Effect of Biologics and Targeted Synthetic DMARDs on Fatigue in Rheumatoid Arthritis

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Abstract

Fatigue is common and the debilitating symptom in patients with rheumatoid arthritis (RA). Since 2007, fatigue has been included as one of the core outcome measures in RA. Clinical trials of biologic disease modifying antirheumatic drugs (bDMARDs) and targeted synthetic disease modifying antirheumatic drugs (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 biological agents 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 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 messages:

1. Biologic DMARDs reduce fatigue in patients with RA.

2. Janus kinases inhibitors, Tofacitinib and Baricitinib reduce fatigue in patients with RA.

Background

Rheumatoid arthritis (RA) is a chronic inflammatory arthritis associated with increased mortality and morbidities. Joint inflammation and destruction are the dominant clinic features and standard of care focussed on "treat-to-target" based on suppressing joint inflammation to a minimal level 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 over 80% of patients and over 50% of patients have moderate to a 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 Outcome Measure for Rheumatology (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 to be multi-factorial 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 (cs) Disease Modifying Anti-Rheumatic Drugs (DMARDs) on fatigue is unknown since fatigue is rarely assessed in randomised control trials of csDMARDs. With the inclusion of fatigue as a major outcome domain by OMERACT, randomised control trials 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 assessed the effect of bDMARDs in RA was published[9]. This systematic review included 32 randomised control trials or pooled analyses of clinical trials of bDMARDs in RA. Twenty studies of anti-TNF agents and twelve 12 non-anti-TNF biologic agents including 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 had been used in these studies, which included the Functional Assessment of Chronic Illness Therapy Fatigue Domain (FACIT-F), Short Form-36 Vitality Domain (SF-36 VT), visual analogue scale (VAS) and the Numerical Rating Scale NRS (0 to 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 Functional Assessment of Chronic Illness Therapy is also a health-related quality of life instrument, one of its domains is fatigue. FACIT-F score ranges between 0-52 with higher indicates less fatigue. In the Cochrane review, changes in fatigue scores were assessed by standardised mean difference so that different instruments can be pooled for meta-analysis. Standardised mean differences were back transformed into changes in SF-36 VT and FACIT-F. The minimal clinical important difference (MCID) for SF-36 VT is 5 points and for FACIF-F is between 3 to 4 points.

The Cochrane review concluded that bDMARDs had a moderate effect on reducing fatigue with a standardised mean difference of −0.43 (95% CI −0.49 to −0.38), which was statistically significant ($p < 0.00001$). This equates to a difference of 6.45 units (95% CI 5.70 to 7.35) of FACIT-F score (range 0-52) or 7.65 units (95% CI 6.76 to 8.72) of SF-36 VT. The number needed to treat was 5. In a sub-analysis, categorising bDMARDs into 2 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 intervention and control groups were −0.42 ($P < 0.00001$). This equates to a difference of 6.3 units of FACIT-F score or 7.5 units of SF-36 vitality. 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 FACIT-F score or 8.19 units of SF-36 VT.

Since the publication of this Cochrane review, an anti-IL-6 receptor monoclonal antibody, Sarilumab, and two Janus Kinase Inhibitors (JAKi), Tofacitinib and Baricitinib have been approved for the treatment of RA.

Sarilumab

Sarilumab was approved by the Food and Drug Administration and European Medicine Agency for the treatment of RA in 2017. It is a human anti-IL6 receptor monoclonal

antibodies similar to Tocilizumab. Fatigue has been assessed in phase 3 clinical trials of Sarilumab.

Mobility was a phase III randomized controlled trial in patients with RA who had an inadequate response to methotrexate[10]. Patients were randomised to either placebo or subcutaneous Sarilumab 150 or 200 mg fortnightly plus stable doses of methotrexate. Changes in FACIT-F score at week 24 in the placebo group was 5.8 ± 0.5 compared with 8.6 ± 0.5 and 9.2 ± 0.5 in the Sarilumab 150 mg and 200 mg (Table 1). These differences were statistically significant. Similarly, the SF-VT reduction was statistically significantly higher in the Sarilumab 150 mg (13.9 ± 1.1) and 200 mg groups (18.0 ± 1.0) compared with 9.8 ± 1.2 in the placebo group. In the 150mg group, 15.6% of patients achieved MCID (defined as $\geq$ 4 for FACIT-F and $\geq$ 5 for VT) for in both FACIT-F and SF-36 VT scores whilst in the 200mg group 21.8% and 23.6% achieved MCID in FACIT-F and SF-36 VT scores respectively. The number needed to treat for achieving MCID in fatigue was 6 for 150 mg and 4-5 for 200mg groups.

Target was a phase III randomized controlled trial similar to MOBILITY except in patients with RA who had an inadequate response to bDMARDs[11]. Change in FACIT-F score at week 24 in the placebo group was 6.8 ± 0.9 compared with 9.9 ± 0.8 and 10.1 ± 0.8 in the Sarilumab 150 mg and 200 mg respectively. These differences were statistically significant. Similarly, the SF-VT reduction was statistically significantly higher in the Sarilumab 150 mg (14.5 ± 1.6) and 200 mg groups (16.6 ± 1.5) compared with 9.2 ± 0.8 in the placebo group. In the 150mg Sarilumab group, 16.6% of patients achieved MCID in FACIT-F and 13.8% SF-36 VT whilst in the 200mg group 16.8% and 17.8% achieved MCID in FACIT-F and SF-36 VT

scores respectively. The number needed to treat was 6-7 for 150 mg and 6 for 200mg groups.

In Monarch, a head-to-head double-blind, double-dummy placebo-control trial compared the efficacy of 200mg Sarilumab versus Adalimumab monotherapy[12]. Efficacy as assessed by disease activity score 28 and American College of Rheumatology Response Criteria was statistically significantly higher with Sarilumab. However, changes in FACIT-F (10.18±0.7 vs 8.4±0.71) and SF-36 VT (17.95±1.42 vs 14.39±1.43) were numerically higher in the Sarilumab group but the difference versus Adalimumab was not statistically significant.

Table 1: Changes in FACIT-F and SF-36 VT scores in phase III trials of Sarilumab

	Comparison Group		**Sarilumab 150mg**		**Sarliumab 200mg**	
	FACIT-F	**SF-36 VT**	**FACIT-F**	**SF-36 VT**	**FACIT-F**	**SF-36 VT**
Mobility	5.8±0.5	9.8±1.2	8.6±0.5	13.9±1.1	9.2±0.5	18.0±1.0
Target	6.8±0.9	9.2±1.7	9.9±0.8	14.5±1.6	10.1±0.8	16.6±1.5
Monarch (Adalimumab)	8.4±0.71	14.39±1.43	NA	NA	10.18±0.7	17.95±1.42

FACIT-F: Functional Assessment of Chronic Illness Therapy Fatigue Domain; SF-36 VT: Short Form-36 Vitality Domain, NA: not applicable

Janus Kinase Inhibitors

Janus kinase (JAK) are intracellular molecules which are important for signalling of many cytokines[13]. Oral JAKi have been developed for the treatment of RA. Currently, two JAKi, Tofacitinib and Baricitinib, are licensed for the treatment of RA. They are categorised as

targeted synthetic DMARDs (tsDMARDs) to differentiate them from bDMARDs and csDMARDs.

Tofacitinib

Tofacitinib is a selective JAK1 and JAK3 inhibitor13. The effect of Tofacitinib on fatigue has been reported in 5 phase III clinical trials (Table 2). In these studies, Tofacitinib 5 and 10mg bid were evaluated, however, only 5mg bid has been approved for the treatment of RA. These clinical trials included patients with inadequate response to methotrexate (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 effect of tofacitinib were compared with placebo. In Oral Start, comparisons were made against active treatment by methotrexate. Table 2 shows the effect of treatment on FACIT-F on SF-36 VT at week 12 which is the primary endpoint of these trials.

Table 2: Changes in FACIT-F and SF-36 VT scores at week 12 in phase III trials of Tofacitinib

	Comparison Group		**Tofacitinib 5mg**		**Tofacitinib 10mg**	
	FACIT-F	**SF-36 VT**	**FACIT-F**	**SF-36 VT**	**FACIT-F**	**SF-36 VT**
Oral Sync	2.1±0.6	2.6 ± 0.7	5.8±0.5	6.3±0.5	6.9±0.5	6.5±0.5
ORAL Step	1.11±1.04	2.20±0.90	6.27±1.01	6.40±0.89	4.57±1.03	6.71±0.91
ORAL Solo	2.84±0.82	2.03±0.81	6.70±0.56	6.56±0.55	8.01±0.58	8.49±0.57
ORAL Standard	1.57±0.79	2.21±0.82	5.85±0.59	4.97±0.61	6.88±0.59	7.21±0.61

ORAL Start (Methotrexate)	5.33±0.67	5.06±0.70	8.19±0.48	8.20±0.50	8.72±0.46	8.84±0.48

FACIT-F: Functional Assessment of Chronic Illness Therapy Fatigue Domain; SF-36 VT: Short Form-36 Vitality Domain

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

Baricitinib

Baricitinib is a JAK-1 and JAK-2 selective inhibitor[13]. Changes in fatigue in four randomised placebo control trials have been reported. These trials were conducted in RA patients with inadequate response to methotrexate (RA-Beam), csDMARDs (RA-Build) and bDMARDs (RA-Beacon) as well as patients with early RA (RA-Begin).

In RA-BEAM, patients with inadequate response to methotrexate were randomised 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 FACIT-F score at week 12 was statistically significantly higher in Baricitinib and Adalimumab treated patients when compared with placebo. Percentages of patients who achieved at MCID improvement were also higher in these groups (Table 3).

In RA Build, patients with inadequate response to csDMARDs[20], were randomised to receive either placebo or Baricitinib 2 or 4mg daily. Improvement in fatigue as measured by FACIT-F score was statistically significantly higher at week 24 for Baricitinib 4 mg when compared to

placebo but not at week 12. Changes in FACIT-F in the 2mg group were numerically higher than placebo but were not statistically significant. Percentages of the patient who achieved MCID in FACIT-F score was 43%, 59% and 60% at week 24 (p=0.001 for both Baricitinib groups vs placebo not statistically significant at week 12 which was 59%, 63% and 65% for placebo, Baricitinib 2 mg and Baricitinib 4 mg, respectively.

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

RA-Early is a double-blind, phase III study of Baricitinib as monotherapy or combined with methotrexate versus methotrexate monotherapy in patients with active early RA[22]. Changes in FACIT-F score after 24 weeks was 8.9 (95% confidence interval 7.6 to 10.1) in the methotrexate group, 13.3 (95% confidence interval 11.8, 14.7) in Baricitinib monotherapy group and 12.2 (95% confidence interval 11.0, 13.5) in the methotrexate plus Baricitinib group. The differences between the Baricitinib groups versus the methotrexate group were statistically significant. Percentages of patients achieving MCID (defined as $\geq$ 3.56 for FACIT-F and $\geq$ 5 for VT) at week 24 were was 65%, 75%, and 71% for methotrexate, Baricitinib monotherapy, and Baricitinib plus methotrexate, respectively.

Table 3: Percentage of Patients with improvement in FACIT-F score more than the minimum clinically important difference of 3.56 at week 12 in phase III trials of Baricitinib

	Comparison Group	Baricitinib 2mg	Baricitinib 4mg
	FACIT-F	**FACIT-F**	**FACIT-F**
RA-Beam	59%	NA	66%*
RA-Build	59%	63%	65%
RA-Beacon	48%	64%*	63%*
	Methotrexate	**Baricitinib 4mg monotherapy**	**Baricitinib 4mg plus methotrexate**
RA-Early	65%	75%	71%

FACIT-F: Functional Assessment of Chronic Illness Therapy Fatigue Domain; NA: Not applicable

Discussion

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 is consistent with this conclusion and the effect size of Sarilumab was similar to other bDMARDs including tocilizumab. Clinical trials of the tsDMARDs, Tofacitinib and Baricitinib, also suggested they may reduce fatigue. However, it is difficult to compare their effects with bDMARDs as the primary endpoint 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 mindfulness of the fact that these studies were designed to examine clinical the 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 methotrexate, their true effect size on fatigue is less certain.

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