


# Effect of biologics and targeted synthetic disease-modifying anti-rheumatic drugs on fatigue in rheumatoid arthritis

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## Abstract

Fatigue is a common and debilitating symptom in patients with RA. Since 2007, fatigue has been included as one of the core outcome measures in RA. Clinical trials of biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) have included fatigue as a secondary endpoint. A Cochrane review in 2016 concluded that the bDMARDs have a moderate effect on improving fatigue in RA. More recent clinical trials of the new biologic agent sarilumab and the Janus kinase inhibitors tofacitinib and baricitinib showed similar benefits. It remains unclear whether the effect of bDMARDs and tsDMARDs on fatigue is mediated by direct effects or through a reduction in inflammation. As fatigue was a secondary endpoint, many analyses did not adjust for potential confounding factors, including pain, mood and anaemia, which is a significant limitation.

**Key words:** rheumatoid arthritis, outcome measures, DMARDs, biologic therapies, systematic review

### Rheumatology key messages

- Biologic DMARDs reduce fatigue in patients with RA.
- The Janus kinase inhibitors tofacitinib and baricitinib reduce fatigue in patients with RA.

## Introduction

RA is a chronic inflammatory arthritis associated with increased mortality and morbidity. Joint inflammation and destruction are the dominant clinical features and the standard of care is focussed on ‘treat-to-target’, based on suppressing joint inflammation to a minimal level, i.e. either remission or, failing this, low disease activity [1]. From the patients’ perspective, the dominant symptoms in RA are pain and fatigue [2, 3]. Fatigue is common in RA patients, affecting >80% of patients, and >50% of patients have a moderate to high level of fatigue [4]. Fatigue was associated with disability and reduced quality of life. Patients consider fatigue more difficult to manage than pain and a major reason for disability [3]. Consequently, fatigue was included as a major outcome domain of RA in 2007 by the OMERACT [5]. However,

there is no recommendation on the best instrument for assessing fatigue and no approved treatment for fatigue in RA [6].

The precise biologic mechanism that leads to fatigue in RA remains unknown, but it is likely multifactorial, involving complex pathways [7]. Inflammation has been implicated in the pathobiology of fatigue since it is a common symptom in many chronic inflammatory diseases [8]. Therefore, reducing inflammation may reduce fatigue. However, the effect of conventional synthetic DMARDs (csDMARDs) on fatigue is unknown since fatigue is rarely assessed in randomized control trials (RCTs) of csDMARDs. With the inclusion of fatigue as a major outcome domain by the OMERACT, RCTs of biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) have assessed changes in fatigue before and after treatment.

## Effect of bDMARDs on fatigue

In 2016, a Cochrane systematic review assessing the effect of bDMARDs in RA was published [9]. This systematic review included 32 RCTs or pooled analyses of clinical trials of bDMARDs in RA: 20 studies of anti-TNF agents and 12 non-anti-TNF biologic agents, including

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abatacept, rituximab, tocilizumab and canakinumab. In total, these studies assessed almost 15 000 patients. Although fatigue has been a core outcome domain for RA since 2007, in the absence of a recommended outcome measure for assessing fatigue, different instruments were used in these studies, which included the Functional Assessment of Chronic Illness Therapy Fatigue Domain (FACIT-F), 36-item Short Form Vitality Domain (SF-36 VT), visual analogue scale and the numerical rating scale (0–10). SF-36 VT and FACIT-F were the most commonly used outcome measure. SF-36 is a validated outcome measure for health-related quality of life. It consists of eight domains. Four domains are physical and four are mental. The four physical domains are physical functioning, role physical, bodily pain and general health. The four mental domains are mental health, vitality, role emotional and social functioning. Many studies used the SF-36 VT score as an inverse measure of fatigue. The FACIT is also a health-related quality of life instrument, and one of its domains is fatigue. FACIT-F scores range between 0 and 52, with higher scores indicating less fatigue. In the Cochrane review, changes in fatigue scores were assessed by standardized mean difference so that different instruments can be pooled for meta-analysis. Standardized mean differences were back-transformed into changes in the SF-36 VT and FACIT-F. The minimal clinically important difference (MCID) for the SF-36 VT is 5 points and for the FACIT-F is 3–4 points.

The Cochrane review concluded that bDMARDs had a moderate effect on reducing fatigue, with a standardized mean difference of  $-0.43$  (95% CI  $-0.49, -0.38$ ), which was statistically significant ( $P < 0.00001$ ). This equates to a difference of 6.45 units (95% CI 5.70, 7.35) of the FACIT-F score (range 0–52) or 7.65 units (95% CI 6.76, 8.72) of the SF-36 VT score. The number needed to treat was five. In a subanalysis, categorizing bDMARDs into two groups—anti-TNF agents and non-TNF bDMARDs—found similar effects on fatigue.

Anti-TNF bDMARDs included 19 studies with 8946 participants. The standardized mean difference between the intervention and control groups was  $-0.42$  ( $P < 0.00001$ ). This equates to a difference of 6.3 units of the FACIT-F score or 7.5 units of the SF-36 VT score. A sensitivity analysis found that studies in early RA reported larger effects on fatigue.

For non-TNF bDMARDs, 5682 patients from 11 studies were included in the Cochrane review. Non-TNF bDMARDs reduced fatigue with an effect size similar to anti-TNF bDMARDs. The standardized mean difference was  $-0.46$  ( $P < 0.00001$ ). This equates to 6.9 units of the FACIT-F score or 8.19 units of the SF-36 VT score.

Since the publication of this Cochrane review, an anti-IL-6 receptor monoclonal antibody, sarilumab, and two Janus kinase (JAK) inhibitors, tofacitinib and baricitinib, have been approved for the treatment of RA.

## Sarilumab

Sarilumab was approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of RA in 2017. It is a human anti-IL-6

receptor monoclonal antibody similar to tocilizumab. Fatigue has been assessed in phase 3 clinical trials.

Mobility was a phase 3 RCT in patients with RA who had an inadequate response to MTX [10]. Patients were randomized to either placebo or subcutaneous sarilumab 150 or 200 mg fortnightly plus stable doses of MTX. The change in the FACIT-F score at week 24 in the placebo group was 5.8 (s.d. 0.5) compared with 8.6 (s.d. 0.5) and 9.2 (s.d. 0.5) in the sarilumab 150 mg and 200 mg groups, respectively (Table 1). These differences were statistically significant. Similarly, the SF-36 VT reduction was statistically significantly higher in the sarilumab 150 mg [13.9 (s.d. 1.1)] and 200 mg groups [18.0 (s.d. 1.0)] compared with 9.8 (s.d. 1.2) in the placebo group. In the sarilumab 150 mg group, 15.6% of patients achieved MCID (defined as  $\geq 4$  for FACIT-F and  $\geq 5$  for SF-36 VT) in both the FACIT-F and SF-36 VT scores, while in the 200 mg group, 21.8% and 23.6% achieved MCID in the FACIT-F and SF-36 VT scores, respectively. The number needed to treat for achieving MCID in fatigue was six for the 150 mg group and four to five for the 200 mg group.

TARGET (NCT01709578) was a phase 3 RCT similar to MOBILITY (NCT01061736), except in patients with RA who had an inadequate response to bDMARDs [11]. The change in FACIT-F score at week 24 in the placebo group was 6.8 (s.d. 0.9) compared with 9.9 (s.d. 0.8) and 10.1 (s.d. 0.8) in the sarilumab 150 mg and 200 mg groups, respectively. These differences were statistically significant. Similarly the SF-36 VT reduction was statistically significantly higher in the sarilumab 150 mg [14.5 (s.d. 1.6)] and 200 mg [16.6 (s.d. 1.5)] groups compared with 9.2 (s.d. 0.8) in the placebo group. In the sarilumab 150 mg group, 16.6% of patients achieved MCID in FACIT-F and 13.8% in SF-36 VT, while in the 200 mg group 16.8% and 17.8% achieved MCID, respectively. The number needed to treat was six to seven for the 150 mg group and six for 200 mg group.

MONARCH (NCT02332590), a head-to-head double-blind, double-dummy, placebo-controlled trial, compared the efficacy of sarilumab 200 mg vs adalimumab monotherapy [12]. Efficacy as assessed by the 28-joint DAS and the American College of Rheumatology Response Criteria were statistically significantly higher with sarilumab. However, changes in the FACIT-F [10.18 (s.d. 0.7) vs 8.4 (0.71)] and SF-36 VT [17.95 (s.d. 1.42) vs 14.39 (1.43)] were numerically higher in the sarilumab group, but the difference vs adalimumab was not statistically significant.

## JAK inhibitors

JAKs are intracellular molecules that are important for signalling of many cytokines [13]. Oral JAK inhibitors have been developed for the treatment of RA. Currently two JAK inhibitors, tofacitinib and baricitinib, are licenced for the treatment of RA. They are categorized as tsDMARDs to differentiate them from bDMARDs and csDMARDs.

## Tofacitinib

Tofacitinib is a selective JAK1 and JAK3 inhibitor [13]. The effect of tofacitinib on fatigue has been reported in five phase 3 clinical trials (Table 2). In these studies, tofacitinib

**TABLE 1** Changes in FACIT-F and SF-36 VT scores in phase 3 trials of sarilumab

Trials	Comparison group		Sarilumab 150 mg		Sarilumab 200 mg	
	FACIT-F	SF-36 VT	FACIT-F	SF-36 VT	FACIT-F	SF-36 VT
MOBILITY	5.8 (s.d. 0.5)	9.8 (s.d. 1.2)	8.6 (s.d. 0.5)	13.9 (s.d. 1.1)	9.2 (s.d. 0.5)	18.0 (s.d. 1.0)
TARGET	6.8 (s.d. 0.9)	9.2 (s.d. 1.7)	9.9 (s.d. 0.8)	14.5 (s.d. 1.6)	10.1 (s.d. 0.8)	16.6 (s.d. 1.5)
MONARCH (adalimumab)	8.4 (s.d. 0.71)	14.39 (s.d. 1.43)	NA	NA	10.18 (s.d. 0.7)	17.95 (s.d. 1.42)

NA: not applicable.

**TABLE 2** Changes in FACIT-F and SF-36 VT scores at week 12 in phase 3 trials of tofacitinib

Group	Comparison group		Tofacitinib 5 mg		Tofacitinib 10 mg	
	FACIT-F	SF-36 VT	FACIT-F	SF-36 VT	FACIT-F	SF-36 VT
Oral Sync	2.1 (s.d. 0.6)	2.6 (s.d. 0.7)	5.8 (s.d. 0.5)	6.3 (s.d. 0.5)	6.9 (s.d. 0.5)	6.5 (s.d. 0.5)
Oral Step	1.11 (s.d. 1.04)	2.20 (s.d. 0.90)	6.27 (s.d. 1.01)	6.40 (s.d. 0.89)	4.57 (s.d. 1.03)	6.71 (s.d. 0.91)
Oral Solo	2.84 (s.d. 0.82)	2.03 (s.d. 0.81)	6.70 (s.d. 0.56)	6.56 (s.d. 0.55)	8.01 (s.d. 0.58)	8.49 (s.d. 0.57)
Oral Standard	1.57 (s.d. 0.79)	2.21 (s.d. 0.82)	5.85 (s.d. 0.59)	4.97 (s.d. 0.61)	6.88 (s.d. 0.59)	7.21 (s.d. 0.61)
Oral Start (MTX)	5.33 (s.d. 0.67)	5.06 (s.d. 0.70)	8.19 (s.d. 0.48)	8.20 (s.d. 0.50)	8.72 (s.d. 0.46)	8.84 (s.d. 0.48)

5 and 10 mg twice a day were evaluated, however, only 5 mg twice a day has been approved for the treatment of RA. These clinical trials included patients with inadequate response to MTX (Oral Standard) [14], csDMARDs (Oral Sync) [15] or bDMARDs (Oral Step) [16], as well as patients with early arthritis (Oral Start) [17] and used as monotherapy (Oral Solo) [18]. In Oral Standard, Oral Sync, Oral Step and Oral Solo, the effects of tofacitinib were compared with placebo. In Oral Start, comparisons were made against active treatment with MTX. Table 2 shows the effect of treatment on the FACIT-F and SF-36 VT at week 12, which is the primary endpoint of these trials.

Tofacitinib statistically significantly reduced fatigue when compared with placebo in the Oral Standard, Oral Sync, Oral Step and Oral Solo groups. In the Oral Start group, improvement in fatigue was statistically significantly superior to MTX.

## Baricitinib

Baricitinib is a JAK1 and JAK2 selective inhibitor [13]. Changes in fatigue in four randomized placebo-controlled trials have been reported. These trials were conducted in RA patients with inadequate response to MTX [RA-Beam (NCT01710358)], csDMARDs [RA-Build (NCT01721057)] and bDMARDs [RA-Beacon (NCT01721044)] as well as patients with early RA [RA-Begin (NCT01711359)].

In RA-BEAM, patients with inadequate response to MTX were randomized to receive placebo, baricitinib 4 mg once daily or fortnightly adalimumab 40 mg in addition to

their existing csDMARDs [19]. The primary endpoint was at week 12. Changes in the FACIT-F score at week 12 were statistically significantly higher in baricitinib- and adalimumab-treated patients when compared with placebo. The percentages of patients who achieved an MCID improvement were also higher in these groups (Table 3).

In RA-Build, patients with inadequate response to csDMARDs [20] were randomized to receive either placebo or baricitinib 2 or 4 mg daily. Improvement in fatigue as measured by the FACIT-F score was statistically significantly higher at week 24 for baricitinib 4 mg when compared with placebo, but not at week 12. Changes in the FACIT-F scores in the 2 mg group were numerically higher than placebo but were not statistically significant. The percentages of patients who achieved MCID in the FACIT-F score were 43%, 59% and 60% at week 24 ( $P=0.001$  for both baricitinib groups vs placebo) but not statistically significant at week 12 (59%, 63% and 65% for placebo, baricitinib 2 mg and baricitinib 4 mg, respectively).

RA-Beacon is a phase 3 study of baricitinib in patients with RA and an inadequate response to bDMARDs [21]. Patients were randomized to receive either placebo or baricitinib 2 or 4 mg daily. Improvement in fatigue as measured by the FACIT-F score was statistically significantly higher in the baricitinib 2 mg and 4 mg groups at week 12 when compared with placebo. The percentages of patients who achieved at least MCID improvement were also statistically significantly higher (Table 3).

RA-Early is a double-blind phase 3 study of baricitinib as monotherapy or combined with MTX vs MTX

**TABLE 3** Percentage of patients with improvement in the FACIT-F score more than the MCID of 3.56 at week 12 in phase 3 trials of baricitinib

Group	Comparison group	Baricitinib 2 mg	Baricitinib 4 mg
RA-Beam	59	NA	66*
RA-Build	59	63	65
RA-Beacon	48	64*	63*
	MTX	Baricitinib 4 mg monotherapy	Baricitinib 4 mg plus MTX
RA-Early	65	75	71

NA: Not applicable. \*: statistically significant when compared with controls.

monotherapy in patients with active early RA [22]. Changes in the FACIT-F score after 24 weeks were 8.9 (95% CI 7.6, 10.1) in the MTX group, 13.3 (95% CI 11.8, 14.7) in the baricitinib monotherapy group and 12.2 (95% CI 11.0, 13.5) in the MTX plus baricitinib group. The differences between the baricitinib groups vs the MTX group were statistically significant. The percentages of patients achieving MCID (defined as  $\geq 3.56$  for the FACIT-F and  $\geq 5$  for the SF-36 VT) at week 24 were 65%, 75% and 71% for MTX, baricitinib monotherapy and baricitinib plus MTX, respectively.

## Conclusion

The Cochrane review in 2016 concluded that bDMARDs have a moderate effect in reducing fatigue in patients with RA. Since then, data from trials of sarilumab on fatigue are consistent with this conclusion and the effect size of sarilumab was similar to that of other bDMARDs, including tocilizumab. Clinical trials of the tsDMARDs tofacitinib and baricitinib also suggest they may reduce fatigue. However, it is difficult to compare their effects with bDMARDs, as the primary endpoints were at 12 weeks rather than 24 weeks. Given the effect size of treatment was similar, this would suggest bDMARDs and tsDMARDs improve fatigue by reducing disease activity.

One should be mindful of the fact that these studies were designed to examine the clinical efficacy of bDMARDs and tsDMARDs in RA, and fatigue was only assessed as a secondary endpoint rather than the primary endpoint. It is unclear whether improvement in fatigue is sustained with long-term therapy. Furthermore, analysis of fatigue in these studies did not adjust for possible confounding factors such as changes in pain, haemoglobin or mood. In addition, most of the studies compared bDMARDs or tsDMARDs in combination with MTX, thus their true effect size on fatigue is less certain.

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