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ORIGINAL RESEARCH

Efficacy of pharmacological interventions: a systematic review informing the 2023 EULAR recommendations for the management of fatigue in people with inflammatory rheumatic and musculoskeletal diseases

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ABSTRACT

Objective To identify the best evidence on the efficacy of pharmacological interventions in reducing fatigue in people with inflammatory rheumatic and musculoskeletal diseases (I-RMDs) and to summarise their safety in the identified studies to inform European Alliance of Associations for Rheumatology recommendations for the management of fatigue in people with I-RMDs.

Methods Systematic review of adults with I-RMDs conducted according to the Cochrane Handbook. Search strategy ran in Medline, Embase, Cochrane Library, CINAHL Complete, PEDro, OTseeker and PsycINFO. Only randomised controlled trials (RCTs) or controlled clinical trials were eligible. Assessment of risk of bias, data extraction and synthesis performed by two reviewers independently and in duplicate. Data pooled in statistical meta-analyses.

Results From 4151 records, 455 were selected for full-text review, 99 fulfilled the inclusion criteria and 19 RCTs were included in meta-analyses. Adalimumab was superior to placebo in reducing fatigue at 12 and 52 weeks in rheumatoid arthritis (RA) (n=3 and 2 RCTs; mean difference (MD)= −3.03, p<0.001; MD=−2.25, p=0.03, respectively). Golimumab (n=2 RCTs; 24 weeks: MD=−5.27, p<0.001), baricitinib (n=2 RCTs; 24 weeks: MD=−4.06, p<0.001), sarilumab (n=2 RCTs; 24 weeks: MD=−3.15, p<0.001), tocilizumab (n=3 RCTs; 24 weeks: MD=−3.69, p<0.001) and tofacitinib (n=3 RCTs; 12 weeks: MD=−4.44, p<0.001) were also superior to placebo in reducing fatigue in RA. A dose/effect relationship was observed for sarilumab, tocilizumab and tofacitinib. In spondyloarthritis (excluding psoriatic arthritis), secukinumab was superior to placebo in reducing fatigue at 16 weeks (n=2 RCTs; MD=−4.15, p<0.001), with a dose/effect relationship also observed. The narrative results of the RCTs not included in the meta-analysis indicated that several other pharmacological interventions were efficacious in reducing fatigue, with reassuring safety results.

Conclusions Several pharmacological interventions are efficacious and generally safe for managing fatigue in people with I-RMDs.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Fatigue is one of the most common and debilitating symptoms of inflammatory rheumatic and musculoskeletal diseases (I-RMDs); however, interventions to manage fatigue are complex and challenging to implement.

⇒ Evidence regarding the effects of pharmacological interventions on fatigue in all I-RMDs has never been systematically assessed.

WHAT THIS STUDY ADDS

⇒ This systematic review reinforces the importance of pharmacological interventions, especially biologics, for fatigue in people with I-RMDs, suggesting that control of inflammatory disease activity coadjuvates the reduction of fatigue levels.

⇒ There is a strong evidence that pharmacological interventions, particularly biologics, are efficacious and safe in reducing fatigue. In some cases (eg, sarilumab, tocilizumab, tofacitinib and secukinumab), a dose/effect relationship was observed.

INTRODUCTION

Inflammatory rheumatic and musculoskeletal diseases (I-RMDs) include a set of chronic, inflammatory and autoimmune conditions, such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), axial spondyloarthritis

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ It can be communicated to patients that several pharmacological interventions are also effective and safe for the management of fatigue in people with I-RMD.

⇒ Future research should examine the efficacy and safety of interventions in specific inflammatory RMDs where evidence for fatigue management is still scarce (e.g.eg, systemic sclerosis, idiopathic inflammatory myopathies, and giant cell arteritis).

(axSpA), gout, systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjogren's syndrome (SjS), idiopathic inflammatory myopathies (IIM), vasculitis and undifferentiated arthritis, among others. I-RMDs can affect the joints, bones, cartilage, ligaments, tendons, muscles, glands, skin and other organs or systems. They are typically chronic conditions that impose a heavy burden on people's life and can impair daily self-care and quality of life. I-RMDs often require complex treatment regimens, which, if started early, reduce the risk of long-term structural damage, the need for surgeries and the number of complications.[1]

Fatigue is one of the most common and can be one of the most debilitating symptoms of I-RMD.[2] An international consensus statement has proposed that it should be measured in all RA clinical trials,[3] and international delegates at Outcome Measures in Rheumatology eighth meeting endorsed fatigue as an addition to the 'core set' of outcome measures for all future RA studies.[3] Nevertheless, there is still a significant unmet need in the management of fatigue, which is mainly due to the lack of evidence on the cost-effectiveness of providing fatigue therapies using different treatment modalities, the lack of training available for healthcare professionals to provide evidence-based fatigue therapies,[2 4 5] and the complexity of fatigue itself, since it is a multidimensional symptom that varies from patient-to-patient and over time,[6] making it more difficult to manage effectively.

There is evidence that pharmacological interventions, including biological therapies, can improve inflammation, disease activity and function in I-RMDs, and fatigue has increasingly been included as a secondary outcome of I-RMDs clinical trials. However, no systematic review (SR) has established the evidence for the pharmacological management of fatigue in all I-RMD, although few SRs are available in specific conditions.[7–9]

Several European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of people with specific I-RMDs have pointed out the relevance of pharmacological interventions in the management of the condition, including fatigue.[10–16] However, these recommendations are either disease-specific or focusing on specific therapeutic groups (eg, certain biological drugs), and lack an integrated view of the overall evidence for fatigue management in the wider context of all I-RMD. The current conceptual models of mechanisms and factors that can cause and maintain fatigue, and how to measure and assess them, are integrative aspects of fatigue management and need a holistic rather than fragmented view if they are to be widely implemented in clinical practice.[17]

To inform the task force responsible for the 2023 EULAR recommendations for the management of fatigue in people with I-RMD, we performed an SR that aimed to identify and evaluate the evidence on the efficacy of pharmacological interventions in reducing fatigue in people with I-RMD and to describe their safety, if reported, in the included studies.

METHODS

This SR was conducted according to the Cochrane Handbook[18] and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19]

The steering group of the EULAR task force (BF, EJFS, ED and PMM) established and published the SR protocol in PROSPERO (CRD42021282899). Although this protocol refers to all interventions to manage fatigue, the interventions were subsequently divided into pharmacological and non-pharmacological, and two SRs were generated given the high number of included studies. The SR for non-pharmacological interventions was published elsewhere.

The outlined research questions, as approved by the task force at the first meeting, were:

1. Which pharmacological interventions are efficacious in reducing fatigue in people with I-RMD?
2. Which pharmacological interventions are safe in reducing fatigue in people with I-RMD?

These questions were framed and structured according to the EULAR standardised operating procedures[20] using the 'Patients, Intervention, Comparator or Control, Outcome, Type of study' format, as follows:

Participants

A study was eligible for inclusion if the included participants were adults (aged 18 years or over) with I-RMD, specifically, RA, axSpA, peripheral SpA, PsA, gout, SLE, SSc, SjS, IIM (dermatomyositis, polymyositis, immune-mediated necrotising myopathy, antisynthetase syndrome, inclusion body myositis) and primary systemic vasculitis (large-vessel vasculitis: giant cell arteritis (GCA) (and the related condition polymyalgia rheumatica), Takayasu's arteritis; medium-vessel vasculitis: polyarteritis nodosa; small-vessel vasculitis limited to the antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis: granulomatosis with polyangiitis (GPA, previously named Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic GPA (previously named Churg-Strauss); and variable-vessel vasculitis: Behçet syndrome, also known as Behçet disease). Only studies in which patients were formally diagnosed with I-RMDs or who satisfied internationally accepted disease classification criteria were included to maximise accuracy.[21–24] Studies

focusing on information regarding people with other concomitant diseases were summarised separately and by subgroups, whenever possible.

Interventions

Regarding the eligible interventions, all pharmacological interventions were included. Pharmacological interventions were classified as medicinal products in accordance with the EU Directive 2001/83/EEC (EU 2001),[25] which states: 'any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis'.[25]

Comparator or control

The comparator was placebo or usual care (standard care).

Outcomes

Regarding outcomes, the core concept was fatigue. Fatigue is a complex, multifaceted phenomenon. Importantly, most people have experienced fatigue during their everyday life, but qualitative research suggests differences between fatigue associated with chronic diseases and 'usual' or premorbid fatigue. The most distinguishing features of fatigue associated with chronic diseases include the perception of fatigue as having no obvious 'explanation', a lack of improvement with rest, variability in severity, unpredictability and the experience of profound or overwhelming fatigue.[26] In that sense, we accepted self-reported fatigue scores using quantitative and validated measures, such as Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F),[27] Rheumatoid Arthritis Impact of Disease-Fatigue,[28 29] Fatigue-Visual Analogue Scale (VAS),[30] 36-Item Short Form Survey (SF-36) vitality scale,[31] the Multidimensional Assessment of Fatigue,[32] Profile of Mood States-subscale fatigue,[33] Checklist Individual Strength,[34] Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAF MDQ),[35 36] BRAF Numerical Rating Scales for severity, effect and coping,[35 36] among others.

Type of study

Only SRs and randomised controlled trials (RCTs) or controlled clinical trials were eligible because they are considered the most robust study designs and represent the strongest evidence.[37] The studies integrating SRs were extracted for joint analysis with the remaining primary studies. SRs were not analysed.

Regarding the context, there were no constraints.

SEARCH STRATEGY AND STUDY SELECTION

A search strategy was run by one of the authors (EJFS) in Medline through PubMed, Embase, Cochrane Library, CINAHL Complete, PEDro, OTseeker and PsycINFO. The start date was the date of inception of the database, and the end date was 27 December 2021. Studies published in English, French, Portuguese, Spanish and Turkish language, with no restriction on the publication date, were considered for inclusion. Details on complete search strategies are provided in online supplemental material S1.

All identified citations were uploaded into an EndNote V.X9 (Clarivate Analytics, Pennsylvania, USA) library and the duplicates removed. Titles and abstracts were screened by two independent reviewers (BF and EJFS) to assess eligibility criteria. The full articles were retrieved for all studies that met or had insufficient information to assess the inclusion criteria, and two reviewers (BF and EJFS) independently examined them in detail. Any disagreements between the reviewers were resolved through discussion or adjudication by a third reviewer (PMM). The study selection was performed using Rayyan.

RISK OF BIAS (QUALITY) ASSESSMENT

Two reviewers (BF and EJFS) assessed the risk of bias in each included study using the Cochrane Collaboration's tool for RCTs.[38] Any disagreements between the reviewers were resolved through discussion or adjudication by a third reviewer (PMM).

DATA EXTRACTION AND SYNTHESIS

Data were extracted from the selected reports by the same two independent reviewers (BF and EJFS), and disagreements were discussed until consensus was achieved, or with adjudication by the third reviewer (PMM), whenever necessary. Authors of papers were contacted to request missing or additional data, where required.

Studies were pooled for statistical meta-analysis using Review Manager V.5.2.8. and SPSS Statistics, V.28 (IBM), if the needed statistics were available. Effect sizes were expressed as mean differences (MD) or final postintervention standardised MDs (SMD), and their 95% CIs were calculated. MD is the difference between effect estimates for intervention and control on a specific scale. Because pooling of the MD from individual RCTs is done after weighting the values for precision, this pooled MD is also known as the weighted MD. The selection of SMD was determined primarily because all studies reported the outcome using different scales/metrics.[18] We imputed SD where necessary according to sections 6.5.2.2 and 6.5.2.3 of the Cochrane Handbook.[18] Heterogeneity was assessed statistically using the standard χ^2 and I^2 tests. For a value of I^2 equal to 0%, we assume no heterogeneity between studies (homogeneity), around 25% low heterogeneity, around 50% moderate heterogeneity and around or greater than 75% high heterogeneity.[39] Statistical analyses were performed using random effects models only in the presence of moderate to high heterogeneity (I^2>50%) and, in their absence, fixed effect models were used instead.[40 41] Where statistical pooling was not possible, the findings were presented in narrative form, including tables and figures, where appropriate.

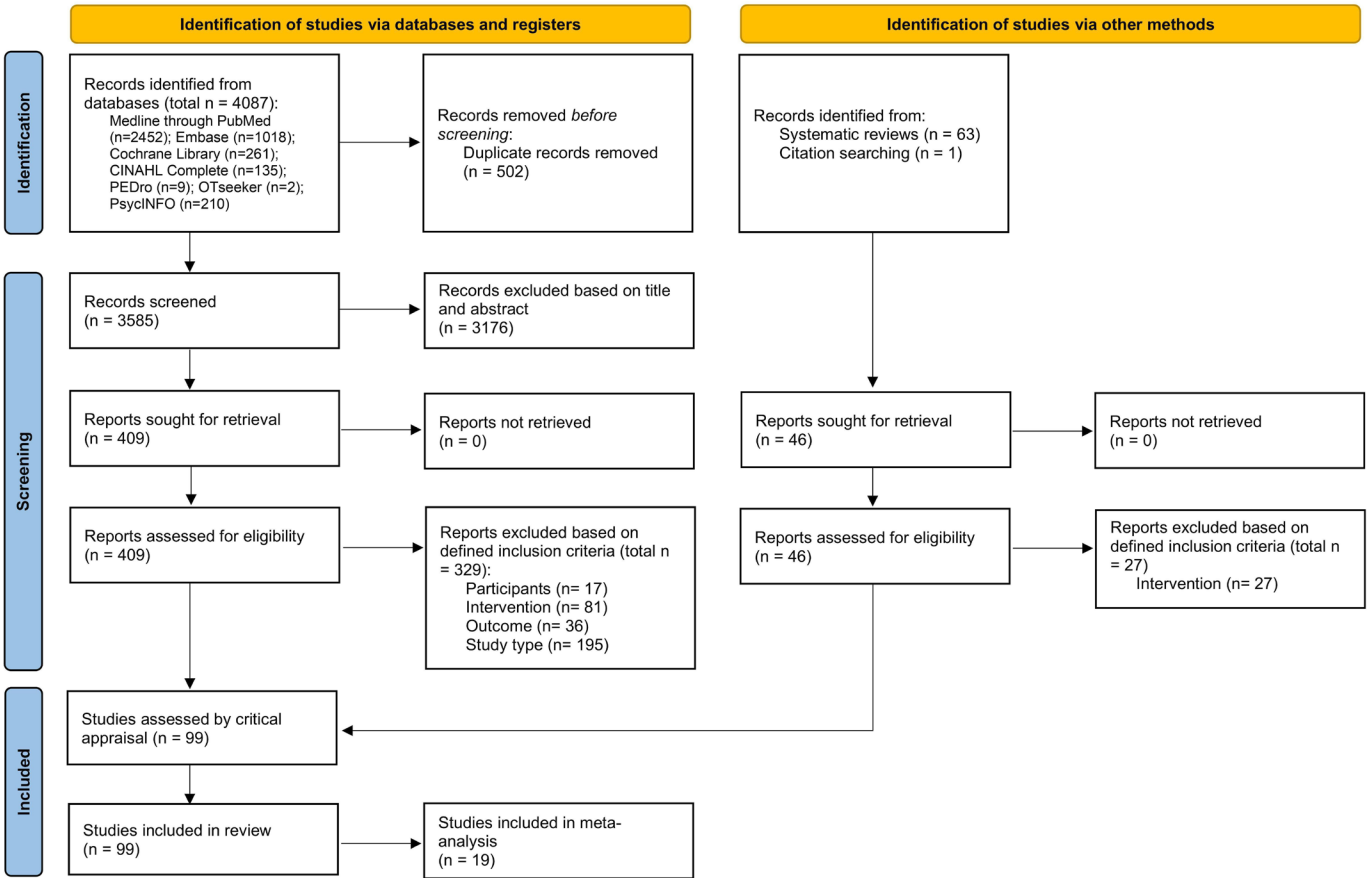

Figure 1 Flow chart of the study selection and inclusion process.

Subgroup analyses were conducted if sufficient data was provided, with subanalyses being based on different diseases categories and pharmacological doses. Sensitivity analyses were conducted to test decisions made. At last, the level of evidence was assigned for each intervention using the 2011 Oxford Centre for Evidence Based Medicine Levels of Evidence.[37]

RESULTS

Out of a total of 4151 records (3585 non-duplicate records, 502 duplicate records, 63 SRs and 1 record obtained by citation searching), 455 were selected for full-text review, and 99 studies fulfilled the inclusion criteria and were included in this SR. Of these, 19 RCTs were included in the meta-analysis. There was no need to contact the authors of the papers to request additional information. The results of the searches are shown in a flow diagram (figure 1).

Methodological quality

The critical appraisal of results for each study are summarised in figure 2 and online supplemental file 2. There was agreement among the reviewers to include all the studies that were appraised. In general, the RCTs included were of high quality, corresponding to level 1 of evidence according to the 2011 Oxford Centre for Evidence Based Medicine Levels of Evidence.[37] All RCTs complied with a random sequence generation. Regarding allocation concealment, there was an unclear risk of bias in almost 50% of the studies but this was probably due to a reporting bias or/and poor reporting. On several occasions, the authors implied that they complied with the allocation concealment without referring to it specifically and without reporting the description of the procedure. There were residual issues with participant, personnel, and outcome assessment blinding, but overall, these attributes were met, which is expected given that these were RCTs of pharmacological interventions.

Characteristics of included studies and interventions

Study characteristics are detailed in online supplemental file 3. Pharmacological interventions where fatigue was included as an outcome were tested in the following I-RMD among the 99 RCTs: RA (n=50),[42–91] SpA (excluding PsA) (n=13),[92–104] SjS (n=15),[105–119] PsA (n=10),[120–129] SLE (n=8),[130–137] SSc (n=1),[138] IIM (n=1)[139] and GCA (n=1).[140]

The summary of findings integrating all included RCTs, the interventions tested per I-RMD and their impact on outcome is presented in table 1. Overall, we found pharmacological interventions to be efficacious in reducing fatigue. The most commonly tested pharmacological interventions were biologicals (82%) and the most common comparator was placebo (95%). The most

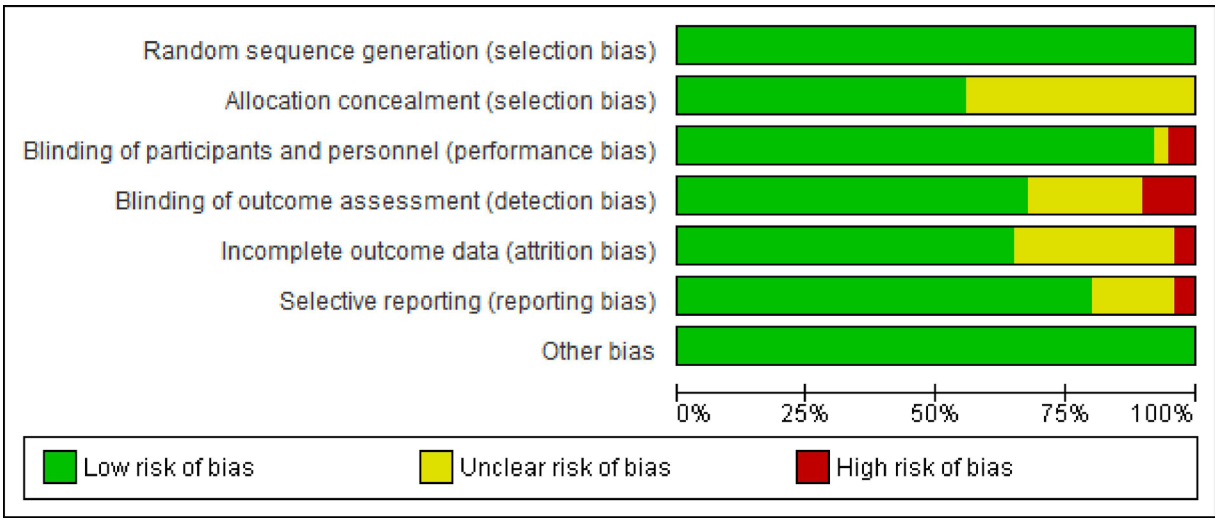

Figure 2 Risk of bias summary graph for included clinical trials. Review authors' judgements about each risk of bias item presented as percentages across all included studies using the Cochrane RoB tool.

used time points for outcome assessment were 12, 16, 24, 36, 48 and 52 weeks.

Meta-analysis and narrative synthesis

Meta-analyses of the results are detailed in online supplemental file 4. The summary of the meta-analyses was grouped into a single forest plot (figure 3).

Fatigue was a secondary outcome in approximately two-thirds of studies, as disease-specific treatment response measures of drug efficacy were commonly the primary outcome in the RCTs (with results being consistent between studies irrespective of fatigue being the primary or secondary endpoint).

The main fatigue scale/instrument used in the studies integrated in the meta-analysis comparisons was the FACIT-F. The only exception was the comparison between Etanercept 50 mg and placebo in SpA (excluding PsA) at 12 weeks, which used the Multidimensional Fatigue Inventory (MFI) and the Fatigue Severity Scale (FSS).

The meta-analysis showed that adalimumab was superior to placebo in reducing fatigue at 52 and 12 weeks in RA (MD=−2.25, 95% CI −4.23 to −0.27, p=0.03; MD=−3.03, 95% CI −4.19 to −1.87, p<0.001, respectively). Adalimumab was not superior in PsA (MD=−3.16, 95% CI −8.64 to 2.33, p=0.26). Golimumab (MD=−5.27, 95% CI −6.71 to −3.84, p<0.001, at 24 weeks), baricitinib (MD=−4.06, 95% CI −5.22 to −2.91, p<0.001, at 24 weeks), sarilumab (MD=−3.15, 95% CI −3.51 to −2.78, p<0.001, at 24 weeks), tocilizumab (MD=−3.69, 95% CI −4.59 to −2.79, p<0.001, at 24 weeks) and tofacitinib (MD=−4.44, 95% CI −5.22 to −3.66, p<0.001, at 12 weeks) were also superior to placebo in reducing fatigue in RA. Subgroup meta-analyses revealed a dose/effect relationship for sarilumab, tocilizumab and tofacitinib, that is, the higher the dose, the greater the reduction in fatigue measures. In SpA (excluding PsA), secukinumab was superior to placebo in reducing fatigue at 16 weeks (MD=−4.15, 95% CI −4.60 to −3.71, p<0.001), with a dose/effect relationship also being observed. Finally, in SpA (excluding PsA), etanercept was not superior to placebo in reducing fatigue at 12 weeks (SMD=3.07, 95% CI −3.86 to 10.01, p=0.39).

It should be noted that in 6 of the meta-analyses performed there was no heterogeneity (I^2=0%) (adalimumab 40 mg in RA at 52 weeks and at 12 weeks, baricitinib 4 mg in RA at 24 weeks, tocilizumab 4 and 8 mg in RA at 24 weeks, golimumab 100 mg in RA at 24 weeks, and tofacitinib 5 and 10 mg in RA at 12 weeks). In 4 of the meta-analyses, we found high heterogeneity (I^2>75%) (adalimumab 40 mg in PsA at 12 weeks, sarilumab 150 and 200 mg in RA at 24 weeks, secukinumab 75 and 150 mg in SpA (excluding PsA) at 16 weeks, and etanercept 50 mg in SpA (excluding PsA) at 12 weeks).

As mentioned above, the narrative results of the RCTs not included in the meta-analysis were globally integrated in table 1 and showed that many of the investigated pharmacological interventions, including other biologics not included in the meta-analysis, were efficacious in reducing fatigue. However, in some specific I-RMDs, the evidence was still limited and did not allow us to draw strong conclusions (eg, SSc, IIM and GCA).

Regarding the safety of pharmacological interventions, most studies reported that they were well tolerated or similar to placebo.[44 50 56 57 59 60 62 64 65 71 73 77 78 80 82 86 88 91–94 97 98 101 102 105 108 111 112 114 115 117–120 122–124 131–133 135 136 138 139] A few studies reported more adverse events in the intervention arm,[45 51 106 107 109 116 125 130 137] and a minority of studies in the placebo arm.[46 121] However, detailed safety information was not available in 42 RCTs.[42 43 47–49 52–55 58 61 63 66–70 72 74–76 79 81 83 85 87 89 90 95 96 99 100 103 104 113 126–129 134 140]

DISCUSSION

This SR shows strong evidence that pharmacological interventions, especially biologics, are efficacious in reducing fatigue in people with I-RMDs, suggesting that control of inflammatory disease activity coadjuvates the

Table 1 Summary of findings

Disease	Intervention	Drug class/type	No of RCTs	Impact on outcome	References
Rheumatoid arthritis	Prednisone	Glucocorticoids	1	Reduced fatigue	42
			1	No difference	44
	Tocilizumab	bDMARD	4	Reduced fatigue	45–48
	Etanercept	bDMARD	3	Reduced fatigue	43 49 50
	Certolizumab pegol	bDMARD	4	Reduced fatigue	51–54
	Adalimumab	bDMARD	4	Reduced fatigue	55–58
	Rituximab	bDMARD	5	Reduced fatigue	59–63
	Canakinumab	bDMARD	1	Unclear	64
	Tofacitinib	tsDMARD	6	Reduced fatigue	65–69 91
			1	Unclear	70
	Abatacept	bDMARD	4	Reduced fatigue	71–74
	Golimumab	bDMARD	4	Reduced fatigue	75–78
	Anti-TNF	bDMARD	1	Reduced fatigue	79
	Filgotinib	tsDMARD	2	Reduced fatigue	80 81
	Sarilumab	bDMARD	2	Reduced fatigue	82 83
			1	No difference	84
	Baricitinib	tsDMARD	5	Reduced fatigue	85–89
	Upadacitinib	tsDMARD	1	Reduced fatigue	90
Systemic lupus erythematosus	Dehydroepiandrosterone	Other	1	No difference	130
	Hydroxychloroquine	csDMARD	1	No difference	131
	Abatacept	bDMARD	1	Reduced fatigue	132
	Belimumab	bDMARD	2	Reduced fatigue	133 134
	Blisibimod	bDMARD	1	Reduced fatigue	135
	Tabalumab	bDMARD	1	No difference	136
	N-Acetylcysteine	Other	1	Reduced fatigue	137
Psoriatic arthritis	Certolizumab Pegol	bDMARD	1	Reduced fatigue	120
	Adalimumab	bDMARD	2	Reduced fatigue	121 122
	Secukinumab	bDMARD	1	Reduced fatigue	123
	Ustekinumab	bDMARD	1	Reduced fatigue	124
	Infliximab	bDMARD	1	Reduced fatigue	125
	Upadacitinib	tsDMARD	2	Reduced fatigue	126 127
	Tofacitinib	tsDMARD	2	Reduced fatigue	128 129
Sjogren's syndrome	Rituximab	bDMARD	3	No difference	106–108
			1	Reduced fatigue	105
	Infliximab	bDMARD	1	No difference	109
	Dehydroepiandrosterone	Other	2	No difference	110 111
	Gammalinolenic acid	Other	1	No difference	112
	Doxycycline	Other	1	Increased fatigue	113
	RSLV-132	Other	1	Reduced fatigue	114
	Interleukin-1 receptor antagonist	bDMARD	1	No difference	115
	Total glucosides of peony	Other	1	Reduced fatigue	116
	Hydroxychloroquine	csDMARD	2	No difference	117 118
	Ianalumab	bDMARD	1	Reduced fatigue	119

Continued

Table 1 Continued

Disease	Intervention	Drug class/type	No of RCTs	Impact on outcome	References
Spondyloarthritis (excluding psoriatic arthritis)	Etanercept	bDMARD	3	Reduced fatigue	92 93 95
			2	No difference	94 96
	Certolizumab pegol	bDMARD	1	Reduced fatigue	97
	Adalimumab	bDMARD	1	Reduced fatigue	98
	Secukinumab	bDMARD	3	Reduced fatigue	99–101
	Probiotic therapy	Other	1	No difference	102
	Ixekizumab	bDMARD	1	No difference	103
	Infliximab	bDMARD	1	Reduced fatigue	104
Systemic sclerosis	Tocilizumab	bDMARD	1	No difference	138
Inflammatory myopathies	Creatine supplements	Other	1	No difference	139
Giant cell arteritis	Tocilizumab	bDMARD	1	Reduced fatigue	140

Green colour indicates 'reduced fatigue', yellow indicates 'no difference' and red indicates 'increased fatigue' when compared with the control group.
Reduced fatigue—there was a statistically significant decrease in the fatigue outcome between study arms in the original studies or/and the difference has moderate magnitude; No difference—there was no statistically significant difference in the fatigue outcome between study arms in the original studies; Unclear—there was a statistically significant difference in the fatigue outcome between study arms in the original studies and the difference has a weak magnitude and the results are from individual RCTs; Increased fatigue—there is a statistically significant increase in the fatigue outcome between study arms in the original studies.
bDMARD, biological disease-modifying antirheumatic drug; csDMARD, conventional synthetic DMARD; RCT, randomised controlled trial; tsDMARD, targeted synthetic DMARD.

reduction of fatigue levels. This trend was observed after evaluating several specific I-RMDs, namely RA (n=49),[42–91] SpA (excluding PsA) (n=13),[92–104] SjS (n=15),[105–119] PsA (n=10),[120–129] SLE (n=8),[130–137] SSc (n=1),[138] IIM (n=1)[139] and GCA (n=1).[140]

Safety results were reassuring and in line with known safety profiles and summaries of product characteristics of the respective pharmacological intervention. However, safety information was often lacking in the retrieved studies and mentioning safety in detail in future fatigue intervention studies is advisable.

Regarding the quality of the included studies, most of them were of high quality, as mentioned previously, corresponding to level 1 of evidence according to the 2011 Oxford Centre for Evidence Based Medicine Levels of Evidence.[37] Among bias items, high risk was more frequently present in the 'blinding' items (participants, personnel and outcome assessment), however, this was only observed in 10 of the 99 included RCTs.

Among the 99 studies that fulfilled inclusion criteria, fatigue was evaluated with one scale in 92 studies and two scales in 7. The assessment scale of fatigue was the FACIT-F in more than half of the studies (57 studies), followed by Fatigue-VAS (24 studies), MFI (7 studies), Fatigue Assessment Scale (FAS; 5 studies), Bath Ankylosing Spondylitis Disease Activity Index-fatigue item (5 studies), FSS (1 study), SF-36 fatigue item (1 study), Chalder Fatigue score (1 study), Brief fatigue index (BFI; 1 study), BRAF-MDQ (1 study), asking fatigue for presence and severity compared with previous visit (1 study), Health Assessment Questionnaire-fatigue item (1 study) and Profile of Fatigue (1 study). Although the lack of a gold standard measurement for fatigue and the evaluation of fatigue with 13 different measurements represent study limitations, causing difficulties in meta-analysis integration, the use of the FACIT-F in most of the studies is reassuring in terms of overall data assessment. In the future, agreement on a standardised scale for the assessment of fatigue will allow easier data pooling and better generalisability of results.

Regarding the limitations of this SR, it should be noted that the safety analysis of pharmacological interventions was restricted to RCTs and did not encompass observational studies, which affects the quality of the safety component of the SR. The task force made this decision because the safety profile of the studied drugs is already well documented in other disease-specific safety SRs.[141 142] Including observational studies within the scope of the current task force would have required the inclusion of a substantially larger number of articles, resulting in duplicated data without substantial additional value. Another limitation is that we could only perform a meta-analysis on 19 out of the 99 included RCTs, primarily due to the insufficient number of studies available for specific comparisons in the meta-analysis; in a few remaining cases, the necessary data for pooling was unavailable. Finally, the small number of studies and the small number of participants in some studies may have resulted in lack of statistical power and non-significant/wider CIs despite potentially clinically relevant effect sizes.

In conclusion, in this review, we collected the existing evidence on the efficacy of pharmacological interventions

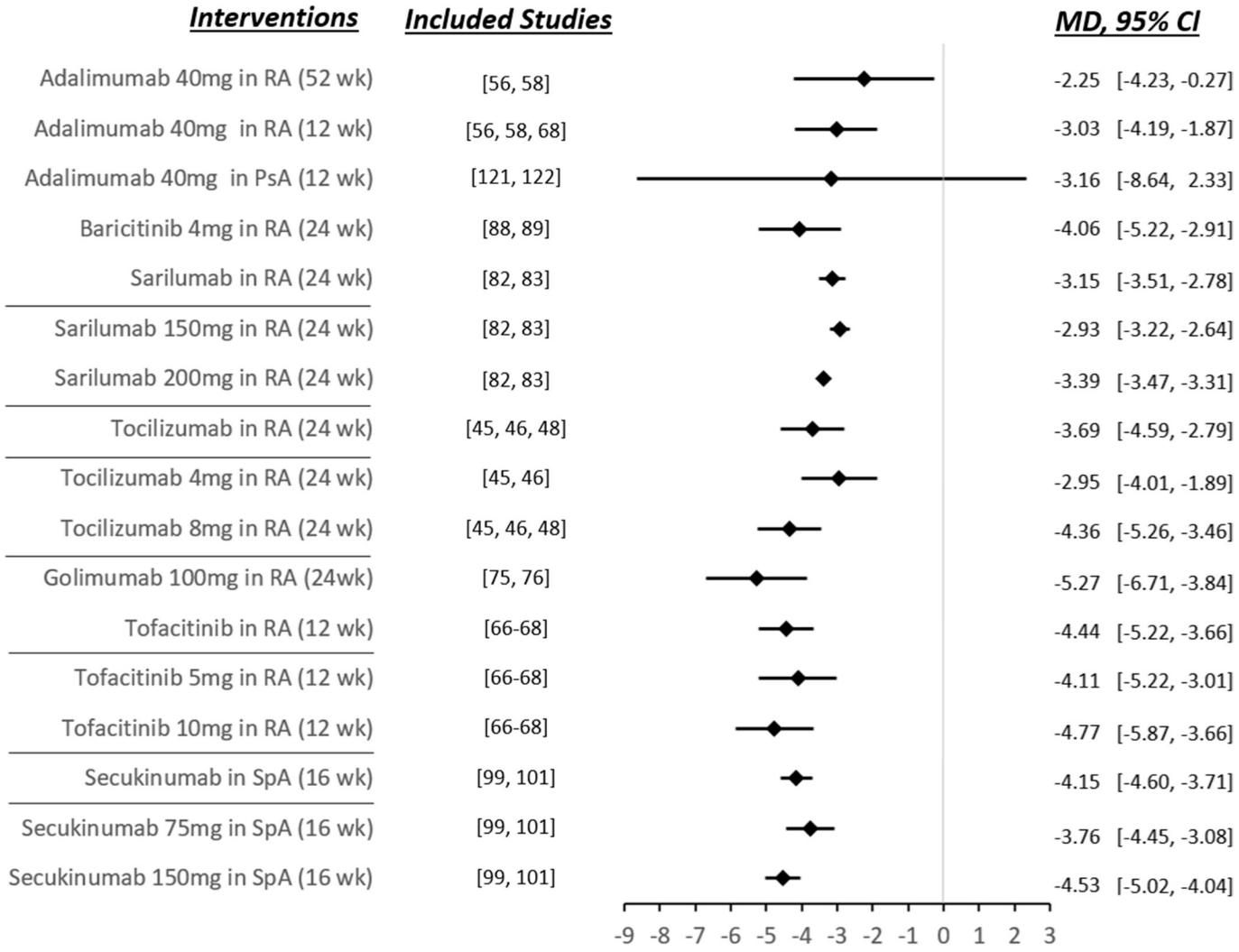

Figure 3 Meta-analyses summary. The values shown are mean differences in overall fatigue levels and their 95% CIs from the comparison of the identified pharmacological intervention versus placebo. A negative value indicates a reduction in fatigue levels. MD, mean difference; RA, rheumatoid arthritis; SpA, spondyloarthritis.

in reducing fatigue in people I-RMDs, with fatigue having been evaluated either as a primary or secondary outcome measure. This has important clinical implications, because it is evidence-based information that can be communicated to patients and used to inform patient management. To reduce clinical heterogeneity, each I-RMD was evaluated separately and grouped according to pharmacological intervention. This SR provides robust evidence on the efficacy and safety of several pharmacological interventions in the majority of I-RMDs. However, in some specific I-RMDs (eg, SSc, IIM, and GCA), the evidence is still limited, and future well-designed pharmacological intervention studies should investigate their role in managing fatigue in these conditions.

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