Patient-reported fatigue in patients with rheumatoid arthritis who commence biologic therapy: A longitudinal study

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Aims and objectives. To examine changes in patient-reported fatigue, over a twelve month period, in rheumatoid arthritis patients who commence biologic treatment, and to identify possible predictors for such changes.

Background. Fatigue is a burdensome symptom for patients with rheumatoid arthritis. Despite biologics being effective in reducing disease activity, patients still report fatigue.

Design. A longitudinal observational study.

Methods. A total of 48 patients were enrolled in the study. Fatigue was measured by the Fatigue Severity Scale. Independent samples T-tests were used to test gender differences, and paired samples T-tests were used to measure differences between repeated measures. Bivariate and multiple regression analyses were used to examine potential predictors for changes in fatigue, such as age, sex, Disease Activity Score 28, pain and physical and emotional well-being.

Results. Forty-seven patients completed the study. From baseline to 12-month follow-up, fatigue decreased significantly in both women and men. Analyses of predictors were performed step-wise, and the final model included sex and physical well-being. The results from this final step showed that female sex was the only significant predictor for changes in fatigue.

Conclusion. Patients commencing biologic therapy reported a significant reduction in fatigue. Female sex was a significant predictor of changes in fatigue.

Relevance to clinical practice. Despite improvements in pharmacological treatment, patients with rheumatoid arthritis still report fatigue. This is a multifaceted health problem encompassing personal and emotional factors in addition to the clinical factors directly connected to the disease.

1 **Title of the research paper**
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46 Relevance to clinical practice.

47   Despite improvements in pharmacological treatment, patients with rheumatoid arthritis still

48   report fatigue. This is a multifaceted health problem encompassing personal and emotional

49   factors, in addition to the clinical factors directly connected to the disease.

50   **What does this paper contribute to the wider global clinical community?**

51   *Fatigue is one of the most burdensome symptoms from the patient perspective.

52   * The reduction in fatigue observed after twelve months was higher in women than in men.

53   *Female sex was the most important predictor of changes in fatigue.

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Introduction

Rheumatoid arthritis (RA) is an inflammatory joint disease which may cause joint damage,

disability and fatigue (Scott, Wolfe, & Huizinga, 2010). RA patients experience fatigue as

unpredictable, overwhelming and different from normal tiredness (Feldthusen et al., 2013).

Fatigue is caused by numerous factors. This might due to immunological disorders, hormonal

imbalances, decrease in oxygenation, and exogenous processes induced by drugs (Dupond,

2010). A conceptual model for fatigue suggests inter-relationships between and within the RA

disease process, personal issues, feelings, thoughts and behaviors (Hewlett et al., 2011a). Fatigue

in RA is under-recognized and undertreated (Hewlett et al., 2005). Furthermore, it is one of the

most burdensome symptoms from the patient perspective (Kirwan et al., 2007; van Tuyl et al.,

2007). Over the last decades biologic agents have caused a paradigm shift in the treatment of

RA, and biologics are effective in reducing disease activity, inflammation, pain and joint damage

in RA (Scott et al., 2010). This reduction of disease-related components may affect the level of

RA fatigue, and previous research has shown that both anti-tumor necrosis factor (anti-TNF) and

non-anti-TNF biologics produce similar improvements in fatigue (Almeida et al., 2016).

However, patient-reported consequences of disease activity may differ from the assessments

made by health professionals (Studenic et al., 2012).

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Background

93   Recommendations endorsed by the European League Against Rheumatism and the American

94   College of Rheumatology encourage all clinical trials to report fatigue (Aletaha et al., 2008;

95   Kirwan et al., 2007). Fatigue is a patient-reported measure and can incorporate one single item or

96   multiple items. Furthermore, the scales can have a unidimensional or multidimensional structure.

97   The Fatigue Severity Scale (FSS) is a disease-specific questionnaire intended to assess fatigue in

98   multiple sclerosis and systemic lupus patients, but it is also used in RA studies (Diniz et al.,

99   2017; Gok Metin & Ozdemir, 2016; Hussain et al., 2015). The FSS is better at detecting changes

100   than generic questionnaires (Hewlett, Dures, & Almeida, 2011b). As fatigue in RA patients is

101   measured by various patient-reported outcome measures (Hewlett, Dures, & Almeida, 2011b;

102   Pouchot et al., 2008), and as results from these measures are difficult to compare, the review

103   below will mainly refer to research based on the FSS.

104

105   **Effect of biologic therapy on fatigue**

106   Only a few previous studies have examined the effect of biologic therapy on fatigue measured with a

107   disease-specific scale. In a double-blinded study, patients with Primary Sjögren's syndrome received

108   biologic therapy or placebo, and fatigue was measured using both the FSS and Visual Analogue Scale

109   (VAS). After four weeks of treatment there was no significant reduction in fatigue in these patients

110   (Norheim et al., 2012). On the other hand, another study has evaluated the effect of biologic therapy on

111   work ability, fatigue and functional disability in RA patients after six months. In this study, fatigue was

112   measured using the FSS and VAS, and the results demonstrated that biologics had a beneficial effect on

113   fatigue in patients with RA (Hussain et al., 2015).

114

115   **Predictors for changes in fatigue**

116   As stated by Ahmed and colleagues, patient-reported outcomes are important as they represent

117   information from the patient perspective that has not been interpreted by health personnel

118   (Ahmed et al., 2012) and such measures might provide additional and different information that

119   is relevant for both RA patients and physicians (Gossec, Dougados, & Dixon, 2015).

120   Previous research has identified both patient-reported factors and more objective measures

121   evaluated by health personnel as predictors for fatigue. In a review containing both cross-

122   sectional and longitudinal studies, as well as several measures of fatigue, the results showed a

123   correlation between fatigue and patient-reported pain, physical function and depression

124   (Nikolaus et al., 2013). In a systematic review of cross-sectional, observational and cohort

125   studies examining psychological factors as predictors for fatigue, there was a consistent

126   correlation between patient-reported mood and fatigue, with low mood being associated with

127   increased fatigue (Matcham et al., 2015). The most common health personnel-reported measure

128   of disease activity in patients with RA is the Disease Activity Scale 28 (DAS28) (van Riel,

129   2014). To our knowledge, no previous studies including both patient-reported and health

130   personnel-reported measures have measured fatigue using the FSS. In a previous study of both

131   patient-reported and health personnel-reported outcomes, results showed that disease activity,

132   pain, sleep disturbance, and mental health were related to fatigue (Thyberg, Dahlstrom, &

133   Thyberg, 2009). A review of correlations between different disease activity measures, pain and

134   fatigue showed that pain was the strongest factor associated with fatigue (Madsen et al., 2016).

135   In these studies gender has not been considered as a possible predictor for change in fatigue. In a

136   study of patients in remission or with low disease activity, pain was a significant predictor of

137   fatigue (Olsen et al., 2016).

138   Regarding sociodemographic data, gender differences have been observed in previous research.

139   Female patients reported significantly higher fatigue measured by the FSS compared with

140   healthy controls (Buyuktas et al., 2015), and female participants reported more persistent fatigue

141   after four years than men did (Druce et al., 2015a). In a study, Thyberg et al. (2009) found that

142   women reported more fatigue measured by the VAS than men. Furthermore, one study found a

143   difference between the patient and physician assessment of global disease activity, and this

144   difference was more pronounced in women than in men (Lindstrom Egholm et al., 2015).

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148   The aims of the present study were:

149   •   To examine changes in patient-reported fatigue in RA patients who commence biologic

150   treatment.

151   •   To identify possible predictors (sociodemographic as well as patient-reported and health

152   personnel-reported variables) for changes in fatigue.

153

154   **Methods**

155   **Design**

156   The study was carried out at a rheumatology specialist department in Western Norway. It was a

157   longitudinal study comparing fatigue levels over 12 months. Patients were assessed at baseline

158   (T0) and after 3 (T1), 6 (T2) and 12 months (T3). The study was part of an observational study

159   to explore ultrasonographic differences in total synovitis between seropositive and seronegative

160 rheumatoid arthritis patients. The patients consented to participate in both studies at the same

161 time.

162 Inclusion criteria were as follows and the same as in the main study: 1) male or non-pregnant,

163 non-nursing female; 2) age between 18 and 75 years; 3) patient classified as having RA

164 according to the 2010 American College of Rheumatology/ European League Against

165 Rheumatism criteria (Aletaha et al., 2010); 4) treating rheumatologist and patient have decided

166 that biologic treatment is needed; 5) patient has had no prior biologic treatment; and 6) patient is

167 able and willing to give written informed consent and comply with the requirements of the study

168 protocol. Exclusion criteria: 1) abnormal renal function (serum creatinine > 142 μmol/L in

169 female and > 168 μmol/L in male, or GFR < 40 mL/min/1.73m²; 2) abnormal liver function

170 (ASAT/ALAT > 3 times normal), active or recent hepatitis, cirrhosis; 3) major co-morbidities

171 like severe malignancies, severe diabetic mellitus, severe infections, uncontrollable hypertension,

172 severe cardiovascular disease (New York Heart Association Functional Class 3-4) and/or severe

173 respiratory disease; 4) leukopenia and/or thrombocytopenia; 5) inadequate birth control,

174 pregnancy, and/or breastfeeding; 6) indications of active tuberculosis; and 7) psychiatric or

175 mental disorders, alcohol abuse or other abuse of substances, language barriers or other factors

176 which make adherence to the study protocol impossible.

177

178 **Data collection**

179 During the period from October 2011 to December 2014, all eligible patients were invited to

180 enter the study. A physical examination, including checking for co-morbidities and joint

181 counting, was performed by a rheumatologist. A study nurse coordinated the physical

182 examinations and blood testing, and managed the patient-reported questionnaires. When the last

183 enrolled patient had been followed for 12 months the study was closed. The number of

184 participants is low, because the study was a subproject under the multicenter study

185 "Ultrasonographic differences in total synovitis between seropositive and seronegative

186 rheumatoid arthritis patients", and the Fatigue Severity Scale was not included in all subprojects.

187

188 **Treatment**

189 The patients in this study commenced their first biologic therapy (certolizumab, etanercept,

190 golimumab, infliximab or rituximab) according to standard procedures and doses.

191 38 patients were on stable doses of methotrexate 3 months before baseline and until visit T1. 6

192 patients were taking leflunomide or hydroxychloroquine, and 4 patients had no synthetic disease-

193 modifying antirheumatic drugs (DMARDs).

194 A total of 28 patients were on a stable low dose of corticosteroids the last month before inclusion

195 and until visit T1. Patients were told to avoid analgesics for 24 hours prior to the visits if

196 possible.

197 **Assessments**

198 Fatigue was measured using the FSS, which is a 9-item questionnaire rated on a scale from 1 to

199 7, where 1 indicates strongly disagree and 7 indicates strongly agree. The FSS contains

200 statements on the severity of fatigue, and also the effect on a person's activities and lifestyle. The

201 developers of the FSS have suggested a cut-off of 4 for severe fatigue (Krupp et al., 1989). The

202 FSS is used in a number of diseases and is a reliable instrument for measuring fatigue (Valko et

203 al., 2008). The FSS has demonstrated good psychometric properties and is one of the few

204 measures that are able to detect change over time (Whitehead, 2009). There are different

205 Norwegian versions of the Fatigue Severity Scale questionnaire. In this study we used a

206   questionnaire translated in 1995. As far as we know, this version of the questionnaire has not

207   been tested for psychometric properties. Nevertheless, it has been used in research and clinical

208   practice for several years (Johansen et al., 2018; Asprusten et al., 2018; De Rodez Benavent et

209   al., 2017).

210   Rheumatoid Arthritis Impact of Disease (RAID) was used to measure pain and physical and

211   emotional wellbeing (Gossec et al., 2009). The scale goes from 0-10. Pain is assessed from none

212   to extreme and physical and emotional wellbeing are assessed from very good to very bad. RAID

213   has been validated (Heiberg et al., 2011).

214   Disease activity can be measured by the Disease Activity Score 28 (DAS28). The purpose is to

215   combine single measures such as swollen and tender joints, erythrocyte sedimentation rate (ESR)

216   or C-reactive protein (CRP), and to include or exclude a general health assessment (Fransen,

217   Stucki, & van Riel, 2003). In this study we wanted to use an objective tool for measuring disease

218   activity. Therefore, we chose DAS28 based on three variables: tender and swollen joint counts

219   and ESR (Fransen, Creemers, & Van Riel, 2004). DAS28 has been validated to monitor disease

220   activity in RA (van Riel, 2014).

221

222   **Statistical analyses**

223   Descriptive statistics were used to describe sociodemographic, patient-reported and health

224   personnel-reported variables. The independent samples *t*-test was used to test for differences

225   between women and men. The paired samples *t*-test was used to test for differences between

226   measures at different points in time.

227   Linear mixed effect analyses were used to identify possible predictors of change in fatigue. In the

228   analyses, we added clinical variables such as DAS28, sociodemographic variables such as sex

229   and age, and patient-reported variables such as pain and physical and emotional wellbeing. First,

230   a 0-model containing time only was made using simple contrasts in time domain, i.e. a

231   comparison of each time point with baseline. In step 1, to estimate the main effect and interaction

232   effect, each predictor was put into a model containing time. The Akaikes information criterion

233   (AIC) was used as a criterion to decide whether the model fitted the data and also to compare the

234   models to the 0-model by measuring the p-value and performing a likelihood ratio test. In step 2,

235   significant predictors were put into a model one by one. RAID subscales were added in order of

236   their AIC score. In step 3 only predictors contributing to the model were added.

237   We used a linear mixed effects model with simple contrasts including all time points, i.e. the

238   model has a built-in-adjustment for baseline. The main effect of a predictor is the effect at

239   baseline, while the interaction describes if and how the baseline effect changes over time.

240   The significance level was set to 0.05. SPSS 23 for Windows (IBM Corp., Armonk, NY) and R

241   3.3.0 (R Core team, 2016) with the package nlme 3.1(Pinheiro et al., 2016) were used for the

242   statistical analyses.

243

244   **Ethical considerations**

245   The study was approved by the Regional Ethics committee for Medical Research (REK,

246   2011/490). All the patients received both oral and written information, and signed informed

247   consent.

248

249   **Results**

250   A total of 48 patients met the inclusion criteria, and gave consent to participate in the study. One

251   patient was excluded after 3 months because of acute illness and need of surgery. 47 patients

252   completed the study (Figure 1).

253   At baseline the patients had a median age of 55 years [range 24-73 years], and more than half of

254   the patients (56 %) were women. The mean disease duration was 5 years (SD 7.5), [range <1- 40

255   years]. Sociodemographic and clinical baseline characteristics are shown in Table 1.

256   The mean fatigue measurements and their changes are shown in Table 2. At baseline we

257   observed significantly more severe fatigue in female than in male patients. The severity of

258   fatigue decreased significantly for both women and men between baseline and visit T1 and then

259   stabilized. This improvement was stronger for women (mean (CI) = 1.3 (0.7,1.9), p < 0.001) than

260   for men, mean (CI) = 0.6 (0.8,1.2), p = 0.026).

261   As shown in Table 3 the disease activity measured by DAS28 decreased significantly between

262   baseline and 3 months (mean (CI) = 1.4 (1.1,1.7), p < 0.001) and was stable in later visits. The

263   same development was observed for the selected RAID subscales. In the linear mixed effects

264   model, sex and RAID emotional well-being contributed significantly to the model (Step 2 in

265   Table 4), while change in fatigue was not explained by disease activity (Step 1 in Table 4).

266   Analysis of predictors (Table 4) showed a higher reduction in fatigue values at follow-up visit T2

267   (6 months) for women than men (p = 0.019). At follow-up visit T3 (12 months) there was a

268   significant change in fatigue for females (p = 0.015). The changes in fatigue and the RAID

269   variables pain and physical and emotional wellbeing are explained by the gender component.

270   The change in fatigue is explained by both female sex and physical wellbeing, but in the end

271   female sex had stronger influence than physical wellbeing and turned out to be a significant

272   predictor for change in fatigue (p = 0.010).

273

Discussion

Changes in patient-reported fatigue

276 This study found that both female and male RA patients commencing biologic therapy reported

277 lower levels of fatigue during treatment. Previous research has shown somewhat inconsistent

278 results and, to our knowledge, has not examined gender differences. In a randomized clinical

279 trial, Norheim et al. (2012) reported no significant effect of biologics on fatigue in Sjögren's

280 patients. However, a post hoc analysis showed that six out of 12 patients in the group treated

281 with biologics reported a 50% reduction in fatigue compared to one out of 13 in the placebo

282 group, and this result was significant. Another study investigated the effect of biologics on work

283 ability, functional disability and fatigue. The results from this observational study showed

284 significant improvements in fatigue after six months of biologic therapy (Hussain et al., 2015).

285 These inconsistencies may be explained by the fact that fatigue is a patient-reported symptom

286 with individual variations in severity and etiology and by the different diseases studied. In some

287 patients, fatigue may persist despite biologic therapy (Emery, 2014) and the explanation for this

288 may be found in the etiology of fatigue as a symptom with multiple causes, some connected to

289 disease activity and others to personal factors (Hewlett et al., 2011a). When RA patients with

290 fatigue were interviewed and encouraged to describe this problem in their own words, they

291 described fatigue as an experience that was always present, preventing them from finding

292 solutions to everyday problems and affecting both themselves and their social life (Bala et al.,

293 2016). A broader approach covering all aspects of this health problem is needed.

294

Possible predictors for changes in fatigue

296   In bivariate analyses, disease activity and age turned out to be insignificant predictors for change

297   in fatigue at all follow-up visits. Pain also turned out to be an insignificant predictor for change

298   in fatigue in both bivariate and multivariate analyses. Emotional wellbeing turned out to be a

299   significant predictor for change in fatigue at the 6-month follow-up visit in bivariate analyses and

300   at the 12-month follow-up visit in multivariate analyses. In bivariate analyses physical well-

301   being was a statistically significant predictor of change in fatigue, but in multivariate analyses

302   only the 3-month follow-up visit showed a significant change in fatigue. Female sex was a

303   significant predictor in both bivariate and multivariate analyses. As far as we know, in previous

304   research sex has rarely been a variable in analyses of predictors of change in fatigue, and the

305   results of this study may be difficult to compare to other studies. However, it might be possible

306   to compare the results of the patient and health personnel-reported outcomes in this study. In a

307   systematic review, Madsen et al. (2016) found that disease activity was positively related to

308   fatigue when pain was not considered, and that pain was the dominating factor related to fatigue.

309   However, in these studies disease activity was measured using different components of DAS28,

310   and the various components of DAS28 have different weightings, with some of them being more

311   related to inflammation than others. It might therefore be difficult to compare the results of these

312   studies (Madsen et al., 2016).

313   In this study, women reported statistically significantly higher fatigue at baseline than men.

314   During the study the mean fatigue score was higher in women at all follow-up visits. Previous

315   work has shown that women report higher values of fatigue than men (Rat et al., 2012; Thyberg

316   et al., 2009), and several factors, such as genetic and hormonal factors and other exposures that

317   may be experienced differently by women and men, have been suggested as explanations for the

318   difference between men and women in terms of RA disease impact (van Vollenhoven, 2009).

319   Pain and related measurements are often discussed as being non-sex-neutral. In a review, somatic

320   symptom reporting in women and men has been examined. Results showed that women reported

321   more numerous, more intense and more frequent bodily symptoms than men (Barsky, Peekna, &

322   Borus, 2001). Moreover, women and men may react differently to treatment. In a register-based

323   observational study of predictors of response to biologic therapy, there was a lower remission

324   rate among female RA patients (Hyrich et al., 2006).

325   In this present study, multivariate analyses showed that change in fatigue is explained by both

326   female sex and physical wellbeing. Still, in the final model only female sex turned out to be a

327   significant predictor for change in fatigue.

328

329   **Strengths and limitations of the study**

330   The strength and importance of this study of fatigue in patients with rheumatoid arthritis is the

331   insight and information gained on patient-reported outcomes. The data are based on the

332   implementation of outcome measures recommended by experts (Hewlett, Dures, & Almeida,

333   2011b), and guidelines from the European League Against Rheumatism and the American

334   College of Rheumatology (Aletaha et al., 2008), and recommendations from the international

335   research cooperation Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT)

336   (de Wit et al., 2013).

337   This study is a cohort study, without a control group. Therefore, it is difficult to determine

338   whether biologic therapy affects fatigue or not. On the other hand, the patients in the study had

339   tried standard treatment with synthetic DMARDs before commencing biologics. The patients'

340   level of fatigue was followed up for twelve months, and data collection was performed four

341   times, and this may provide valuable insight into how fatigue occurs. Furthermore, the number of

342 participants was small, which means that the analyses have low statistical power, and they were

343 all recruited from the same rheumatology department. However, the participants were recruited

344 consecutively and were all in need of their first biologic treatment, and had no major co-

345 morbidities. The patients in the study live along the west coast of Norway, but we assume the

346 selection is not very different from the majority of RA patients living in other parts of Norway

347 (Brinkmann et al., 2018, Olsen et al., 2016).

348 **Conclusion**

349 Female RA patients commencing biologics report reductions in fatigue after 3 and 6 months.

350 After 12 months there is a slight increase in the fatigue level. Male RA patients report reductions

351 in fatigue after 3 and 12 months. When comparing sociodemographic, patient-reported and

352 health personnel-reported variables, female sex was a significant predictor of changes in fatigue.

353 This result is important and may indicate gender differences in the impact of RA. Further

354 research is needed in order to understand the complexity of fatigue and to evaluate non-

355 pharmacological treatment.

356

357 **Relevance to clinical practice**

358 Fatigue is a burdensome symptom in RA patients, and despite improvements in the

359 pharmacological treatment of RA, patients still report fatigue (van Hoogmoed et al., 2013; Druce

360 et al., 2015b; Madsen et al., 2016). Therefore, additional therapies are needed to combat fatigue.

361 These therapies should take into account that fatigue is a multifaceted health problem

362 encompassing personal and emotional factors in addition to the clinical factors directly

363 connected to the disease.

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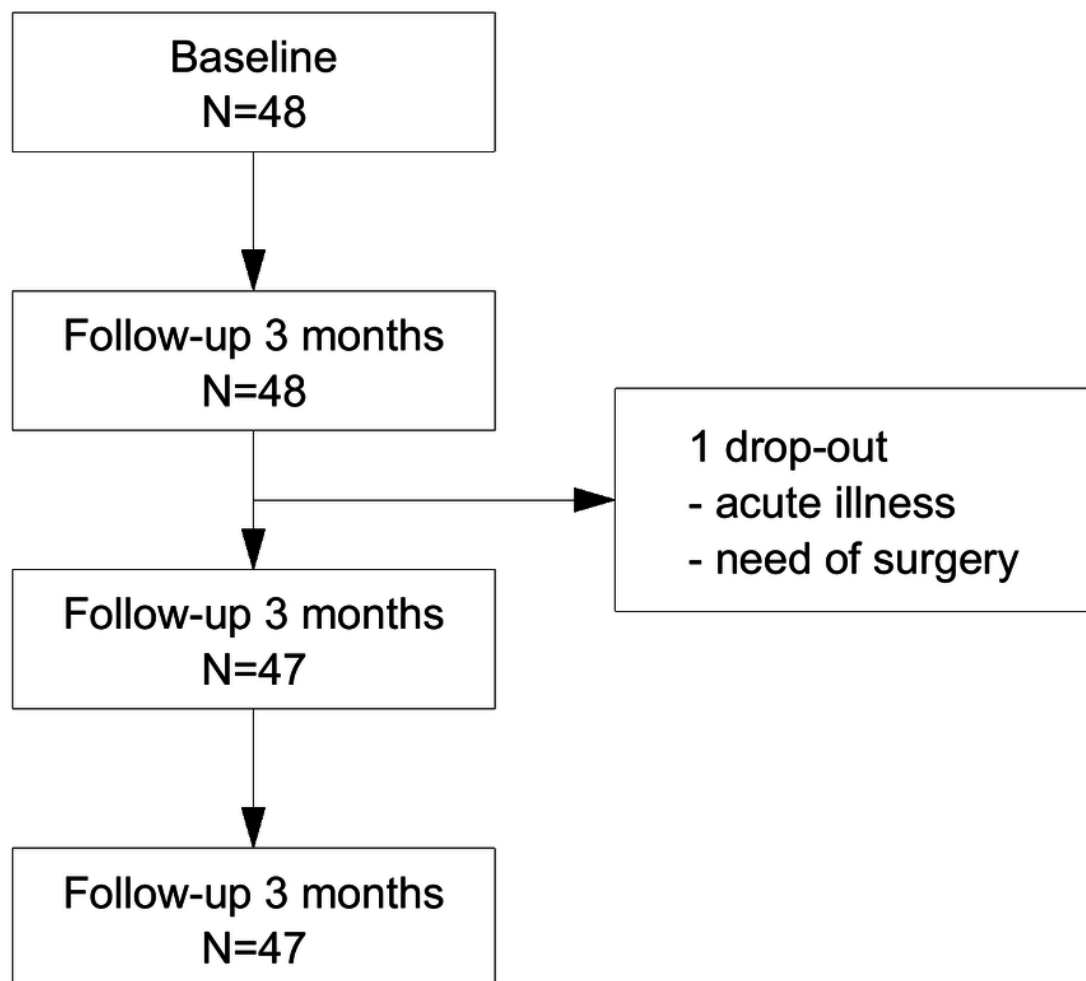
Figure 1

Flowchart

Flowchart to show number of participants who completed the study.

Sociodemographic and clinical characteristics

Sociodemographic characteristics such as age, sex, civil status, children living at home, occupational activity.

Clinical characteristics such as disease duration, rheumatoid factor, anti-cyclic citrullinated peptide, erythrocyte sedimentation rate, C-reactive protein, Disease Activity Score of 28 joints, Fatigue Severity Scale, Rheumatoid Arthritis Impact of Disease.

Table 1 Sociodemographic and clinical characteristics

Sociodemographic characteristics	*n*=48
Age, years, median (range)	55.0 [24-73]
Sex, female, n (%)	27 (56%)
Married/living with partner, n (%)	34 (71%)
Children living at home, n (%)	22 (46%)
Working or studying (full-time or part-time), n (%)	24 (50%)
Working or studying patients on sick leave, n (%)	10 (21%)
Disability benefits (full-time or part-time), n (%)	10 (21%)
Retired, n (%)	4 (8%)

Clinical characteristics	
Disease duration, years, mean (SD)	5.0 (7.5)
RF, n (%)	33 (69%)
Anti-CCP, n (%)	38 (79%)
ESR (mm/h), median (range)	22.5 [0-75]
CRP (mg/L), median (range)	9.0 [0-58]
Prednisolon dosage, mean (SD)[a]	6.0 (3.2)
Methotrexate dosage, mean (SD)[b]	20.0 (4.8)
FSS, (1-7), mean (SD)[c]	4.4 (1.5)
DAS28, mean (SD)	4.5 (1.2)
RAID - pain, mean (SD)[d]	5.5 (2.1)
RAID - emotional well-being, mean (SD)[e]	3.9 (2.1)
RAID - physical well-being, mean (SD)[d]	4.9 (1.9)

2 RF, rheumatoid factor; Anti-CCP, anti-cyclic citrullinated peptide; ESR, erythrocyte
3 sedimentation rate; CRP, C-reactive protein; DAS28, Disease Activity Score of 28 joints; FSS,
4 Fatigue Severity Scale; RAID, Rheumatoid Arthritis Impact of Disease
5 [a]n=28, [b]n=38, [c]n=47, [d]n=45, [e]n=44

Changes in fatigue, and gender differences

Changes in fatigue, and gender differences

Table 2 Mean, 95% confidence intervals and p-values of changes in fatigue during the study, and test of differences between women and men

Time point	Missing	Women		FSS change from T0		Men		FSS change from T0		FSS difference Men/women
		FSS				FSS				
		n	Mean (95% CI)	Mean (95% CI)	p	n	Mean (95% CI)	Mean (95% CI)	p	p
Baseline (T0)	1	26	5.0 (4.5,5.5)	-	-	21	3.6 (2.9,4.3)	-	-	0.001*
3 months (T1)	0	27	3.7 (3.1,4.4)	1.3 (0.7,1.9)	<0.001†	21	3.0 (2.3,3.6)	0.6 (0.8,1.2)	0,026†	0.113*
6 months (T2)	0	27	3.4 (2.7,4.1)	1.6 (0.9,2.3)	<0.001†	20	3.0 (2.3,3.7)	0.6 (-0.3,1.5)	0,155†	0.368*
12 months (T3)	2	25	3.7 (2.9,4.4)	1.4 (0.7,2.0)	<0.001†	20	2.7 (1.9,3.5)	0.9 (0.1,1.6)	0,024†	0.078*

FSS, Fatigue severity scale, scale 0-7: lower scores represent less fatigue
Confidence interval, CI
† paired *t*-test
**t*-test

Disease activity, pain, physical and emotional well-being during the one-year observation study of fatigue, including both women and men

2
3 **Table 3** Mean changes, 95% confidence intervals and *p*-values during the one-year observation study of fatigue, including both
4 women and men

Measure	T1: change from T0		T2: change from T0		T3: change from T0	
	Mean (95% CI)	*p*	Mean (95% CI)	*p*	Mean (95 CI)	*p*
DAS28	1.4 (1.1,1.7)	< 0.001†	1.4 (1.1,1.8)	< 0.001†	1.6 (1.3,1.9)	< 0.001†
RAID pain¹	2.4 (1.6,3.3)	< 0.001†	2.2 (2.8,0.4)	< 0.001†	3.2 (2.3,4.0)	< 0.001†
RAID physical well-being²	1.8 (1.1,2.5)	< 0.001†	2.0 (1.2,2.7)	< 0.001†	2.3 (1.5,3.1)	< 0.001†
RAID emotional well-being²	1.4 (0.7,2.1)	< 0.001†	1.7 (1.0,2.4)	< 0.001†	1.3 (0.3,2.2)	0.012†

*T*0: before the intervention; *T*1: after three months; *T*2: after six months; *T*3: after twelve months
¹Scale 0-10: lower scores represent less pain
²Scale 0-10: lower scores represent more well-being
DAS28, Disease activity score 28
RAID, Rheumatoid Arthritis Impact of Disease
Confidence interval, CI
† paired *t*-test

Predictors of fatigue: Mean changes, 95% confidence intervals and p -values, including both women and men

Predictors of fatigue. Model 1 with one predictor (main effect and interaction). Model 2

including sex, RAID physical well-being, RAID emotional well-being and RAID pain. Model 3

including sex and RAID physical well-being. Mean changes, 95% confidence intervals and p -

values, including both women and men

Table 4 Predictors of fatigue: Mean changes, 95% confidence intervals and *p*-values, including both women and men

Predictor	Effect type	Step 1[1] B (95%CI)	p-value	Step 2[2] B (95%CI)	p-value	Final model[3] B (95%CI)	p-value
DAS28	Main effect	0.06 (-0.26, 0.38)	,706	-	-	-	-
	Effect change: BL -> 3 months	0.34 (-0.09, 0.76)	,126	-	-	-	-
	Effect change: BL -> 6 months	0.13 (-0.32, 0.59)	,569	-	-	-	-
	Effect change: BL -> 12 months	-0.02 (-0.46, 0.43)	,937	-	-	-	-
Age	Main effect	-0.04 (-0.08, 0)	,081	-	-	-	-
	Effect change: BL -> 3 months	0 (-0.04, 0.04)	,856	-	-	-	-
	Effect change: BL -> 6 months	0.03 (-0.02, 0.07)	,234	-	-	-	-
	Effect change: BL -> 12 months	0.02 (-0.03, 0.06)	,450	-	-	-	-
Sex	**Main effect**	**1.49 (0.54, 2.43)**	**,003**	**1.27 (0.34, 2.2)**	**,013**	**1.29 (0.36, 2.23)**	**,010**
	Effect change: BL -> 3 months	-0.56 (-1.45, 0.34)	,235	0.09 (-0.17, 0.34)	,524	0.12 (-0.08, 0.32)	,255
	Effect change: BL -> 6 months	-1.13 (-2.05, -0.21)	,019	0.03 (-0.16, 0.22)	,802	-0.57 (-1.46, 0.32)	,220
	Effect change: BL -> 12 months	**-0.58 (-1.52, 0.36)**	**,236**	**0.04 (-0.16, 0.25)**	**,687**	**-1.19 (-2.11, -0.27)**	**,015**
RAID physical well-being	Main effect	0.2 (0.01, 0.39)	,047	-0.69 (-1.56, 0.18)	,144	-0.38 (-1.31, 0.55)	,440
	Effect change: BL -> 3 months	0.13 (-0.13, 0.38)	,336	-1.15 (-2.03, -0.28)	,016	0.19 (-0.06, 0.45)	,155
	Effect change: BL -> 6 months	0.04 (-0.21, 0.28)	,773	-0.38 (-1.27, 0.5)	,423	0.14 (-0.11, 0.4)	,284
	Effect change: BL -> 12 months	-0.06 (-0.32, 0.2)	,649	0.15 (-0.19, 0.49)	,418	0.02 (-0.25, 0.28)	,912
RAID emotional well-being	Main effect	0.14 (-0.03, 0.31)	,113	-0.15 (-0.54, 0.23)	,464	-	-
	Effect change: BL -> 3 months	0.16 (-0.08, 0.39)	,199	-0.12 (-0.52, 0.27)	,561	-	-
	Effect change: BL -> 6 months	0.31 (0.07, 0.56)	,016	0.09 (-0.21, 0.39)	,591	-	-
	Effect change: BL -> 12 months	0.02 (-0.2, 0.23)	,882	0.39 (0.09, 0.68)	,015	-	-
RAID pain	Main effect	0.1 (-0.08, 0.29)	,283	0.04 (-0.26, 0.35)	,782	-	-
	Effect change: BL -> 3 months	0.08 (-0.17, 0.32)	,540	0.01 (-0.25, 0.28)	,919	-	-
	Effect change: BL -> 6 months	0.14 (-0.1, 0.38)	,257	0.11 (-0.23, 0.45)	,541	-	-
	Effect change: BL -> 12 months	0.08 (-0.19, 0.35)	,552	0.14 (-0.18, 0.46)	,422	-	-

[1]Model with one predictor (main effect and interaction).[2]Model including sex, RAID physical well-being, RAID emotional well-being, RAID pain.[3]Model including sex, RAID physical well-being

BL, baseline; CI, confidence interval; DAS28, Disease Activity Score of 28 joints; RAID, Rheumatoid Arthritis Impact of Disease