Fatigue in rheumatoid arthritis: quantitative findings on the efficacy of tocilizumab and on factors associated with fatigue. The French multicentre prospective PEPS study

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Abstract

Objective

Fatigue is an important aspect of rheumatoid arthritis (RA). The objective was to assess fatigue levels and its determinants over the first 4 months of tocilizumab (TCZ) treatment in RA patients.

Methods

We performed a multicentre prospective study of RA patients treated with intravenous TCZ in open-label prescription conditions. The first 5 infusions (4 months) were assessed. The primary endpoint was the percentage of patients with variation of the FACIT fatigue scale from inclusion to 4 months, above the minimal clinically important difference (MCID) of 4 points. Fatigue was also assessed by the patient acceptable symptom state for fatigue (PASS) question. Variables related with fatigue and with fatigue improvement including other patient reported outcomes, depression and anxiety, and disease activity, were assessed before and after treatment. Analyses: univariate and multivariate logistic regressions.

Results

Of 719 patients, 610 had evaluable data: mean age 56±13 years, disease duration 12±10 years, 490 (81%) women. At baseline, fatigue levels were high: 73% patients had unacceptable fatigue. At 4 months, 378 patients (62%) reached MCID improvement for fatigue. Fatigue reduction was rapid, seen as early as after 2 weeks. Fatigue was mainly related to functional status (HAQ score), depression and anxiety, both before and after TCZ treatment. Moderate predictors of fatigue improvement were evidenced.

Conclusion

In these long-standing RA patients, fatigue levels were high and mainly explained by HAQ and psychological distress but improved with treatment indicating a link with disease activity. The pathophysiological basis of RA fatigue should be further explored.

Key words

rheumatoid arthritis, outcomes research, patient perspective, fatigue, FACIT, quality of life, response criteria

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Introduction

Fatigue is an important aspect of disease which has an impact on quality of life for patients suffering from rheumatoid arthritis (RA). Over the last few years, several studies have revealed that fatigue is a major aspect of disease impact for RA patients, alongside pain and functional disability (1-4).

Fatigue in RA appears to be different from normal tiredness (5). It is described by RA patients as severe and overwhelming (2). In patient focus groups, RA fatigue has also been described as exhaustion, lack of energy, 'feeling drained' (6, 7). RA fatigue has an important impact on family, professional and social life in particular due to its unpredictable nature. In fact, patients place fatigue as the third domain of health in terms of impact on their life (3) and in terms of priority for improvement (8).

Thus, fatigue characteristics are well known in RA. However, several important questions remain unclear. Firstly, what are the drivers of fatigue in RA? And secondly, how can we treat RA-related fatigue?

Concerning the drivers of fatigue in RA, to date, the link between fatigue and disease activity remains unclear (9-11). Fatigue may be associated with patient-related variables (*e.g.* demographics or depression) as much as disease-related variables (*e.g.* disease activity) (1, 9, 12). It is also possible that the link between fatigue and disease activity may differ, according to the disease activity level, *e.g.* for patients with very active disease *versus* with moderate to low disease activity.

Biologic therapies have shown some efficacy on RA-related fatigue (5). In particular, in phase III studies, tocilizumab (TCZ) has shown its efficacy on several aspects of the disease, including fatigue (13-17). However, there are differences between randomised clinical trials and open-label prescription conditions (18). Most patients seen at the clinic could not be included in trials, and efficacy and tolerance may differ in usual conditions compared to clinical trials with selected patients. Furthermore, to date, no study has examined whether certain patient characteristics are able to identify those most likely to respond.

Therefore, this study was set up in order to describe the effects of TCZ on fatigue in RA in an open-label setting, and to explore the factors related with fatigue and its improvement in RA patients, before and after a biologic therapy.

Patients and methods

Study design

The PEPS (Etude Pharmaco Epidémiologique de l'imPact en vie réelle d'un traitement par RoActemra® sur la fatigue des patientS avec polyarthrite rhumatoïde) study was a French prospective observational multicentre study conducted in secondary or tertiary-care hospitals in 2010-11. (clinicaltrials.gov registration number NCT01667458).

Patients

Eligible patients were patients with moderate to severe RA, requiring TCZ according to their physicians, who able to complete questionnaires, and were informed about their study participation.

Treatment

The patients received intravenous TCZ as prescribed by the treating physician according to the French regulations for RA, with no specific protocol, and with or without co-medication with conventional synthetic disease-modifying drugs and/or corticosteroids. Treatment duration for the study was 4 months, which usually corresponds to the first 5 infusions of TCZ.

Fatigue

Fatigue was the primary outcome of this study and was assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT fatigue) questionnaire (19, 20): this widely-used questionnaire comprises 13 questions, each assessed through a 5-point Likert scale with a score range of 0–52, where higher results indicate less fatigue.

The patient acceptable symptom state (PASS) question for fatigue was also assessed: here patients rate their fatigue as 'acceptable' or 'unacceptable' (21). Finally, fatigue was also assessed by a visual analogue scale (0–100 VAS) (22).

Factors potentially associated with fatigue and fatigue improvement

Three types of data were analysed, demographic data, disease activity variables and patient-reported outcomes.

The Disease Activity Score (DAS28) (23) and its components swollen joint count, tender joint count, patient's global assessment of disease activity VAS (0–100) and erythrocyte sedimentation rate were collected at each time point, as were patient reported outcomes including the health assessment questionnaire disability index (HAQ), pain VAS (0–100), sleep quality VAS (0–100), and anxiety and depression with the Hospital Anxiety and Depression Scale (HADS) scale (24, 25). The HADS can be analysed as absence/doubtful/definite status for anxiety and depression (25).

Efficacy data were collected at baseline, day 15 (only for fatigue), and then at 1, 2, 3 and 4 months. Safety was monitored according to usual practice throughout the study.

Statistical analyses

• *Effect of TCZ on fatigue*

The primary endpoint of the PEPS study was the percentage of patients with a variation of FACIT-fatigue score from inclusion to 4 months above the minimal clinically important difference (MCID). The MCID was previously defined as 4 points (19). Efficacy analyses were performed on all patients who were in accordance with the inclusion and non-inclusion criteria, received at least one TCZ infusion and had a FACIT-fatigue score available at inclusion and at least once following administration of TCZ. For the primary analysis, missing FACIT-fatigue score at 4 months was handled using the last observation carried forward method. DAS28 response was assessed using non-responder missing data imputation.

• *Variables related with fatigue and fatigue improvement*

To define variables related with fatigue and with fatigue improvement (above MCID), and to assess whether the treatment modified the relationship between fatigue and these associated variables, multiple linear regressions (for fatigue) and univariate ($p \leq 0.15$) then multivariate stepwise logistic regressions (for fatigue improvement) were conducted. The following variables were analysed in the multiple linear regressions: HAQ, HADS, global and sleep VAS, joint counts, haemoglobin (age, disease duration, acute phase reactants and pain were correlated to the other variables so were taken out of the analyses). Here, no missing data imputation was performed. In the logistic regressions, quantitative variables were analysed as 2 classes according to the median value where relevant.

We also explored whether fatigue responders (change above MCID) were DAS 28 responders (EULAR response [23]) in order to further assess relation between fatigue and disease activity.

Finally, the determinants of an acceptable fatigue (according to the PASS question) at month 4 were assessed by logistic regression on all collected baseline variables.

The sample size of 650 patients was calculated to allow an accuracy of 4% (width of the 95% confidence interval, CI of 8%) around the estimated effect (MCID planned to be reached by 65% of patients) with a type I error of 5% and an estimated 10% of patients with non-evaluable data (13-15).

Quantitative data were expressed as mean (standard deviation) and qualitative data as number and percentages (percentages were calculated excluding missing data).

All tests were two-sided with α risk at 5%. Statistical analyses were performed using SAS version 8.2 (SAS Institute Inc. Cary, NC, USA).

Table I. Patient characteristics at baseline and after 4 months of TCZ.

	Baseline	Month 4
Mean age (years)	56 ±13	
Women (n, %)	490 (81%)	
Mean RA duration (years)	12 ± 10	
Rheumatoid factor or ACPA positive (n, %)	463 (81%)	
Erosive disease on plain radiographs (n,%)	444 (76.9%)	
Mean DAS 28-ESR	5.3 ± 1.1	2.8 ± 1.2
Mean swollen joint count (out of 28)	7 ± 5	2 ± 3
Mean patient global disease activity VAS	64 ± 22	37 ± 26
Mean FACIT-fatigue	24 ± 11	33 ± 11
Fatigue considered acceptable by the patient (PASS question)	27%	67%
Mean Fatigue VAS	61 ± 23	41 ± 26
Mean HAQ	1.6 ± 0.7	1.2 ± 0.8
Anxiety (definite score by HADS)	46%	29%
Depression (definite score by HADS)	27%	23%

ACPA: anti-citrullinated protein antibodies; VAS: visual analogue scale (0–100); HAQ: Health Assesment Questionnaire disability index (range 0–3); HADS: Hospital Anxiety and Depression Scale.

Results

Patient characteristics (Table I)

One hundred and ninety-three investigators from secondary and tertiary-care centres across France included 719 patients between January 2010 and May 2011. The efficacy analysis was performed on 610 patients. The reasons for exclusion of the efficacy population were by decreasing frequency: FACIT-fatigue questionnaire not evaluable, non compliance with inclusion criteria and no TCZ infusion. A total of 108 patients were prematurely discontinued from the study due to lack of treatment efficacy (28 patients), poor tolerance (39 patients), loss to follow-up (19), patient wish (10) or other reasons (12).

Eighty-four percent of the patients were started on TCZ as a second-line or more biologic. Concomitant treatments included oral corticosteroids for 69% of patients, and a conventional disease-modifying drug (mainly methotrexate) for 66%.

Fatigue at baseline (Table I)

Fatigue levels at baseline were high in these long-standing active RA patients with a mean FACIT fatigue score of 24±11 and 73% of the patients considering their fatigue level as unacceptable (PASS question).

Improvement of fatigue in RA patients treated with TCZ

Sixty-two percent (95% CI: 58–66) of the patients had a clinically significant improvement of their fatigue as assessed by an increase of at least 4 points of the FACIT-fatigue score between inclusion and month 4. Furthermore, the percentage of patients considering their fatigue as acceptable increased from 27% to 67% between baseline and month 4.

Efficacy on fatigue appeared early: at day 15, the median reduction in fatigue was of 9% and reached 31% at 4 months with seemingly a plateau after month 3 (Fig. 1).

As expected, TCZ also lead to improvements for the other RA activity parameters (Table I and Supplementary online Fig. 1): mean DAS decreased from 5.3±1.1 to 2.8±1.3 over 4 months with 29% of patients in DAS28 defined remission at 4 months (of note DAS28 at 4 months was only available for 390 patients). TCZ efficacy on patient global assessment and on pain was similar to the efficacy on fatigue. Furthermore, safety assessments (on the safety population, *i.e.* 713 patients) did not identify new or unexpected safety signals (Supplementary online Fig. 1).

Determinants of fatigue improvement

In the multivariate logistic regression analysis on 417 patients with full data, 3 determinants of clinically significant improvement in fatigue at month 4 were identified (Table II): more recent RA diagnosis, higher CRP level, and higher levels of fatigue at inclusion. When excluding baseline fatigue from the analysis, a third significant determinant was also identified: higher baseline pain VAS value (for a value > median value =66: odds ratio=2.2, 95%CI (1.4–3.5), $p<0.001$).

Relation between fatigue improvement and DAS response

There was a positive significant but weak correlation (r=0.42, $p<0.00001$) between improvement of FACIT-Fatigue and of DAS-28 between baseline and month 4. Furthermore, 65% of fatigue responders were in low disease activity according to the DAS 28 at month 4, *versus* only 45% of fatigue non responders ($p<0.0001$).

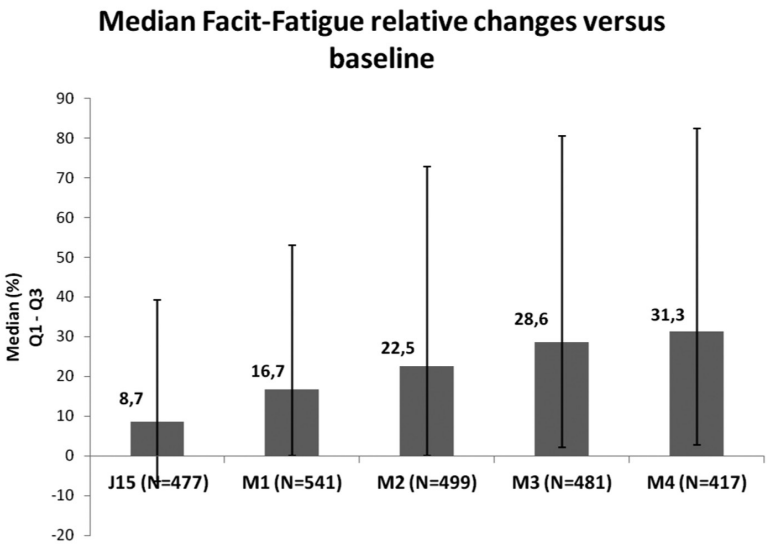

Fig. 1. FACIT-fatigue score relative changes *versus* baseline over 4 months of TCZ treatment. Results are presented as median percentage change and the bar represents the interquartile range (Q1–Q3). Results are presented successively for 2 weeks after the first infusion (J15), then 1 month, 2 months, 3 months and 4 months after the first infusion (M1 to M4). The N is the number of patients with data available at each timepoint.

Table II. Determinants of fatigue improvement during TCZ treatment.

n=358 patients	Odds ratio [95% confidence interval] (*p*-value)
High level of fatigue at baseline (FACIT fatigue score ≤median of 23)	3.4 [2.1–5.3] ($p<0.001$)
More recent RA diagnosis (<10 years)	1.6 [1.0–2.6] ($p=0.036$)
High level of CRP at baseline (odds ratio for an increase of 10 mg/l)	1.1 [1.0-1.3] 1.2 ($p=0.013$)

Multivariate logistic regression analysis to explain an improvement above the minimal clinically important difference of 4 points between baseline and month 4.

Determinants of an acceptable fatigue after treatment

The determinants at inclusion of obtaining an acceptable level of fatigue (according to the PASS question) at month 4 were lower anxiety HADS (doubtful anxious status: odds ratio=1.9 [1.0–3.7]; no anxiety: odds ratio=4.4 [2.0–9.5], $p<0.001$), and lower depression HADS (doubtful depression status: odds ratio=2.4 [1.2–4.7]; no depression: odds ratio=2.6 [1.3–5.3], $p=0.008$).

Relationship between fatigue and other variables before and after TCZ

Fatigue was mainly associated with HAQ and psychological status, rather than disease-related variables such as swollen joint count. The relationships between fatigue and these variables were not modified by the introduction of TCZ (Table III).

Discussion

To our knowledge, this study is the first study of a biologic in RA, where the primary endpoint was fatigue. This study is important for the RA field due to the current relative lack of quantified data on fatigue in RA. It brings to light several interesting new findings on fatigue in RA.

Firstly, we confirmed the high levels of fatigue in RA, in particular in patients with active disease such as this population of patients starting a biologic (Table IV). Indeed, 73% of these patients estimated their fatigue as unacceptable. Secondly, we found that during TCZ

Table III. Relationships before and after TCZ treatment between fatigue and other variables, at baseline and after 4 months of TCZ, when fatigue levels were much lower.

	Variables analysed for association with baseline fatigue n=505	Variables analysed for association with 4-month fatigue n=337
R2 of the model	0.54	0.62
HAQ disability index	**- 3.58 (p<0.0001)**	**- 2.92 (p<0.0001)**
Depression (definite score by HADS)	**- 0.77 (p<0.0001)**	**- 0.93 (p<0.0001)**
Anxiety (definite score by HADS)	**- 0.24 (p=0.007)**	**- 0.24 (p=0.038)**
Patient global assessment	**- 0.10 (p<0.0001)**	**- 0.07 (p=0.0004)**
Sleep VAS	**- 0.07 (p<0.0001)**	**- 0.08 (p<0.0001)**
Swollen joint count	0.08 (p=0.20)	0.19 (p=0.17)
Haemoglobin	0.13 (p=0.57)	-0.33 (p=0.27)

HAQ: Health Assesment Questionnaire disability index (range 0–3); VAS: visual analogue scale (0–100); HADS: Hospital Anxiety and Depression Scale.

Table IV. FACIT-fatigue scores at baseline assessment in several randomised controlled trials of biologic drugs, for comparative purposes (from ref. 5).

Trial	FACIT-Fatigue score (/52), mean (standard deviation) Treatment	Placebo
STAR	29.4 (11.1)	28.9 (11.0)
ARMADA	28.4 (11.3)	28.1 (9.4)
DEO19	30.6 (10.6)	28.3 (11.4)
DANCER	27.0 (10.4)	27.6 (10.7)
OPTION	27.7 (10.6)	26.7 (11.1)
GO-FORWARD	26.6 (11.0)	28.7 (10.5)
REFLEX	30.4 (10.8)	30.2 (11.8)
GO AFTER	23.0 (12.2)	24.0 (10.3)

treatment, fatigue improved indicating a link with disease activity; however, response to fatigue was not strongly related to DAS response but there was a link with baseline CRP, indicating that the inflammatory process plays a role in fatigue determinants. It was, however, difficult to determine who would respond in terms of fatigue, since the main predictor of a significant improvement in fatigue after treatment was severe fatigue at baseline. And thirdly, we found fatigue levels were strongly related to HAQ and psychological distress, both before and after treatment with TCZ.

This study has some potential limitations. The main weakness is the study design with no control group. However, this is a weakness only to assess the efficacy of TCZ, not to assess factors related with fatigue or with fatigue improvement in RA. Patients may have suffered from a selection bias, since this is a population of patients with active RA, starting a biologic. Thus, fatigue levels observed here are only applicable to such a population with active disease. However, again here, this should not invalidate our findings regarding factors associated with fatigue or its improvement. Furthermore, this large population of RA patients was issued from both secondary and tertiary centres and is probably at least representative of patients starting biologics in Western European countries in 2011. Indeed, fatigue levels were a little higher, but still similar, to data from published randomised clinical trials (Table IV). Many patients had incomplete data after treatment, which lead us to apply imputation techniques to our data. This is, however, often the case in observational studies. We chose to assess fatigue through the FACIT-fatigue scale (19). The results of the FACIT-fatigue scale may be less intuitive to interpret than a fatigue VAS; however, the FACIT-fatigue is a widely validated scale which has been used often in RA trials (Table IV) (19). Furthermore, the improvements noted in the fatigue VAS were consistent with the FACIT-fatigue results (Table I), and the correlation between FACIT and fatigue VAS was high in the present study (data not shown).

This study has strengths which include a focus on fatigue as primary outcome and the collection of many variables of interest in the context of fatigue, including, for example, psychological distress and sleep, which have rarely been assessed in studies evaluating fatigue (9). Interestingly, psychological distress was strongly related to fatigue, whereas sleep quality (assessed by VAS) was only slightly related to fatigue.

Fatigue levels were high in this population of RA patients. This is in accordance with previous reports on fatigue and its importance and magnitude in RA, although the levels of fatigue observed here were somewhat higher than in randomised controlled trials (Table IV) (2, 4, 5, 9, 26-28). As fatigue is partly country-driven, these higher levels of fatigue might be culturally explained (29). The originality of our approach is to have asked for a rating of the acceptability of fatigue using the PASS question, which allowed us to assess that 73% of patients judged their fatigue as unacceptable before treatment. The interpretation of such a finding should take into account the other aspects of impact of RA in patients with very active disease such as this population. Indeed, coping capacities probably play a role in the patients' assessment of fatigue consequences (30).

This study confirmed the efficacy of TCZ on fatigue outside of the context of randomised clinical trials. In phase III clinical trials of TCZ, the mean change in FACIT-Fatigue at 6 months was of 8 to 9 points in the TCZ 8 mg/kg groups (13, 14, 31), and in the open label TAMARA study conducted in a setting close to usual care in Germany on 286 patients treated with TCZ 8mg/kg in addition to their stable DMARD treatment, the FACIT-Fatigue score increased by 8.6 points at 6 months (32). This is very similar to the results observed in the present study (mean increase in FACIT-fatigue of 9 points over 4 months). To compare this efficacy on fatigue to the efficacy of other biologics, the effect size of TCZ in this study was calculated as 0.42. In a recent meta-analysis, the effect size of biolog-

ics on fatigue was of 0.38 to 0.57 at 6 months in established RA (5). Thus, although baseline levels of fatigue were higher, the efficacy and effect size in the present study are similar both to what was observed in phase III clinical trials of TCZ, and in randomised controlled studies of other biologics.

In the present study, two thirds of these long standing active RA patients achieved a clinically relevant improvement in their fatigue level, with an onset of action on fatigue which was rapid, as early as the second week of treatment. This study thus brings interesting new information on the rapidity of onset for fatigue relief in RA. TCZ had been shown to be an effective treatment of RA and indeed, its efficacy on other aspects of RA disease activity is rapid also, with in particular an extremely rapid decrease in acute phase reactants. Fatigue is associated with an increased risk for work disability (33) and the fast onset of TCZ efficacy on fatigue may be useful for RA patients with fatigue and who are still working (34). In the present study, the rapidity of efficacy on fatigue and on other aspects of RA, namely pain and patient global assessment, were similar which leads to hypotheses on the link between fatigue and RA disease activity (35).

The link between fatigue and other features of active RA disease is unclear (9). A recent review indicated studies inconsistently reported fatigue as related to RA (in particular pain and HAQ), to female gender, to psychological distress and to social support (9). The relationships between fatigue and acute phase reactants or DAS28 were unclear; and inconsistent results were also found for the influence of disease duration on fatigue. A modelisation of RA fatigue has been proposed which suggests interactions between 3 factors: RA processes, cognitive and behavioral factors, and personal life issues (36). Several studies have confirmed links between fatigue and psychological status (12, 37-39).

The present study evidenced a strong relation of fatigue with HAQ, pain and anxiety and depression, whereas the relationship with joint counts and DAS was more tenuous. We did not explore social and environmental aspects in our work. Depression appeared to play a greater role than anxiety, in fatigue; we suggest the assessment of fatigued patients should perhaps include a psychological assessment (38, 39). However, the association of fatigue with other patient-reported outcomes rather than with joint counts may reflect the usually observed correlations between patient-reported outcomes, partly due to the similar method for data collection (*i.e.* questionnaires), thus reflecting partly a 'methodology bias'. On the other hand, the link with disease activity is evidenced by the good efficacy of TCZ and other biologics on fatigue.

Concerning the prediction of a clinically relevant improvement in fatigue, this is an important question for clinicians, since for many patients fatigue is such an important aspect of disease that they are very concerned about possible improvements in their fatigue. Although we showed TCZ is indeed effective on fatigue in many patients, it was not possible to determine fully who would most benefit in terms of fatigue. The predictors evidenced were moderate, probably due to the heterogeneity of patients and to the multifactorial origin of fatigue in RA: depression, pain, psychosocial factors, sleep disorders, disease activity including CRP, disability, anaemia and other co-morbidities can play a role in RA fatigue.

Solutions to RA-related fatigue may perhaps be based not only on medications, but also on non-pharmacological treatments. Indeed, fatigue self-management in RA by cognitive behavioural therapy appeared efficacious in a recent study; the standardised effect size was 0.59–0.77 after 18 weeks of intervention (40). But this study was conducted in patients with a fatigue VAS above 60 at baseline which maximises the effect size. Furthermore, applicability to clinical practice remains to be established for this type of intervention.

Conclusion

In conclusion, further studies are needed on fatigue in RA in order to confirm the link between fatigue and the pathophysiological process of RA, and to put forward more possible solutions to this frequent and severe symptom.

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