Effect of biotherapies on fatigue in rheumatoid arthritis: a systematic review of the literature and meta-analysis

Karine Chauffier¹, Carine Salliot², Francis Berenbaum¹ and Jéréme Sellam¹

Abstract

Objectives. To assess the effect of biotherapies vs placebo on fatigue in two situations: inadequate response to conventional treatments (IR-DMARD) and inadequate response to anti-TNF (IR-anti-TNF) in RA.

Methods. A systematic review of the literature and meta-analysis were performed. We included randomized controlled trials (RCTs) assessing the effect of biotherapies vs placebo on fatigue, in combination with DMARDs. Fatigue was measured using the functional assessment of chronic illness therapy-fatigue (FACIT-F) or short-form 36 (SF-36) vitality scores at baseline and at Week 24. The results were in effect size (ES) for each biotherapy (or class of biotherapy) vs placebo. An ES of <0.5 was considered as small, between 0.5 and 0.8 as moderate and >0.8 as important.

Results. From the 763 published studies, 10 RCTs were included in the analysis: seven involved IR-DMARD RA and three IR-anti-TNF. Among the 3837 included patients with established RA, 1227 patients were treated with an anti-TNF, 420 with rituximab, 258 with abatacept, 205 with tocilizumab and 1727 received placebo. The overall ESs of all biotherapies vs placebo on fatigue were small (ES = 0.45; 95% CI 0.31, 0.58) as well as for anti-TNFs (ES = 0.36; 95% CI 0.21, 0.51). The ESs were small in IR-DMARD RA (ES = 0.38; 95% CI 0.30, 0.46), similar between anti-TNF and non-anti-TNF agents and moderate in IR-anti-TNF RA (ES = 0.57; 95% CI 0.27, 0.86).

Conclusion. Few studies reported the impact of biotherapies on fatigue. The effect of biotherapies on fatigue in RA is small.

Key words: fatigue, rheumatoid arthritis, biotherapies, meta-analysis, systematic review

Introduction

RA is an inflammatory joint disease that can lead to structural damage, disability and alteration of quality of life. All available biotherapies have demonstrated significant improvement of these outcomes. Up to 80% of patients with RA report fatigue, which is infrequently assessed in published studies [1–3]. Biotherapies, which have largely improved their efficacy on the course of RA, may also have an impact on fatigue, directly or indirectly, by improving disease activity [4]. The fatigue in RA is due to endogenous processes (immunological disorders involving IL-1, IL-6, and TNF-α, hormonal imbalances and decrease in oxygenation of tissue) and exogenous processes (drugs, notably MTX) [5]. So it could be interesting to think that biotherapies could decrease fatigue in RA.

Considering the available data, it is difficult to estimate this impact mainly for two reasons. First, because several validated scales are used in these trials such as visual analogue scale (VAS), the functional assessment of chronic illness therapy-fatigue (FACIT-F) scale, the short-form 36 vitality (SF-36-V) subscale or other scales [6]. Second, the clinical relevance of the variations in fatigue scores between baseline and end-point is not certain in randomized control trials (RCTs). Likewise, the use of effect size (ES)
reflects more accurately the clinical impact of such drugs on fatigue [7].

Our objective was to assess the clinically relevant effect of available biotherapies on fatigue vs placebo in patients with established RA in two clinical situations: (i) inadequate response to conventional DMARD (IR-DMARD) and (ii) inadequate response to anti-TNF (IR-anti-TNF).

**Methods**

Systematic literature search and selection of the relevant studies

We performed a systematic review of the literature according to the Cochrane guidelines (http://www.cochrane-handbook.org/, 22 July 2010, date last accessed). Relevant publications were selected using PubMed, Embase and Cochrane databases without limitation of time (up to October 2009). The search was completed by hand search using the references of the most relevant studies. For unpublished data, it was extended to the ACR and European League against Rheumatism (EULAR) meeting abstracts of the past 4 years (2007–10). Moreover, to complete our search with unpublished data, the manufacturers of biologic agents were contacted.


To select the relevant studies, we established a priori inclusion criteria: adult with established RA (according to the ACR criteria 1987); RCTs comparing a biotherapy in association with conventional DMARD with placebo with conventional DMARD as concomitant treatment; and available data regarding the fatigue (whatever the scale used and the time points) [8]. The flow-chart shows the selection process based first on titles and abstracts, and then on the full texts (Fig. 1). We excluded trials without available data necessary for the calculation of the ES, such as mean change in each group (between baseline and end-point) and s.d. at baseline.

**Data extraction**

We collected data regarding the design of the studies: intention to treat (ITT) analysis, number of patients randomly assigned to a drug and number of withdrawals. Regarding the regimens of biological agents, we focused on dosages used in clinical practice: 50 mg weekly for etanercept, 40 mg every other week for adalimumab, 3–10 mg/kg per 8 weeks for infliximab, 400 mg at Weeks 0, 2, and 4 followed by 200 mg every other week for certolizumab, 50 mg every 4 weeks for golimumab, 1000 mg at Days 1 and 15 for rituximab, 10 mg/kg/month for abatacept and 8 mg/kg/month for tocilizumab.

The population’s characteristics were also collected: age at baseline, gender (percentage of women), disease duration, auto-immune profile (percentage of positive RF [9] or anti-CCPs), previous treatments received (steroids,
DMARDs), ongoing treatments with dosage (biottherapy or placebo, concomitant treatments), disease activity and HAQ scores at baseline and end-point.

Data on fatigue were collected as follows: the mean score(s) in each arm with the s.d. at baseline and at time point(s). For the assessment of trial quality, we used the Jadad scale including the description of randomization, blinding and withdrawals [10]. This scale is a 5-point score, and the quality is insufficient if the score is <3.

**Statistical analysis**

As we expected that fatigue would be assessed using different scales, we planned to calculate all the scores normalized on 100. The results are expressed in ES of the biottherapy vs placebo on fatigue using standard mean change of the score from baseline to end-point and baseline s.d. If the ES is inferior to 0.2, the effect of treatment is considered as trivial, between 0.2 and 0.5 as small, between 0.5 and 0.8 as moderate, between 0.8 and 1.2 as important and >1.2 as very important [11]. When more than one study evaluated fatigue at the same time point, we performed a meta-analysis with a fixed effect and a sensitive analysis. Heterogeneity was evaluated using the indicator I^2. When I^2 was considered as too high (I^2 > 50%), a random effect was used for the meta-analysis. We used review manager for meta-analysis and ES calculations (RevMan version 5).

**Results**

**Literature search and characteristics of included trials**

The selection process is detailed in Fig. 1: among the 763 published selected studies, 10 fulfilling inclusion criteria were considered for the analysis. The reasons for exclusion at the last step are detailed in Fig. 1 and supplementary table 1 (available as supplementary data at *Rheumatology* Online). All studies were RCTs with ITT analyses and a conventional DMARD (mainly MTX) as concomitant treatment. Regarding the quality of these RCTs, the mean Jadad score was 4.1 (0-5 points) (Table 1). In seven RCTs, the patients previously received conventional DMARDs and in three others, patients had an IR-anti-TNF. Six studies compared an anti-TNF with a placebo: three with adalimumab [Safety Trial of Adalimumab in Rheumatoid Arthritis (STAR), ARMADA and DE019 trials] [12-15], two with golimumab (GO-FORWARD and GO-AFTER) [16, 17] and one with certolizumab (RAPID1) [18, 19]. No trials assessing etanercept or infliximab were included in the analysis because of missing data mandatory to ES calculation, different time point and/or no concomitant treatment (supplementary table 1 available as supplementary data at *Rheumatology* Online). The four other trials referred to non-anti-TNF biologics: rituximab for two [Dose-ranging Assessment International Clinical Evaluation of Rituximab in RA (DANCER) and Randomized Evaluation of Long-term Efficacy of Rituximab in RA (REFLEX)], abatacept for one [Abatacept Trial in Treatment of Anti-TNF Inadequate Responders (ATTAIN)] and tocilizumab for one study (OPTION) [20-27].

**Patient’s characteristics**

A total of 3837 patients with established RA were randomly assigned to a drug and received at least one dose of their allocated treatment with the defined dose: 1227 had an anti-TNF, 420 received rituximab, 258 abatacept, 205 tocilizumab and 1727 received placebo. Seventy-three per cent of patients were women and 75% of patients had positive RF. At baseline, the mean age was from 50.6 to 57.2 years and mean disease duration was from 4.5 to 12.2 years depending on the trials (Supplementary table 2, available as supplementary data at *Rheumatology* Online). As concomitant treatment, patients received conventional DMARD, mainly MTX (Table 1). Nevertheless, in the GO-AFTER study, 31 and 29% of patients in the placebo and in the biottherapy groups, respectively, did not receive concomitant DMARD [17].

For three trials, patients (n=1198) had an IR-anti-TNF [17, 20, 21, 24]. Anti-TNFs were stopped for inadequate efficacy in 92 and 58% of patients in the REFLEX and GO-AFTER studies, respectively [17, 24]. The proportion of patients who withdrew for lack of efficacy was not available for the abatacept trial [26]. For other trials, RA was active despite DMARDs (n=2639) [12-16, 18, 19, 23, 26]. Nevertheless, the DANCER and OPTION studies also included patients who previously received an anti-TNF: 31% in the rituximab group and 27% in the placebo group for the DANCER study and 5% in the treatment group and 9% in the placebo group for the OPTION trial [20, 23].

Fatigue was assessed using four validated scores at baseline and at various time points: FACIT-F scale (eight trials), SF-36-V (four trials), VAS (one trial) and fatigue assessment scale (FAS) (one trial) (Table 1). The DANCER and REFLEX trials used both FACIT-F and SF-36-V scores [20, 21, 24, 27]. In the ATTAIN study, VAS and SF-36-V were used and in the RAPID1 study, SF-36-V and FAS were used [18, 19, 22]. Thus, for analysis we used FACIT-F and SF-36-V scores (supplementary table 1, available as Supplementary data at *Rheumatology* Online). FACIT-F is strongly associated with SF-36-V and these scores are sensitive to change [28]. FACIT-F is a score including 13 items ranging from 0 to 52. In the literature, a 3-4 point change is considered clinically significant and high score represents less fatigue [29]. SF-36-V is a subscale from the SF-36, a questionnaire of quality of life with physical and mental components. There are four items (How much of the time during the past week did you feel full of life? Did you have a lot of energy? Did you feel worn out? And did you feel tired?). The score is from 0 to 100. The higher the score, the lower the fatigue [30]. Supplementary table 3 (available as supplementary data at *Rheumatology* Online) gives the mean scores with s.d. of FACIT-F and SF-36-V at baseline and Week 24.
<table>
<thead>
<tr>
<th>Study [Ref]</th>
<th>Jadad scale</th>
<th>Biotherapies</th>
<th>Doses of administration</th>
<th>Concomitant treatment, % of MTX</th>
<th>Previous anti-TNF, % of patients</th>
<th>Fatigue score(s), time points</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAR [13]</td>
<td>5</td>
<td>Adalimumab</td>
<td>40mg every other week</td>
<td>DMARD, 36% MTX</td>
<td>NO</td>
<td>FACIT-F, Weeks 0, 12 and 24</td>
</tr>
<tr>
<td>ARAMADA [14]</td>
<td>3</td>
<td>Adalimumab</td>
<td>40mg every other week</td>
<td>DMARD, 100% MTX</td>
<td>NO</td>
<td>FACIT-F, Weeks 0, 12 and 24</td>
</tr>
<tr>
<td>DEO19 [15]</td>
<td>4</td>
<td>Adalimumab</td>
<td>40mg every other week</td>
<td>DMARD, 100% MTX</td>
<td>NO</td>
<td>FACIT-F, Weeks 0, 12, 24 and 52</td>
</tr>
<tr>
<td>DANCER [20]</td>
<td>3</td>
<td>Rituximab</td>
<td>1000mg D1 and D15</td>
<td>DMARD, 100% MTX</td>
<td>YES, 31% in tt gp and 27% in placebo gp</td>
<td>FACIT-F, SF-36-V, Weeks 0 and 24</td>
</tr>
<tr>
<td>OPTION [23]</td>
<td>5</td>
<td>Tocilizumab</td>
<td>8mg/kg/4/weeks</td>
<td>DMARD, 100% MTX</td>
<td>YES, 5% in tt gp and 9% in placebo gp</td>
<td>FACIT-F, Weeks 0 and 24</td>
</tr>
<tr>
<td>GO-FORWARD [32]</td>
<td>5</td>
<td>Golimumab</td>
<td>50mg/4 weeks</td>
<td>DMARD, 100% MTX</td>
<td>NO</td>
<td>FACIT-F, Weeks 0 and 24</td>
</tr>
<tr>
<td>REFLEX [24]</td>
<td>3</td>
<td>Rituximab</td>
<td>1000mg D1 D15</td>
<td>DMARD, 100% MTX</td>
<td>YES, 100%</td>
<td>FACIT-F, SF-36-V, Weeks 0 and 24</td>
</tr>
<tr>
<td>ATTAIN [22, 25]</td>
<td>5</td>
<td>Abatacept</td>
<td>if &lt;60 kg: 50mg 60-100kg: 750mg 100kg: 1000mg D1 D15 D19 then/28 days</td>
<td>DMARD, 100% MTX for 76% of pts in tt gp and 82% in placebo gp</td>
<td>YES, 100%</td>
<td>VAS, SF36-V, Weeks 0, 24 and 104</td>
</tr>
<tr>
<td>GO-AFTER [31]</td>
<td>5</td>
<td>Golimumab</td>
<td>50mg/4 weeks</td>
<td>DMARD, 66% MTX</td>
<td>YES, 100%</td>
<td>FACIT-F, Weeks 0, 14 and 24</td>
</tr>
<tr>
<td>RAPID 1 [18, 25]</td>
<td>3</td>
<td>Certolizumab</td>
<td>400mg at Weeks 0, 2 and 4, followed by 200mg every 2 weeks</td>
<td>DMARD, 100% MTX</td>
<td>NO</td>
<td>SF-36-V, FAS, Weeks 0, 1, 24 and 52</td>
</tr>
</tbody>
</table>

*31% of placebo group and 29% of treatment group did not receive concomitant DMARD. tt: treatment; Gp: group; Ref: reference; D: day.
Fig. 2 Forest plot showing the overall ES (95% CI) of biotherapies + DMARD vs placebo + DMARD on fatigue in established RA with IR-DMARDs or IR-anti-TNF [12–26, 31, 32]. Std. mean difference: standard mean difference.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Control Mean (S.D.)</th>
<th>Biotherapies Mean (S.D.)</th>
<th>Total Mean (S.D.)</th>
<th>Total Weight, %</th>
<th>IV, random (95% CI)</th>
<th>IV, random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEO19</td>
<td>15.38 (20.38)</td>
<td>207 11.57 (21.92)</td>
<td>200</td>
<td>10.6</td>
<td>0.18 (–0.01, 0.37)</td>
<td></td>
</tr>
<tr>
<td>STAR</td>
<td>11.4 (21.35)</td>
<td>318 6.48 (21.15)</td>
<td>318</td>
<td>11.6</td>
<td>0.23 (0.08, 0.39)</td>
<td></td>
</tr>
<tr>
<td>GOAFTER</td>
<td>11.54 (23.46)</td>
<td>153 5.77 (19.81)</td>
<td>155</td>
<td>9.9</td>
<td>0.27 (0.04, 0.49)</td>
<td></td>
</tr>
<tr>
<td>DANCER</td>
<td>15.77 (20)</td>
<td>122 7.52 (20.58)</td>
<td>122</td>
<td>9.2</td>
<td>0.41 (0.15, 0.66)</td>
<td></td>
</tr>
<tr>
<td>OPTION</td>
<td>16.54 (20.38)</td>
<td>205 7.69 (21.35)</td>
<td>204</td>
<td>10.6</td>
<td>0.42 (0.23, 0.62)</td>
<td></td>
</tr>
<tr>
<td>ARMADA</td>
<td>19.88 (21.73)</td>
<td>67 10.71 (18.08)</td>
<td>62</td>
<td>11.0</td>
<td>0.45 (0.10, 0.80)</td>
<td></td>
</tr>
<tr>
<td>GOFORWARD</td>
<td>14.04 (21.15)</td>
<td>89 4.23 (20.19)</td>
<td>133</td>
<td>8.8</td>
<td>0.48 (0.20, 0.75)</td>
<td></td>
</tr>
<tr>
<td>RAPID 1</td>
<td>15.5 (18)</td>
<td>393 4.7 (17.4)</td>
<td>199</td>
<td>11.2</td>
<td>0.61 (0.43, 0.78)</td>
<td></td>
</tr>
<tr>
<td>ATTAIN</td>
<td>6.9 (8.5)</td>
<td>258 1.2 (9)</td>
<td>133</td>
<td>10.2</td>
<td>0.66 (0.44, 0.87)</td>
<td></td>
</tr>
<tr>
<td>REFLEX</td>
<td>17.58 (20.67)</td>
<td>298 1.04 (22.6)</td>
<td>201</td>
<td>10.9</td>
<td>0.77 (0.58, 0.95)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>2110 1727</td>
<td></td>
<td>100.0</td>
<td>0.45 (0.31, 0.58)</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 0.03; \chi^2 = 35.78, df = 9 (P < 0.0001); F = 75%$

Test for overall effect: $Z = 6.56 (P < 0.00001)$

Fig. 3 Forest plot showing the overall ES (95% CI) of anti-TNFs + DMARD vs placebo + DMARD on fatigue in patients with IR-DMARDs or IR-anti-TNF [12–19, 31, 32]. Std. mean difference: standard mean difference.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Anti-TNF Mean (S.D.)</th>
<th>Control Mean (S.D.)</th>
<th>Total Mean (S.D.)</th>
<th>Total Weight, %</th>
<th>IV, random (95% CI)</th>
<th>IV, random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARMADA</td>
<td>19.88 (21.73)</td>
<td>67 10.71 (18.08)</td>
<td>62</td>
<td>11.0</td>
<td>0.45 (0.10, 0.80)</td>
<td></td>
</tr>
<tr>
<td>DEO19</td>
<td>15.38 (20.38)</td>
<td>207 11.57 (21.92)</td>
<td>200</td>
<td>18.3</td>
<td>0.18 (–0.01, 0.37)</td>
<td></td>
</tr>
<tr>
<td>GOAFTER</td>
<td>11.54 (23.46)</td>
<td>153 5.77 (19.81)</td>
<td>155</td>
<td>16.6</td>
<td>0.27 (0.04, 0.49)</td>
<td></td>
</tr>
<tr>
<td>GOFORWARD</td>
<td>14.04 (21.15)</td>
<td>89 4.23 (20.19)</td>
<td>133</td>
<td>14.2</td>
<td>0.48 (0.20, 0.75)</td>
<td></td>
</tr>
<tr>
<td>RAPID 1</td>
<td>15.5 (18)</td>
<td>393 4.7 (17.4)</td>
<td>199</td>
<td>19.4</td>
<td>0.61 (0.43, 0.78)</td>
<td></td>
</tr>
<tr>
<td>STAR</td>
<td>11.4 (21.35)</td>
<td>318 6.48 (21.15)</td>
<td>318</td>
<td>20.4</td>
<td>0.23 (0.08, 0.39)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>1227 1067</td>
<td></td>
<td>100.0</td>
<td>0.36 (0.21, 0.51)</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 0.02; \chi^2 = 15.17, df = 9 (P = 0.010); F = 67%$

Test for overall effect: $Z = 4.61 (P < 0.00001)$

Overall effect of biotherapies on fatigue in established RA

The overall ES of all biotherapies vs placebo was considered as small at 6 months of treatment with an ES = 0.45 (95% CI 0.31, 0.58) (Fig. 2). Since the DANCER and OPTION studies included patients with IR-anti-TNF, we performed a sensitive analysis excluding first the DANCER study and next the OPTION study [20, 23]. The overall ES of biotherapy did not change dramatically (ES = 0.45; 95% CI 0.30, 0.60) for either analysis.

Adalimumab, golimumab and tocilizumab had a small effect with ES ranging between 0.24 (95% CI 0.12, 0.35) and 0.42 (95% CI 0.23, 0.62) [12–17, 23] (Fig. 2). For rituximab, abatacept and certolizumab overall, the effect on fatigue was moderate with an ES of 0.60 (95% CI 0.24–0.95), 0.66 (95% CI 0.44–0.87) and 0.61 (95% CI 0.43, 0.78), respectively [18–25]. When we pooled all anti-TNF trials (adalimumab, golimumab and certolizumab), we found that the overall ES of anti-TNFs vs placebo on fatigue was small: 0.36 (95% CI 0.21, 0.51) (Fig. 3) [12, 16–18]. In contrast, when we pooled the biotherapies other than anti-TNF, the overall ES was moderate: 0.57 (95% CI 0.39, 0.75) [20–26].

To compare our results with the global impact of biotherapies on quality of life, we have calculated the ES of all the biotherapies on HAQ score at Week 24 in seven studies with available data (two studies with adalimumab, two with golimumab, one with rituximab, one with abatacept and one with tocilizumab): the ES was 0.50 (0.42, 0.58) suggesting that the effect of biologic agents on quality of life is classified as moderate [14–17, 21, 23, 33]. The effect of biologics on HAQ seems to be similar to that on fatigue [the ES on fatigue calculated with the same seven studies is 0.46 (95% CI 0.29, 0.63)]. Unfortunately, we could not estimate the ES of 28-joint DAS (DAS-28) in our meta-analysis because of lack of data.
Effect of biotherapies on fatigue in active RA despite conventional DMARDs and anti-TNF treatments

In patient with IR-DMARD, biotherapies at 6 months had a small impact with an overall ES of 0.38 (95% CI 0.30, 0.46) (Fig. 4). When we pooled together all anti-TNF trials (adalimumab, golimumab and certolizumab) or when we pooled the non-anti-TNF biotherapies, we found that the overall ESs on fatigue were small and similar: 0.36 (95% CI 0.27, 0.45) and 0.42 (95% CI 0.26, 0.57), respectively.

Considering the RA population with IR-anti-TNF, three biologic agents could be assessed (i.e. abatacept, golimumab and rituximab) [17, 21, 21, 31]. Their overall effect on biologic agents could be assessed (i.e. abatacept, golimumab and rituximab) [17, 21, 22, 31]. Their overall effect on biologic agents could be assessed (i.e. abatacept, golimumab and rituximab) [17, 21, 22, 31]. Their overall effect on treatments except for languages. We used three electronic data-bases, completed with hand search and abstracts from international meetings of the past 4 years. One explanation would be that fatigue is an outcome mainly assessed in recent studies: 9 of the 10 included studies have been published in the past 3 years.

Our objective was to assess the effect of available biotherapies on fatigue in RA patients in two clinical situations: (i) inadequate response to conventional treatments and (ii) IR-anti-TNF. For that purpose, we performed a systematic review of the literature and estimated fatigue at 6 months (Week 24) of treatment was small in established populations. Finally, 10 of them could be kept in our analysis, while the others were excluded because the time point was different or the mandatory data used to estimate ES were lacking (Fig. 1). Nevertheless, the literature search was as exhaustive as possible, without limitations except for languages. We used three electronic date-bases, completed with hand search and abstracts from international meetings of the past 4 years. One explanation would be that fatigue is an outcome mainly assessed in recent studies: 9 of the 10 included studies have been published in the past 3 years.

Secondly, the overall effect of biotherapies on fatigue at 6 months (Week 24) of treatment was small in established RA. Non-anti-TNF biologic agents would be more regarded as priorities for patients as well as Less pain, No more joint damage, Able to do everyday things and More mobility [34]. Then, our objective was to assess the effect of available biotherapies on fatigue in RA patients in two clinical situations: (i) inadequate response to conventional treatments and (ii) IR-anti-TNF. For that purpose, we performed a systematic review of the literature and estimated the ES of biotherapies vs placebo. First, only 22 RCTs assessing fatigue in RA receiving biotherapy or placebo were found in the electronic databases, while 763 studies evaluating treatments have been published in the RA population. Finally, 10 of them could be kept in our analysis, while the others were excluded because the time point was different or the mandatory data used to estimate ES were lacking (Fig. 1). Nevertheless, the literature search was as exhaustive as possible, without limitations except for languages. We used three electronic databases, completed with hand search and abstracts from international meetings of the past 4 years. One explanation would be that fatigue is an outcome mainly assessed in recent studies: 9 of the 10 included studies have been published in the past 3 years.

Secondly, the overall effect of biotherapies on fatigue at 6 months (Week 24) of treatment was small in established RA. Non-anti-TNF biologic agents would be more

Discussion

Fatigue represents an important symptom for patients with RA. Indeed, Less fatigue is in the top five outcomes regarded as priorities for patients as well as Less pain, No more joint damage, Able to do everyday things and More mobility [34]. Then, our objective was to assess the effect of available biotherapies on fatigue in RA patients in two clinical situations: (i) inadequate response to conventional treatments and (ii) IR-anti-TNF. For that purpose, we performed a systematic review of the literature and estimated the ES of biotherapies vs placebo. First, only 22 RCTs assessing fatigue in RA receiving biotherapy or placebo were found in the electronic databases, while 763 studies evaluating treatments have been published in the RA population. Finally, 10 of them could be kept in our analysis, while the others were excluded because the time point was different or the mandatory data used to estimate ES were lacking (Fig. 1). Nevertheless, the literature search was as exhaustive as possible, without limitations except for languages. We used three electronic databases, completed with hand search and abstracts from international meetings of the past 4 years. One explanation would be that fatigue is an outcome mainly assessed in recent studies: 9 of the 10 included studies have been published in the past 3 years.

Secondly, the overall effect of biotherapies on fatigue at 6 months (Week 24) of treatment was small in established RA. Non-anti-TNF biologic agents would be more
effective than TNF blockers (small ES for anti-TNF vs moderate ES for non-anti-TNF biotherapies). In IR-DMAARD and IR-anti-TNF populations, the effect of biotherapies was small and moderate, respectively. Sensitive analysis did not change these results. Interestingly, our results are in accordance with observational studies published previously [35, 36]. For example, in a longitudinal study evaluating TNF blockers, the mean change in SF-36-V from baseline to 6 months was 11.6 (22), which is close to what we observed at the same time of analysis (from 6.02 to 15.5) [35].

In conclusion, this review of the literature and meta-analysis of RCTs suggest a small effect of biotherapies on fatigue in established RA after 6 months of treatment. More RCTs are needed to assess the impact of available biotherapies and new trials in RA patients should systematically include fatigue assessment as outcome. Since fatigue is a multi-factorial and subjective symptom, a multi-module approach including pharmacological and non-pharmacological treatments should be evaluated in our patients.

A Rheumatology key messages

- Few studies report the effect of biotherapies on fatigue.
- According to meta-analysis, the effect of biotherapies on fatigue in RA is small.

Acknowledgements

The authors have no financial interest in the subject matter or materials discussed in the manuscript. The authors thank Laure Gossec and Maxime Dougados (AP-HP, Cochin Hospital, Paris V University, Paris, France) for helpful discussions.

Funding: Abbott France pharmaceutical company provided support by organizing a meta-analysis methods workshop, but played no further role in the project.

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at Rheumatology Online.

References


30 Kay J, Doyle MK, Smolen J et al. Golimumab significantly improves physical function and fatigue in RA patients previously treated with anti-TNFa agents: results from the GO-AFTER study. EULAR Meeting 2009;Abstract AB0206.

31 Genovese MC, Keystone EC, Hsia EC et al. Golimumab significantly improves physical function, health-related quality of life, and fatigue in patients with active...
rheumatoid arthritis despite methotrexate: results from the GO-FORWARD study. EULAR Meeting 2009;Abstract FR0211.


