Observational Study

OPEN

Correlation of fatigue with other disease related and psychosocial factors in patients with rheumatoid arthritis treated with tocilizumab

ACT-AXIS study

Héctor Corominas, MD, PhD[a,*], Cayetano Alegre, MD, PhD[b], Javier Narváez, MD, PhD[c], Carlos Marras Fernández-Cid, MD, PhD[d], Vicenç Torrente-Segarra, MD, PhD[e], Manuel Rodríguez Gómez, MD[f], Francisco Maceiras Pan, MD[g], Rosa María Morlà, MD, PhD[h], Fernando José Rodríguez Martínez, MD[i], Antoni Gómez-Centeno, MD[j], Laura Losada Ares, MD[k], Rocío González Molina, MD[l], Silvia Paredes González-Albo, MD[m], Joan Dalmau-Carolà, MD[n], Carolina Pérez-García, MD, PhD[o], Ceferino Barbazán Álvarez, MD[p], Liliana Ercole[q], Maria Ángeles Terrancle[q], on behalf of the ACT-AXIS Study Group

Abstract

To assess the hypothesis if tocilizumab (TCZ) is effective on disease activity, and also its effect in fatigue and other clinical and psychological disease-related factors in patients with rheumatoid arthritis (RA) treated with TCZ.

A 24-week, multicenter, prospective, observational study in patients with moderate to severe RA receiving TCZ after failure or intolerance to disease-modifying antirheumatic drugs or tumor necrosis factor-alpha was conducted.

Of the 122 patients included, 85 were evaluable for effectiveness (85% female, 51.9 ± 12.5 years, disease duration 8.7 ± 7.4 years). Mean change in C-reactive protein level from baseline to week 12 was −11.2 ± 4.0 ($P < .001$). Mean Disease Activity Index score (DAS28) decreased from 5.5 ± 1.0 at baseline to 2.7 ± 1.3 ($P < .001$) at week 24. Mean change in Functional Assessment of Chronic Illness Therapy score was −5.4 ± 11.2 points at week 24. Multiple regression analysis showed that the improvement in DAS28, sleep, and depression explained 56% and 47% of fatigue variance at week 12 and 24, respectively.

Tocilizumab is effective in reducing disease activity and results in a clinically significant improvement in fatigue, pain, swollen joint count, morning stiffness, sleepiness, depression, and DAS28; the last 3 were specifically identified as factors explaining fatigue variance with the use of TCZ in RA patients.

Abbreviations: AEs = adverse events, BDI-II = Beck Depression Inventory, version II, CRP = C-reactive protein, DAS28 = Disease Activity Index score, DMARDs = disease-modifying antirheumatic drugs, ESR = erythrocyte sedimentation rate, EULAR = European League Against Rheumatism, FACIT-F = Functional Assessment Chronic Illness Therapy-Fatigue scale, HPA = hypothalamic-pituitary-adrenal, IL = interleukin, PROs = patient-reported outcomes, RA = rheumatoid arthritis, SJC = swollen joint count, TCZ = tocilizumab, TJC = tender joint count, SAEs = serious adverse events, TNF-alfa = tumor necrosis factor-alpha, VAS = visual analog scale.

Keywords: clinical practice, fatigue, patient-reported outcomes, rheumatoid arthritis, tocilizumab

Editor: Ilke Coskun Benlidayi.

Funding: Economical support by Roche Farma S.A. Spain.

The authors have no conflicts of interest to disclose.

[a] *Rheumatology Department, Hospital Sant Joan Despí Moises Broggi,* [b] *Department of Rheumatology, Hospital Vall d'Hebrón,* [c] *Department of Rheumatology, Hospital Universitario de Bellvitge, L'Hospitalet de Llobregat, Barcelona,* [d] *Department of Rheumatology, Hospital Universitario Virgen de la Arrixaca, Murcia,* [e] *Department of Rheumatology, Hospital General de l'Hospitalet, L'Hospitalet de Llobregat,* [f] *Department of Rheumatology, Complejo Hospitalario Cristal Piñor, Ourense,* [g] *Complejo Hospitalario Arquitecto Marcide-Profesor Novoa Santos, A Coruña,* [h] *Department of Rheumatology, Xarxa Sanitaria i Social de Santa Tecla, Tarragona,* [i] *Department of Rheumatology, Hospital General Universitario Santa María del Rosell, Cartagena, Murcia,* [j] *Department of Rheumatology, Corporació Sanitària Parc Taulí, Barcelona,* [k] *Department of Rheumatology, Hospital da Costa Burela, Burela, Lugo,* [l] *Department of Rheumatology, Hospital Rafael Méndez, Lorca, Murcia,* [m] *Department of Rheumatology, Hospital Universitari Sant Joan de Reus, Tarragona,* [n] *Department of Rheumatology, Clínica Girona, Girona,* [o] *Department of Rheumatology, Hospital de Mollet, Mollet del Valles, Barcelona,* [p] *Hospital Xeral Cies, Vigo, Pontevedra,* [q] *Medical Department, Roche Farma S.A., Spain.*

[*] *Correspondence: Héctor Corominas, Rheumatology and Autoimmune diseases Division, Hospital Sant Joan Despí Moisès Broggi, Carrer de Jacint Verdaguer, 90, 08970 Sant Joan Despí, Barcelona, Spain (e-mail: vancor@yahoo.com).*

Medicine (2019) 98:26(e15947)

Received: 8 January 2019 / Received in final form: 9 May 2019 / Accepted: 14 May 2019

http://dx.doi.org/10.1097/MD.0000000000015947

1. Introduction

The clinical picture of rheumatoid arthritis (RA) includes the joint and systemic involvement, and also several psychological aspects may be affected. Importantly, fatigue is 1 of the most common and disabling symptoms of RA. Although it is considered to contribute to a decline in the patient's health status and quality of life, fatigue rarely constitutes a treatment target in RA.[1] Fatigue has not been considered among the recommended criteria for RA management, despite being a reliable and sensitive measure of change in RA.[2]

The mechanisms for fatigue in RA are not entirely clear, as most of current evidence is derived from cross-sectional studies that do not allow identifying long-term predictors and potential causal pathways for RA fatigue. Disease activity and other disease-related factors such as excessive inflammation have been reported to be correlated with fatigue.[3] However, the relationship of fatigue to disease activity seems to be less strong than previously assumed,[4–6] or this association has been found to be secondary or indirectly mediated through pain.[4]

Discrepant findings have also been reported among those studies evaluating pain as a possible cause of fatigue, whose results vary from nonexistent[7,8] to a strong correlation based on cross-sectional and longitudinal studies.[9] The inflammatory process as a factor influencing RA fatigue has not been fully established, as weak associations between fatigue and erythrocyte sedimentation rate (ESR), tender and swollen joints, and Disease Activity Index score (DAS28), or even absent for rheumatoid factor, ESR, and hemoglobin levels, have been described.[10–12]

Psychological factors seem to play a crucial role in explaining fatigue.[4,6,8,12] The contribution of disease activity to fatigue has been explained by mechanisms of mood and sleep disorders.[13] These findings support the widely accepted model of multifactorial etiology for fatigue, which has recently incorporated personal life aspects as factors that may be inter or intrarelated with other RA disease factors, and behavioral/cognitive issues.[14]

Tocilizumab (TCZ) has demonstrated drug efficacy and a safety profile in RA for more than 8 years to date. Considering the complexity of fatigue in RA, it is difficult to obtain conclusive data regarding the effect of treatment on this symptom.[15] Relief of fatigue in RA patients receiving interleukin (IL)-6 blocking agents,[16,17] suggests a biological pathway target for these agents through the hypothalamic-pituitary-adrenal (HPA) axis, given its activation by IL-6.[18,19] The fact that disturbance of the HPA axis may also influence other RA symptoms[18] led us to the hypothesis that a possible change in fatigue with the anti-IL-6 receptor antibody TCZ may be explained not only through its effect on disease activity but also on other RA-related, and physical and psychosocial factors.

The aim of the ACT-AXIS study was to assess efficacy of TCZ on disease activity and to identify factors associated with fatigue, and other clinical and psychological disease-related factors in patients with RA treated with TCZ after failure or intolerance to disease-modifying antirheumatic drugs (DMARDs) or tumor necrosis factor (TNF)-inhibitors.

2. Methods

2.1. Study design

The ACT-AXIS study was a multicenter, prospective observational study conducted in rheumatology units of 15 Spanish hospitals. The study was conducted in accordance with the Declaration of Helsinki and national regulations. The study was approved by the Ethic Committee of the Hospital de Sant Joan Despí Moisès Broggi, Barcelona (Spain), and all patients gave their written informed consent. Patients were followed up for 24 weeks according to clinical practice.

2.2. Study population

Inclusion criteria: adult (age ≥18 years) patients with moderate to severe RA (fulfilling the American College of Rheumatology 1987 revised criteria for RA), nonresponders or intolerant to DMARDs or TNF-inhibitors, and for whom the rheumatologist had decided to initiate TCZ treatment according to routine clinical practice. Exclusion criteria: previous diagnostic of depression or other psychiatric condition, and exclusion of other inflammatory or autoimmune diseases. Administration of TCZ as clinical trial medication or compassionate therapy, an absolute neutrophil count $\leq 2 \times 10^9$/L in the last routine blood test available, and inability to complete the study questionnaires were the exclusion criteria.

2.3. Data collection and assessments

Baseline evaluation at the time of TCZ initiation included a complete medical history along with the following data that were also collected at baseline and at 2 routine follow-up visits closest to weeks 12 and 24: laboratory parameters (hemoglobin, hematocrit, C-reactive protein [CRP] and ESR), RA activity-related data (tender joint count [TJC], swollen joint count [SJC], DAS28 score, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's pain assessment, morning stiffness duration, fatigue, sleepiness, and depression), and personal and social aspects of life (marital status, children living at home, care for dependents employment status, significant events in life, duration of sleep [hours of sleep at night], and physical activity). Moreover, TCZ treatment-related data and adverse events were retrieved at routine monthly visits coinciding with TCZ administration.

The DAS28 was calculated for disease activity using the ESR,[20] and it ranges from 0 to 10, where a score above 5.1 indicates high disease activity, a score 3.2 to 5.1 represents moderate disease activity, and below 3.2 indicates low disease activity. Response to TCZ treatment was evaluated by the European League Against Rheumatism (EULAR) response criteria.[21] Patient's and physician's global assessment of disease activity and pain were evaluated using a 10-cm visual analog scale (VAS). Fatigue was assessed according to the Functional Assessment Chronic Illness Therapy-Fatigue scale (FACIT-F, version 4)[22]; a brief 13-item score ranged from 0 to 52, where a high score represents less fatigue and a 3 to 4-point change is considered clinically significant. Depression was measured using the Beck Depression Inventory, version II (BDI-II),[23,24] which contains 21 questions scored on a scale value of 0 (neutral) to 3 (maximal severity). Total scores range from 0 to 63, and a higher total score corresponds to more severe depressive symptoms. A total score over 18 indicates moderate to severe depression. Sleepiness was evaluated by the Epworth Sleepiness Scale,[25] which is intended to evaluate the probability of falling asleep in 8 situations reflecting activities of daily living in a score from 0 "never doze or sleep" to 3 "high chance of dozing or sleeping." Total score ranges from 0 to 24, where the higher the score, the higher the sleepiness level.

2.4. Statistical analysis

The primary endpoint was to evaluate the correlation between change in fatigue and disease-related factors (serum hemoglobin levels, SJC, morning stiffness, pain, sleepiness, and depression) with the use of TCZ. We also seek for the influence of personal aspects (marital status, children living at home, care for dependents, employment status, important events in life, physical activity, time in hours of sleep at night) on the changes described. A simple linear regression model was used to calculate the individual correlation. The change in fatigue (from baseline to weeks 12 and 24) as the dependent variable was regressed against the change in each of the abovementioned disease-related variables, and personal and social aspects to assess the individual correlation. All variables that had a significance level of $P \leq .10$ were subsequently included in a multivariate linear regression analysis using an automatic stepwise selection model to identify the factors explaining fatigue variance. The β-regression coefficient, beta standardized regression coefficient, and the coefficient of determination (R^2) were calculated, the latter to determine the variance of change in fatigue explained by the independent variables included in the model.

Secondary endpoints included changes from baseline to week 12 and 24 for hemoglobin and CRP levels, SJC, pain score, morning stiffness duration, fatigue, sleepiness, and depression scores. We also evaluated the potential correlation between fatigue and anemia, defined as hemoglobin levels <12 g/dL in women and <13 g/dL in men. CRP, SJC, and DAS28 values were used to assess disease activity and response to the treatment. Clinical efficacy was assessed by a decrease in DAS28 score from baseline to weeks 12 and 24, and EULAR responses. Remission was defined, in accordance with the EULAR definition, as DAS28 <2.6. Safety was assessed by the frequency, severity, and causality of adverse events (AEs) reported during the study period.

Only patients with FACIT questionnaires scores available at baseline and 12 and 24 weeks after treatment initiation were considered evaluable for the effectiveness analysis.

Descriptive analysis was used for secondary endpoints, with continuous variables expressed as either mean ± standard deviation (SD) or as median (interquartile range) according to their distribution, and categorical variables as percentage. The change in each variable from baseline to week 12 and 24 was calculated by paired-samples *t* test (parametric) or Wilcoxon signed-rank tests (nonparametric).

The statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS Inc, Chicago, IL).

3. Results

3.1. Patient characteristics

Between September, 2012 and May, 2015, a total of 122 patients were enrolled in the study. Two patients were excluded from the study since they did not meet selection criteria. Thirty-five patients were excluded from the effectiveness analysis due to the lack of FACIT questionnaire scores at any of the study visits. Therefore, the evaluable population for the effectiveness analysis comprised a total of 85 patients. Premature withdrawal from the study occurred in 4 patients. The patient flowchart is shown in Fig. 1. Patient demographic and clinical baseline characteristics are described in Table 1.

3.2. Tocilizumab treatment

Most patients received TCZ at a dose of 8 mg/kg. Ten (11.8%) patients required treatment dose adjustments due to laboratory abnormalities (n = 4), weight gain (n = 7), adverse events (n = 1), and other unspecified reasons (n = 3). Of these, 8 patients required 1 or 2 dose modifications. Six (7.1%) patients required at least 1 temporary interruption of TCZ, mainly due to adverse events (n = 4). During the 24-week period, 4 (4.7%) patients discontinued TCZ due to insufficient response (n = 3) and adverse events (n = 1). The majority of patients received TCZ combined with MTX for RA (91.8%), and at that time point of the analysis, 68 patients were receiving low doses of prednisone (<5 m/daily).

3.3. Clinical efficacy of tocilizumab

The SJC and CRP levels were significantly reduced after 12 weeks of TCZ treatment (mean change from baseline of -4.0 ± 4.7 [$P < .001$] and -11.2 ± 4.0 [$P < .001$], respectively). By week 24, mean baseline DAS28 had decreased 2.7 ± 1.4 points ($P < .001$) (Table 2). In addition, after 24 weeks of TCZ initiation, EULAR responses were good in 44 (62.0%) patients, moderate in 22 (31.0%) patients, and absent in 5 (7%). The proportion of patients who experienced disease remission within 24 weeks was 45.2% (Fig. 2).

3.4. Effect of tocilizumab on fatigue and RA-related factors in active RA

After 24 weeks of TCZ, there was a clinically significant mean change in FACIT-F score of 5.4 ± 11.2 points from baseline ($P < .001$) (Table 2). Patients with significant fatigue (FACIT-F score <30) decreased from 58.8% at baseline to 37.6% by week 24.

Hemoglobin levels significantly increased in 0.6 ± 1.1 points by week 24 ($P < .001$). Accordingly, patients with anemia decreased from 65.9% at baseline to 47.9% at week 24. Mean scores for pain and depression, and mean duration of morning stiffness were significantly reduced by week 12, with a mean change that was sustained at week 24 (Table 2).

3.5. RA-related factors that may contribute to fatigue in RA

Simple linear regression analysis showed that change on FACIT-F score seen was significantly correlated with change in DAS28e ($\beta = -3.241$, $P < .01$), pain ($\beta = -0.947$, $P = .037$), sleepiness ($\beta = -0.742$, $P = .003$), and depression ($\beta = -0.714$, $P < .001$) at week 12.

When the association with change in FACIT-F score at week 24 was analyzed, significant correlations were observed with the change in DAS28 ($\beta = -2.596$, $P < .01$), SJC ($\beta = -0.600$, $P = .022$), pain ($\beta = -0.838$, $P = .044$), sleepiness ($\beta = -1.193$, $P = .001$), and depression scores ($\beta = -0.777$, $P < .001$).

Fatigue outcome was associated neither with hemoglobin levels and morning stiffness duration, nor with any of the personal life aspects.

Multiple linear regression analysis showed that the independent change in DAS28, sleepiness depression scores explained 56% and 47% of fatigue variance at weeks 12 and 24, respectively (Table 3).

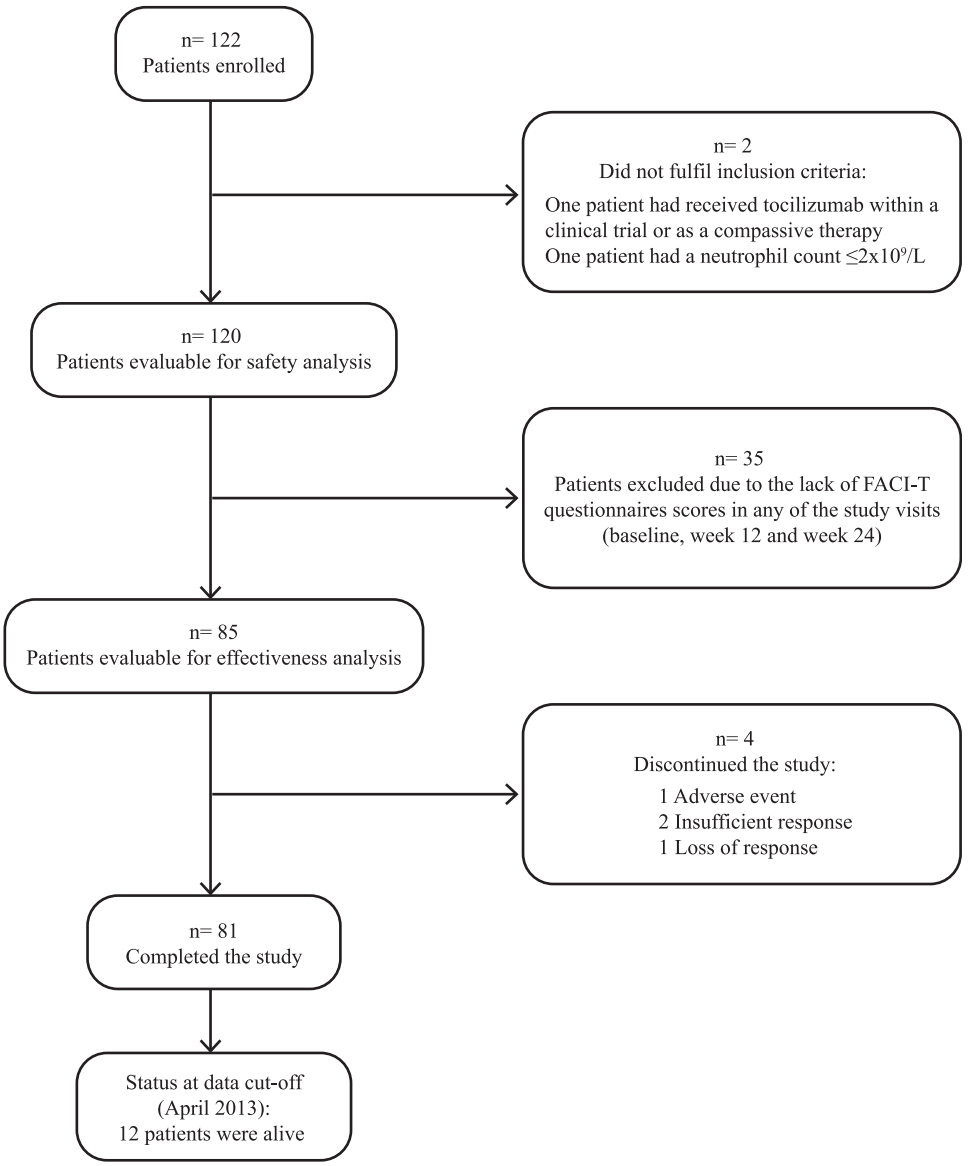

Figure 1. Disposition of patients. Flowchart diagram of the number of patients included in the study.

3.6. Safety

In all, 120 patients were included in the safety analysis. Overall, 195 AEs were reported in 77 (64.2%) patients. Most adverse events were mild (76.9%) to moderate (20.5%), and 48 AEs were considered as related to TCZ in 28 (23.3%) patients. Hypercholesterolemia and hypertransaminasemia were the most common adverse reactions in 11 (9.2%) and 4 (3.3%) patients, respectively. Only 3 patients experienced treatment-related infections. Infusion-related adverse reactions occurred in 7 (5.8%) patients. Seven (3.6%) serious AEs (SAEs) were reported in 6 patients: infectious arthritis, pilonidal cyst, acute endocarditis, acute pyelonephritis, respiratory tract infection, respiratory failure, and rheumatoid lung disease.

4. Discussion

To our knowledge, this is the first study focusing on the correlation of fatigue with other disease-related and psychosocial factors in patients with RA treated with TCZ in routine clinical practice. Our findings show that TCZ results in a clinically significant improvement in fatigue in patients with moderate to severe RA. Fatigue outcome was significantly correlated with improvement in SJC, DAS28, pain, sleepiness, and depression after TCZ treatment, although only depression, sleepiness, and DAS28 seemed to explain fatigue variance.

The efficacy data show that TCZ is effective in reducing disease activity,[26–28] as reflected by the significant decrease in DAS28, in line with clinical trials with this targeted treatment.[26–28] In addition, high remission levels were achieved by week 12 that were maintained and even slightly increased after 24 weeks from treatment initiation. The notable decrease in SJC and CRP levels also revealed a significant improvement in initial inflammatory activity. The high remission rates observed are those expected considering the beneficial effect of TCZ on acute-phase reactants.[29] In addition, we found that hemoglobin levels increased significantly after TCZ therapy as previously seen.[30]

Table 1

Baseline demographics, clinical characteristics, and PROs (n = 85).

Characteristics	Value
Age, y (mean ± SD)	51.9 ± 12.5
Female; n (%)	72 (84.7)
Duration of RA, y (mean ± SD)	8.7 ± 7.4
ESR, mm/h (mean ± SD)*	44.8 ± 26.3
CRP, mg/dL (mean ± SD)†	13.0 ± 19.0
Hemoglobin, g/dL (mean ± SD)	12.5 ± 1.5
Tender joint count (mean ± SD)	8.8 ± 6.9
Swollen joint count (mean ± SD)	6.0 ± 4.6
DAS28 (mean ± SD)‡	5.5 ± 1.0
Tociluzumab in combination with MTX	91.8 (%)
Patient's global assessment (VAS), cm (mean ± SD)	6.8 ± 2.1
Physician's global assessment (VAS), cm (mean ± SD)	6.0 ± 2.1
Pain VAS, cm (mean ± SD)	6.6 ± 2.3
Morning stiffness, h (mean ± SD)	1.4 ± 2.7
FACIT-F fatigue score (mean ± SD)	26.8 ± 12.4
Epworth sleepiness score (mean ± SD)	6.0 ± 4.6
Beck Depression Score (mean ± SD)	17.2 ± 11.8

CRP = C-reactive protein, DAS28 = Disease Activity Index score, ESR = erythrocyte sedimentation rate, FACIT-F = Functional Assessment Chronic Illness Therapy-Fatigue scale, PROs = patient-reported outcomes, RA = rheumatoid arthritis, SD = standard deviation, VAS = visual analog scale.
* Missing data (n = 4).
† Missing data (n = 10).
‡ Missing data (n = 4).

Table 2

Mean changes in fatigue and RA disease factors from baseline to 12 and 24 weeks.

Variable	Week 12	P*	Week 24	P*
Fatigue (FACIT-F score)	4.6 ± 10.5	<.001	5.4 ± 11.2	<.001
Hemoglobin levels (g/dL)	0.7 ± 1.0	<.001	0.6 ± 1.1	<.001
CRP (mg/L)	−11.2 ± 4.0	<.001	−12.5 ± 21.3	<.001
SJC	−4.0 ± 4.7	<.001	−4.2 ± 4.7	<.001
DAS28	−2.5 ± 1.2	<.001	−2.7 ± 1.4	<.001
Morning stiffness (h)	−0.9 ± 2.9	<.001	−1.0 ± 2.7	<.001
Pain VAS (cm)	−2.6 ± 2.5	<.001	−2.6 ± 3.0	<.001
Epworth sleepiness score	−0.4 ± 4.5	.172	−0.8 ± 3.4	<.05
Beck Depression Score	−3.1 ± 9.1	<.001	−3.5 ± 9.0	<.005

CRP = C-reactive protein, FACIT = Functional Assessment Chronic Illness Therapy-Fatigue scale, SJC = swollen joint count, VAS = visual analog scale.
* Based on paired-samples *t* test.

The increase in hemoglobin levels could be reflecting declines in hepcidin after TCZ, which previous research has associated with an improvement of inflammatory anemia together with CRP reductions.[31] Our findings therefore support the beneficial effect of TCZ in decreasing inflammatory activity and improving functioning in patients with active RA under routine clinical practice conditions.

Consistent with previous efficacy reports,[27,32] we found that TCZ treatment resulted in a clinically significant improvement in fatigue (≥4 points in FACIT-F)[33] that was even enhanced over time. Accordingly, the high proportion of RA patients with significant fatigue decreased approximately 20% by week 24. Patient-reported outcomes (PROs) on pain, morning stiffness, and depression were notably improved by week 12, and the beneficial effect was sustained over time. Despite the association of disease activity with morning stiffness,[34] pain, and depression,[35,36] we cannot conclude that the improved PROs are derived from the reduction in disease activity after TCZ treatment. Morning stiffness and pain have been linked to high levels of IL-6 during early morning in patients with active RA.[37,38] Additionally, depression in RA has been reported to be mediated by the up-regulation of cytokines known to be associated to the HPA axis.[39] The potential effect of TCZ to inhibit IL-6 may therefore contribute to its efficacy in reducing these symptoms, providing both clinical and psychosocial benefit in significantly fatigued patients.

Our findings show that fatigue outcome was significantly correlated with improvement in disease activity measured by DAS28 and SJC, and also with pain, sleepiness, and depression after TCZ treatment, although only DAS28, sleepiness, and

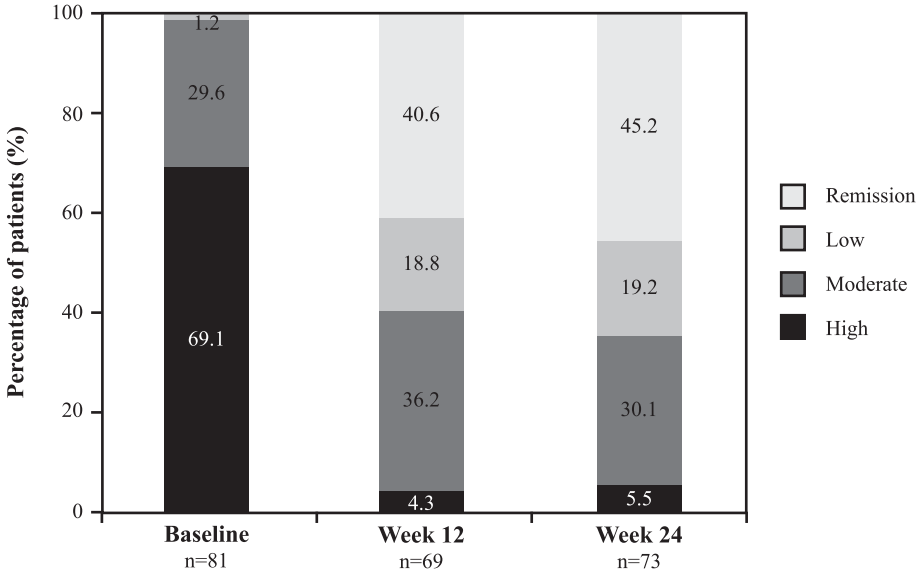

Figure 2. Disease activity over time. Disease activity was assessed according to DAS28 score. Percentage of patients achieving remission, low, moderate and high disease activity according to EULAR criteria are exposed: remission: DAS28 <2.6, low disease activity: 2.6 <DAS28 ≤ 3.2, moderate disease activity: 3.2 < DAS28 ≤ 5.1, high disease activity: DAS28 >5.1. DAS28 = Disease Activity Index score, EULAR = European League Against Rheumatism.

Table 3

Factors associated with fatigue in RA by multiple regression analysis.

Variable	β-coefficient*	Beta†	95% CI	P
Change from baseline to week 12‡				
DAS28 score	−2.200	−0.251	−3.741 to −0.658	<.01
Epworth sleepiness score	−0.944	−0.381	−1.371 to −0.518	<.001
Beck depression score	−0.707	−0.590	−0.919 to −0.494	<.001
Constant term	−2.822			
$R^2 = 0.558$				
Change from baseline to week 24§				
DAS28 score	−1.743	−0.215	−3.242 to −0.244	<.05
Epworth sleepiness score	−0.990	−0.256	−1.694 to −0.285	<.001
Beck depression score	−0.658	−0.517	−0.896 to −0.419	<.001
Constant term	−2.470			
$R^2 = 0.473$				

CI = confidence interval.

* Unstandardized coefficient.

† Standardized coefficient.

‡ Factors from the initial simple linear regression analysis with $P \leq .10$ included in the multivariate linear regression analysis: change in DAS28, pain, sleepiness, and depression scores.

§ Factors from the initial simple linear regression with $P \leq .10$ included in the multivariate regression analysis: change in DAS28, SJC, pain, sleepiness, and depression scores.

depression were retained in the multivariate model as factors explaining the variance in fatigue. The correlation of fatigue with disease activity is consistent with recent evidence.[40] However, the relationship of disease activity with fatigue in RA is unclear, and data available on this issue primarily come from cross-sectional studies,[41–44] while prospective evidence is scarce.[8]

The change in SJC was not identified as a contributor factor to fatigue in multivariate models performed in our series. These findings are in line with studies reporting that inflammatory components of the DAS28 contribute minimally to fatigue.[12] In addition, we found that other inflammatory parameters such as hemoglobin levels did not appear to be related to fatigue in line with previous reports.[6] Consistent with previous evidence, fatigue outcome appears to be independent of anemia.[40]

Regarding pain caused by joint inflammation, the bivariate analyses showed a significant correlation of pain with fatigue, although the multiple regression models did not identify pain as a factor explaining fatigue variance as seen with SJC. This finding is contrary to most cross-sectional studies conducted so far,[6,43,45] but consistent with a previous prospective study identifying predictors of fatigue over 1 year among RA patients.[8]

Taken together, these data suggest that fatigue variance after TCZ does not seem to be only explained by inflammatory activity, but physical and emotional functioning appear to have a greater contribution in our model as previously seen.[6,43] Accordingly, disease activity measured by DAS28 seemed to be contributing less strongly to fatigue variance than sleepiness and depression in the study multivariate models. At both study time points, sleepiness and depression explained variability in fatigue the best, depression being a stronger contributor. Our findings are therefore in line with previous studies that reported a significant association between fatigue variability and sleep quality or sleep disturbances.[6,46] However, it should be taken into account that the mean baseline sleepiness score is 6 and therefore RA patients evaluated in our series did not suffer from sleepiness because the Epworth scale considers a score between 0 and 9 as normal, and a mean reduction of about 1 point after 24 weeks is still within the normal range. In addition, duration of sleep was not found to be correlated with fatigue outcome. We cannot therefore clearly associate improvement in fatigue with changes in sleepiness score, despite its potential association.

Regarding cognitive and emotional functioning, depression was found to be strongly associated with fatigue, consistent with previous reports.[6,43] It is noteworthy that the mean baseline depression score in our series is nearly 18 and therefore patients had symptoms of moderate to severe depression. The baseline depressive mood of patients may be explained by their clinical activity at the time of TCZ treatment initiation, with high baseline disease activity (DAS28) and ESR scores, and a negative global perception of their disease (baseline VAS 6.6). Thus, the negative perception of disease may have contributed to fatigue through the mood state as these significantly fatigued RA patients (mean baseline FACIT <30) may perceive fatigue as frustrating or exhausting as previously seen.[6] The quality of life of patients with arthritis was previously investigated in several observational studies showing that all measures of disease activity and self-efficacy scores were markedly better in patients receiving biologic versus conventional therapy.[47] Therefore, improvement in depressive symptoms through the effect of TCZ on IL-6 levels may also improve fatigue. However, whether depression is the major cause of the improvement in fatigue in active RA cannot be clearly concluded as other psychosocial factors may be involved in RA fatigue besides depression.[8]

Finally, TCZ was reported to be well-tolerated with a withdrawal percentage due to adverse events <1%. The safety profile of TCZ presented no new or unexpected safety signals. The most common SAEs were infections as previously reported in clinical trials with TCZ.[26–28,48–50]

Some limitations of our study should be pointed out. Firstly, even though the change in sleepiness was identified as a contributor to fatigue improvement in the multivariate analyses, patients evaluated in our series did not suffer from sleepiness at that time point. Therefore, whether TCZ may reduce fatigue through the improvement of sleepiness would need to be addressed in RA patients with sleep disturbances. Secondly, our correlation analyses performed included relevant physical and psychosocial factors in addition to disease activity measures that have been involved in explaining fatigue in previous cross-sectional studies. However, we acknowledge that some inflammatory component such as CRP, ESR, and TJC, and other variables associated with RA fatigue such as disability and functioning, health-related quality of life, or self-efficacy were not

assessed in our model, or were not evaluated through a specific instrument. Other limitations to be highlighted are that RA is a heterogeneous disease and multiple comorbidities, and the requirement of drugs could affect some subjective complaints in different scores evaluated.

Despite its limitations, this study offers a welcome addition to the limited available prospective data on factors associated with RA fatigue, given that most evidence comes from cross-sectional studies. Additionally, the data existing on RA fatigue-related factors are heterogeneous mainly due to the use of different scales and questionnaires to evaluate fatigue and other PROs in addition to the assessment of different sets of variables in correlation studies. In this scenario, our study may provide the basis for a better understanding of factors explaining fatigue.

According to this, a recent paper on therapeutic strategies in patients affected by autoimmune rheumatic diseases will help in the near future to improve the unmet needs in the management of patients with RA.[51] Overall, we confirm this study supports and provides further evidence on the efficacy and safety of TCZ in clinical and psychological aspects in the real-world setting.

5. Conclusions

In summary, TCZ treatment results in a clinically significant improvement in fatigue that seems to correlate with disease activity reduction, although improvements in sleep and depressive symptoms appear to be stronger contributors to fatigue variance. Psychosocial factors therefore seem to have a more important role than inflammatory-related factors in explaining fatigue in active RA. Measuring the symptoms of fatigue in RA and individualization of therapeutic management based on mood state and depressive symptoms may therefore be of paramount importance in clinical practice, given that fatigue may be a reliable and feasible target to improve patient outcome.

Acknowledgments

The authors would like to acknowledge the remaining investigators of the ACT-AXIS Study Group participating in the study: DR and DRV. Hospital Sant Joan Despí Moises Broggi, Barcelona (Spain), LFD, BGA., and ADW, Hospital Cristal Piñor, Ourense (Spain); JLGV., MAHR., and JVP Hospital Arquitecto Marcide, Ferrol, A Coruña (Spain); JCF. and MGM., Corporació Sanitària Parc Taulí, Barcelona (Spain); RBMG., Hospital Da Costa Burela, Lugo (Spain); CC. and DRF., Hospital Universitario de Bellvitge, Barcelona (Spain); JABC and DPS, Hospital Rafael Méndez, Murcia (Spain); EGC., Hospital de Mollet, Murcia (Spain); BAD., Hospital Xeral Cies, Vigo (Spain).

We also thank CV and AT, from Dynamic Solutions S.L, for their editorial and medical writing support.

Author contributions

Conceptualization: Hèctor Corominas, Cayetano Alegre, Javier Narváez, Carlos Marras Fernández-Cid, Vicenç Torrente-Segarra, Manuel Rodríguez Gómez, Francisco Maceiras Pan, Rosa María Morlà, Fernando José Rodríguez Martínez, Antoni Gómez-Centeno, Laura Losada Ares, Rocío González Molina, Silvia Paredes González-Albo, Joan Dalmau-Carolà, Carolina Pérez-García, Ceferino Barbazán Álvarez, Maria Ángeles Terrancle.

Data curation: Hèctor Corominas, Cayetano Alegre, Javier Narváez, Carlos Marras Fernández-Cid, Vicenç Torrente-Segarra, Manuel Rodríguez Gómez, Francisco Maceiras Pan, Rosa María Morlà, Fernando José Rodríguez Martínez, Antoni Gómez-Centeno, Laura Losada Ares, Rocío González Molina, Silvia Paredes González-Albo, Joan Dalmau-Carolà, Carolina Pérez-García, Ceferino Barbazán Álvarez.

Formal analysis: Hèctor Corominas, Antoni Gómez-Centeno.

Funding acquisition: Hèctor Corominas, Liliana Ercole, Maria Ángeles Terrancle.

Investigation: Hèctor Corominas.

Methodology: Hèctor Corominas.

Project administration: Hèctor Corominas, Maria Ángeles Terrancle.

Resources: Hèctor Corominas, Liliana Ercole, Maria Ángeles Terrancle.

Supervision: Hèctor Corominas, Javier Narváez, Antoni Gómez-Centeno, Liliana Ercole.

Validation: Hèctor Corominas, Cayetano Alegre, Javier Narváez, Carlos Marras Fernández-Cid, Antoni Gómez-Centeno, Carolina Pérez-García, Ceferino Barbazán Álvarez, Liliana Ercole.

Visualization: Hèctor Corominas, Cayetano Alegre, Carlos Marras Fernández-Cid, Vicenç Torrente-Segarra.

Writing – original draft: Hèctor Corominas.

Writing – review & editing: Hèctor Corominas.

Hèctor Corominas orcid: 0000-0002-7738-6787.

References

[1] Hewlett S, Cockshott Z, Byron M, et al. Patients' perceptions of fatigue in rheumatoid arthritis: overwhelming, uncontrollable, ignored. Arthritis Rheum 2005;53:697–702.

[2] Minnock P, Kirwan J, Bresnihan B. Fatigue is a reliable, sensitive and unique outcome measure in rheumatoid arthritis. Rheumatology (Oxford) 2009;48:1533–6.

[3] Minnock P, FitzGerald O, Bresnihan B. Women with established rheumatoid arthritis perceive pain as the predominant impairment of health status. Rheumatology (Oxford) 2003;42:995–1000.

[4] Pollard LC, Choy EH, Gonzalez J, et al. Fatigue in rheumatoid arthritis reflects pain, not disease activity. Rheumatology (Oxford) 2006;45:885–9.

[5] Repping-Wuts H, Fransen J, van AT, et al. Persistent severe fatigue in patients with rheumatoid arthritis. J Clin Nurs 2007;16:377–83.

[6] van HD, Fransen J, Bleijenberg G, et al. Physical and psychosocial correlates of severe fatigue in rheumatoid arthritis. Rheumatology (Oxford) 2010;49:1294–302.

[7] Stebbings S, Herbison P, Doyle TC, et al. A comparison of fatigue correlates in rheumatoid arthritis and osteoarthritis: disparity in associations with disability, anxiety and sleep disturbance. Rheumatology (Oxford) 2010;49:361–7.

[8] Treharne GJ, Lyons AC, Hale ED, et al. Predictors of fatigue over 1 year among people with rheumatoid arthritis. Psychol Health Med 2008;13:494–504.

[9] Nikolaus S, Bode C, Taal E, et al. Fatigue and factors related to fatigue in rheumatoid arthritis: a systematic review. Arthritis Care Res (Hoboken) 2013;65:1128–46.

[10] Escobar ME, Gerhardt C, Roesler E, et al. Anemia versus disease activity as cause of fatigue in rheumatoid arthritis. Acta Reumatol Port 2010;35:24–8.

[11] Riemsma RP, Rasker JJ, Taal E, et al. Fatigue in rheumatoid arthritis: the role of self-efficacy and problematic social support. Br J Rheumatol 1998;37:1042–6.

[12] Bergman MJ, Shahouri SH, Shaver TS, et al. Is fatigue an inflammatory variable in rheumatoid arthritis (RA)? Analyses of fatigue in RA, osteoarthritis, and fibromyalgia. J Rheumatol 2009;36:2788–94.

[13] Nicassio PM, Ormseth SR, Custodio MK, et al. A multidimensional model of fatigue in patients with rheumatoid arthritis. J Rheumatol 2012;39:1807–13.

[14] Hewlett S, Chalder T, Choy E, et al. Fatigue in rheumatoid arthritis: time for a conceptual model. Rheumatology (Oxford) 2011;50:1004–6.
[15] Chauffier K, Salliot C, Berenbaum F, et al. Effect of biotherapies on fatigue in rheumatoid arthritis: a systematic review of the literature and meta-analysis. Rheumatology (Oxford) 2012;51:60–8.
[16] Illei GG, Shirota Y, Yarboro CH, et al. Tocilizumab in systemic lupus erythematosus: data on safety, preliminary efficacy, and impact on circulating plasma cells from an open-label phase I dosage-escalation study. Arthritis Rheum 2010;62:542–52.
[17] Wendling D, Racadot E, Wijdenes J. Treatment of severe rheumatoid arthritis by anti-interleukin 6 monoclonal antibody. J Rheumatol 1993;20:259–62.
[18] Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med 1995;332:1351–62.
[19] Norheim KB, Jonsson G, Omdal R. Biological mechanisms of chronic fatigue. Rheumatology (Oxford) 2011;50:1009–18.
[20] Prevoo ML, van 't Hof MA, Kuper HH, et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44–8.
[21] van Gestel AM, Prevoo ML, van 't Hof MA, et al. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. Arthritis Rheum 1996;39:34–40.
[22] Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) measurement system: properties, applications, and interpretation. Health Qual Life Outcomes 2003;1:79.
[23] Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–71.
[24] Sanz J, Perdigón A, Carmelo V. Adaptación española del Inventario para la Depresión de Beck-II (BDI-II): Propiedades psicométricas en población general. Clínica y Salud 2014;14:249–80.
[25] Chiner E, Arriero JM, Signes-Costa J, et al. [Validation of the Spanish version of the Epworth Sleepiness Scale in patients with a sleep apnea syndrome]. Arch Bronconeumol 1999;35:422–7.
[26] Burmester GR, Feist E, Kellner H, et al. Effectiveness and safety of the interleukin 6-receptor antagonist tocilizumab after 4 and 24 weeks in patients with active rheumatoid arthritis: the first phase IIIb real-life study (TAMARA). Ann Rheum Dis 2011;70:755–9.
[27] Emery P, Keystone E, Tony HP, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis 2008;67:1516–23.
[28] Genovese MC, McKay JD, Nasonov EL, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum 2008;58:2968–80.
[29] Kishimoto T. Interleukin-6: discovery of a pleiotropic cytokine. Arthritis Res Ther 2006;8(Suppl 2):S2.
[30] Hashimoto M, Fujii T, Hamaguchi M, et al. Increase of hemoglobin levels by anti-IL-6 receptor antibody (tocilizumab) in rheumatoid arthritis. PLoS One 2014;9:e98202.
[31] Isaacs JD, Harari O, Kobold U, et al. Effect of tocilizumab on haematological markers implicates interleukin-6 signalling in the anaemia of rheumatoid arthritis. Arthritis Res Ther 2013;15:R204.
[32] Strand V, Burmester GR, Ogale S, et al. Improvements in health-related quality of life after treatment with tocilizumab in patients with rheumatoid arthritis refractory to tumour necrosis factor inhibitors: results from the 24-week randomized controlled RADIATE study. Rheumatology (Oxford) 2012;51:1860–9.
[33] Kosinski M, Zhao SZ, Dedhiya S, et al. Determining minimally important changes in generic and disease-specific health-related quality of life questionnaires in clinical trials of rheumatoid arthritis. Arthritis Rheum 2000;43:1478–87.
[34] Khan NA, Yazici Y, Calvo-Alen J, et al. Reevaluation of the role of duration of morning stiffness in the assessment of rheumatoid arthritis activity. J Rheumatol 2009;36:2435–42.
[35] Covic T, Tyson G, Spencer D, et al. Depression in rheumatoid arthritis patients: demographic, clinical, and psychological predictors. J Psychosom Res 2006;60:469–76.
[36] Hider SL, Tanveer W, Brownfield A, et al. Depression in RA patients treated with anti-TNF is common and under-recognized in the rheumatology clinic. Rheumatology (Oxford) 2009;48:1152–4.
[37] Perry MG, Kirwan JR, Jessop DS, et al. Overnight variations in cortisol, interleukin 6, tumour necrosis factor alpha and other cytokines in people with rheumatoid arthritis. Ann Rheum Dis 2009;68:63–8.
[38] Straub RH, Cutolo M. Circadian rhythms in rheumatoid arthritis: implications for pathophysiology and therapeutic management. Arthritis Rheum 2007;56:399–408.
[39] Choy E. Understanding the dynamics: pathways involved in the pathogenesis of rheumatoid arthritis. Rheumatology (Oxford) 2012;51(suppl 5):3–11.
[40] Singh H, Arya S, Talapatra P, et al. Assessment of fatigue in rheumatoid arthritis (by Functional Assessment of Chronic Illness Therapy-Fatigue score) and its relation to disease activity and anemia. J Clin Rheumatol 2014;20:87–90.
[41] Davis MC, Zautra AJ, Younger J, et al. Chronic stress and regulation of cellular markers of inflammation in rheumatoid arthritis: implications for fatigue. Brain Behav Immun 2008;22:24–32.
[42] Dhir V, Lawrence A, Aggarwal A, et al. Fibromyalgia is common and adversely affects pain and fatigue perception in North Indian patients with rheumatoid arthritis. J Rheumatol 2009;36:2443–8.
[43] Huyser BA, Parker JC, Thoreson R, et al. Predictors of subjective fatigue among individuals with rheumatoid arthritis. Arthritis Rheum 1998;41:2230–7.
[44] Thyberg I, Dahlstrom O, Thyberg M. Factors related to fatigue in women and men with early rheumatoid arthritis: the Swedish TIRA study. J Rehabil Med 2009;41:904–12.
[45] Lee YC, Cui J, Lu B, et al. Pain persists in DAS28 rheumatoid arthritis remission but not in ACR/EULAR remission: a longitudinal observational study. Arthritis Res Ther 2011;13:R83.
[46] Wolfe F, Hawley DJ, Wilson K. The prevalence and meaning of fatigue in rheumatic disease. J Rheumatol 1996;23:1407–17.
[47] Giacomeli R, Gorla R, Trotta F, et al. Sarzi-Puttini R Quality of life and unmet needs in patients with inflammatory arthropathies: results from the multicentre, observational RAPSODIA study. Rheumatology (Oxford) 2015;54:792–7.
[48] Nishimoto N, Miyasaka N, Yamamoto K, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol 2009;19:12–9.
[49] Nishimoto N, Miyasaka N, Yamamoto K, et al. Long-term safety and efficacy of tocilizumab, an anti-IL-6 receptor monoclonal antibody, in monotherapy, in patients with rheumatoid arthritis (the STREAM study): evidence of safety and efficacy in a 5-year extension study. Ann Rheum Dis 2009;68:1580–4.
[50] Smolen JS, Beaulieu A, Rubbert-Roth A, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet 2008;371:987–97.
[51] Giacomelli R, Afeltra A, Alunno A, et al. International consensus: what else can we do to improve diagnosis and therapeutic strategies in patients affected by autoimmune rheumatic diseases (rheumatoid arthritis, spondyloarthritides, systemic sclerosis, systemic lupus erythematosus, antiphospholipid syndrome and Sjogren's syndrome)? The unmet needs and the clinical grey zone in autoimmune disease management. Autoimmun Rev 2017;16:911–24.