Pain VASa</td>
<td>59.60</td>
<td>71.52</td>
<td>&lt;0.001</td>
<td>61.28</td>
</tr>
<tr>
<td>Fatigue VASa</td>
<td>51.74</td>
<td>68.53</td>
<td>&lt;0.001</td>
<td>52.53</td>
</tr>
<tr>
<td>EQ-5D VASb</td>
<td>51.86</td>
<td>39.85</td>
<td>&lt;0.001</td>
<td>51.55</td>
</tr>
<tr>
<td>SF-36 PCSb</td>
<td>30.84</td>
<td>27.50</td>
<td>&lt;0.001</td>
<td>29.82</td>
</tr>
<tr>
<td>SF-36 MCSIb</td>
<td>47.08</td>
<td>35.15</td>
<td>&lt;0.001</td>
<td>48.02</td>
</tr>
<tr>
<td>ESR</td>
<td>44.23</td>
<td>54.89</td>
<td>&lt;0.001</td>
<td>48.10</td>
</tr>
<tr>
<td>CRP</td>
<td>32.64</td>
<td>43.15</td>
<td>0.006</td>
<td>36.35</td>
</tr>
<tr>
<td>DAS-28</td>
<td>6.26</td>
<td>6.77</td>
<td>&lt;0.001</td>
<td>6.35</td>
</tr>
</tbody>
</table>

Fatigue and pain VAS: 0 (no fatigue or pain) to 100 (maximum imaginable fatigue or pain). EQ-5D VAS: 0 (worst imaginable health state) to 100 (best imaginable health state). SF-36: 0 (worst) to 100 (best). Scores were standardized to a general US population mean of 50. *A lower score indicates better outcome. **A higher score indicates better outcome.

<table>
<thead>
<tr>
<th>Week 104 outcomes</th>
<th>Status at baseline</th>
<th>Status at baseline</th>
<th>Status at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission (DAS-28 ( \leq 2.6 )), %</td>
<td>56.3</td>
<td>42.4</td>
<td>0.007</td>
</tr>
<tr>
<td>Low disease activity (DAS-28 ( \leq 3.2 )), %</td>
<td>69.3</td>
<td>56.3</td>
<td>0.009</td>
</tr>
<tr>
<td>ACR20, %</td>
<td>85.7</td>
<td>74.1</td>
<td>0.004</td>
</tr>
<tr>
<td>ACR50, %</td>
<td>69.7</td>
<td>55.1</td>
<td>0.003</td>
</tr>
<tr>
<td>ACR70, %</td>
<td>52.4</td>
<td>38.6</td>
<td>0.008</td>
</tr>
<tr>
<td>HAQ-DI &lt; 0.5, %</td>
<td>62.8</td>
<td>44.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EQ-5D VAS &gt; 82, %</td>
<td>54.1</td>
<td>29.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
observed for the ACR20, ACR50 and ACR70 responses. In terms of PROs, significantly more patients achieved normal functioning (HAQ-DI ≤ 0.5) and healthy normative status (EQ-5D VAS > 82), if they did not have baseline depression or anxiety symptoms compared with those who did.

Impact of clinical remission on depression and anxiety status at Week 104

Among the cohort of patients with baseline symptoms of depression, those who achieved clinical remission were less likely to remain depressed at Week 104, compared with those who did not achieve clinical remission [Table 3; odds ratio (OR) 0.35; P = 0.0233]. Conversely, patients with no depression at baseline continued without depression at a higher rate (3.1-fold) if they achieved DAS-28 remission, compared with those who failed to achieve remission (P = 0.0484). Change from baseline fatigue was a significant factor in explaining the change in depression status for those with baseline symptoms of depression (P = 0.0002), while change in pain was significant for those without depression at baseline (P = 0.0326).

Anxiety also followed a similar pattern, although not always statistically significant. Those with baseline symptoms of anxiety had a 52% lower odds of continuing with anxiety at Week 104 if they achieved clinical remission compared with non-remitters (Table 3; OR: 0.48; P = 0.0371). Among patients who did not have anxiety at baseline, there was no significant change in their anxiety status at Week 104 stemming from remission (P = 0.9342).

Impact of clinical remission and baseline depression/anxiety on PROs

Overall, clinical remission significantly improved all PRO measures (P < 0.001), while baseline symptoms of depression (Fig. 1) and anxiety (Fig. 2) reduced the level of PRO improvements. Remission had a positive and significant effect on PRO improvements, regardless of baseline status of depression and anxiety. Conversely, the effect of depression and anxiety on PRO improvements was negative and, for most of the PRO measures, statistically significant for patients who failed to achieve clinical remission. As illustrated in Figs 1 and 2, being in clinical remission and not having symptoms of depression at baseline resulted in the best possible PROs, whereas those who achieved remission at Week 104 had the worst outcomes.

Sensitivity analyses

Sensitivity analyses were conducted to further assess the robustness of the study findings. Substituting low disease activity (DAS-28 ≤ 3.2) for disease remission cut-off (DAS-28 ≤ 2.6) resulted in similar improvement in PRO measures. When baseline pain and fatigue VAS were considered as independent variables in the logistic regressions (replacing changes from baseline in these scores), results for clinical remission remained similar.

Table 3: Impact of clinical remission and other variables on change in depression and anxiety status using logistic regression

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Depressed at Week 104</th>
<th>No depression at Week 104</th>
<th>Anxiety at Week 104</th>
<th>No anxiety at Week 104</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>1.00 (0.97, 1.03)</td>
<td>0.9353</td>
<td>1.01 (0.98, 1.03)</td>
<td>0.99 (0.95, 1.02)</td>
</tr>
<tr>
<td>Gender: female</td>
<td>2.66 (0.87, 8.16)</td>
<td>0.0866</td>
<td>3.30 (1.39, 7.83)</td>
<td>0.52 (0.15, 1.89)</td>
</tr>
<tr>
<td>Disease duration</td>
<td>1.00 (1.01, 1.17)</td>
<td>0.0221</td>
<td>0.99 (0.94, 1.05)</td>
<td>1.07 (0.96, 1.20)</td>
</tr>
<tr>
<td>Clinical remission</td>
<td>0.35 (0.14, 0.87)</td>
<td>0.2233</td>
<td>0.48 (0.24, 0.96)</td>
<td>0.1017</td>
</tr>
<tr>
<td>Pain</td>
<td>1.00 (0.98, 1.02)</td>
<td>0.8546</td>
<td>0.99 (0.98, 1.00)</td>
<td>0.9342</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.96 (0.95, 0.98)</td>
<td>0.0002</td>
<td>1.00 (0.99, 1.01)</td>
<td>0.1330</td>
</tr>
<tr>
<td>Log-likelihood</td>
<td>50.01</td>
<td>&lt;0.0001</td>
<td>21.64</td>
<td>0.0014</td>
</tr>
</tbody>
</table>

*Change from baseline to Week 104.
Furthermore, treatment effect on changes in symptoms of anxiety and depression was examined by comparing pooled etanercept plus MTX patients with those who received MTX alone. No significant difference was found between treatment groups. In a separate analysis, the use of antidepressant drugs also did not influence the change in symptoms of depression.

The interaction between baseline symptoms of depression and patient early dropout rates was assessed using a chi-square test. No significant association was found.

Finally, the association between clinical remission and change from baseline in depression and anxiety status was measured for patients concomitantly suffering from both conditions vs those suffering from either condition. As shown in Table 4, proportions of patients having symptoms of depression, anxiety or both dropped significantly from baseline to Week 104 ($P<0.001$), particularly for those who achieved clinical remission.

**Fig. 1** Impact of clinical remission and baseline status of depression symptoms on PROs over 2 years. **(A)** Improvement of HAQ-DI at Week 104 by baseline depression status. *Overall differences remained statistically significant when controlling for age, sex, disease duration and baseline PRO values, in addition to remission and baseline depression and their interaction. All pairwise comparisons were significant ($P<0.05$) except for no remission/depression vs no remission/no depression and remission/depression vs remission/no depression.*

**Fig. 1 (B)** Improvement of PROs at Week 104 by baseline depression status. *Overall differences remained statistically significant when controlling for age, sex, disease duration and baseline PRO values, in addition to remission and baseline depression and their interaction. All pairwise comparisons were significant ($P<0.05$) except for the following: remission/depression vs remission/no depression for all PROs; no remission/depression vs no remission/no depression for fatigue VAS; and no remission/no depression vs remission/depression for SF-36 MCS.*
Previous studies have not investigated in depth the relationship between clinical remission and symptoms of depression and anxiety, especially in early RA patients. Using a patient-reported hedonic instrument of depression and anxiety (HADS questionnaire), this study looks at DAS-28 clinical remission as a predictor of improvement in symptoms of depression and anxiety in addition to assessing the effects of remission and baseline symptoms of depression and anxiety on PROs such as disability, pain, and fatigue.

Recent data suggest that depression in RA patients is both common and under-recognized in the rheumatology setting, and may persist for years after diagnosis [21]. Furthermore, depressive symptoms in RA have been attributed to pro-inflammatory cytokines including TNF-α [22–24]. Newly diagnosed RA patients overwhelmed by,
and trying to cope with, their primary disease at its early stages, may generally exhibit sporadic symptoms of depression and anxiety. As RA disease improves due to therapeutic interventions, depression and anxiety symptoms may potentially improve.

Studies have shown that health outcomes can be worse for RA patients with comorbid depression compared with those without depression [6]. This study finds that fewer patients with baseline symptoms of depression or anxiety achieve clinical remission compared with patients without these conditions. However, patients who achieved DAS-28 clinical remission experienced improvement in depression and anxiety symptoms. Since clinical remission can be closely associated with improvement in pain and fatigue, these variables were used in this study to explain changes in depression and anxiety symptom status following remission. After controlling for pain and fatigue, as well as for patient demographics, the analysis indicates that clinical remission may be a significant predictor of depression status improvement, for patients both with and without baseline depression. Patients with baseline anxiety symptoms were also more likely to improve their anxiety status once they achieved remission. This suggests that, although depression and/or anxiety determine prognosis, effective treatment may change the course of both conditions. It should be kept in mind that clinical remission in RA does not necessarily mean complete disease remission; hence, further implications need to be examined.

Patients without symptoms of depression at baseline who achieved DAS-28 remission had greater odds (~3-fold) of remaining free from depression symptoms at Week 104. In contrast, the odds of continuing with depression symptoms for those with such symptoms at baseline were 65% lower if they achieved clinical remission. These findings reinforce the fact that symptoms of depression and anxiety can be related to the primary disease among RA patients; therefore, clinical improvement in RA disease may be expected to alleviate mental health-related symptoms experienced by patients with RA. Even though the COMET trial did not disallow psychotherapeutic interventions for mental health disorders, there were no reports on confounding interventions in the patient records.

Clinical diagnostic measures of depression and anxiety were not included in this study. Therefore, it is still not clear to what extent depression and anxiety symptoms are indicative of clinical depression and anxiety. However, when the use of antidepressants was taken into account in sensitivity analyses, no significant correlation was found between these drugs and changes in depressive symptoms. One possible explanation is that in early RA, clinical manifestations of depression and anxiety may not be very pronounced or apparent. Further investigation is required to understand the source and depth of these mental illnesses along the course of disease.

The relationships across various health domains including depression, pain and fatigue, and their association with disability and functioning can be fairly complex. Potential exists for considerable interdependence among these health aspects. Previous studies have demonstrated the effect of treatment-induced remission on health outcomes. In patients with established RA where fatigue was associated with pain and depression, the reduction in fatigue VAS scores strongly correlated with DAS-28 improvement [11]. Pain and fatigue scores decreased in early RA patients experiencing disease remission with improved functioning [12]. Consistently, in this study, remission improved PROs such as disability, pain, fatigue and functioning, while depression and anxiety exerted the opposing effect on PROs.

In the absence of symptoms of depression or anxiety at baseline, clinical remission resulted in the best possible PRO improvements. Remission also showed improved PROs in the presence of depression, anxiety or both despite poorer baseline PRO measures under these conditions; in this case, the extent of PRO improvements was reduced compared with patients with no anxiety or depression at baseline. These findings suggest that the positive effect of clinical remission on PROs may offset the negative effects of depression and anxiety in many patients. This may suggest a need to target RA patients suffering from depression and/or anxiety to receive adequate RA treatment so that the additional health care needs arising from the interaction of RA disease and mental illnesses are met.

The current findings point to certain important relationships that require further investigation. For example,
future studies should assess the mechanisms by which remission improves depression, anxiety or both, and whether this occurs directly or via other health domains. A focus on the effect of depression on RA remission and the effect of disease activity on depression should also be considered. Finally, given the importance of remission and depression in determining levels of changes in PROs, it may be useful to examine the concept of ‘depression-free clinical remission’. Simultaneous modelling of all interrelated variables—namely remission, depression, anxiety and PROs such as pain, fatigue and disability—may be needed to better understand the magnitude and direction of these interactions.

This study has some limitations worth mentioning. This is a post hoc analysis of a clinical trial intended to measure the effect of etanercept therapy, and the patient population has been selected accordingly. Thus, the conclusions regarding the effects of depression/anxiety and the interaction with remission and PROs may not generalize in the clinical setting to a similar extent. Patient education by specialized health professionals and cognitive behavioural therapy may help relieve anxiety and depression. Data on these interventions were not collected during the trial, which may lead to biased results. In addition, the effect of depression on DAS-28 remission may result from its impact on patient self-assessed DAS-28 components (i.e. tender joint score and general health VAS), which could introduce confounding errors. To control for this confounder, correlation analyses were performed separately with each of the four DAS-28 components. Although self-assessed components showed higher correlations with depression compared with objective measures (i.e. ESR and swollen joint count), statistically significant relationships were seen under all scenarios \( P < 0.0001 \). Furthermore, the small sample size of the cohorts of patients with no depression or anxiety at baseline, but who had depression and anxiety by the end of the study might have limited some of the statistical comparisons. Finally, the study conclusions may not generalize to established RA patients because their behavioural patterns could become more recalcitrant to change.

In conclusion, this study demonstrates that, among moderate-to-severe active early RA patients, clinical remission improves PROs independently of symptoms of depression and anxiety. Also, symptoms of depression and anxiety adversely affect PROs. Further, clinical remission of early RA reduces symptoms of depression and anxiety compared with baseline, dampening their negative impact on PROs.

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**References**

12. Verschueren P, Esselens G, Westhovens R. Predictors of remission, normalized physical function, and


