Improvement of fatigue in patients with rheumatoid arthritis treated with biologics: relationship with sleep disorders, depression and clinical efficacy. A prospective, multicentre study

M. Genty[1], B. Combe[1], M. Kostine[2], E. Ardouin[3], J. Morel[1], C. Lukas[1]

[1]Department of Rheumatology, Lapeyronie Hospital, Montpellier University, France;
[2]Department of Rheumatology, Bordeaux University Hospital, France;
[3]Department of Rheumatology, Limoges University Hospital, France.

Abstract

Objective

To assess predictive factors of improvement in related fatigue in rheumatoid arthritis (RA) patients newly receiving biologic therapy, and specifically the influence of the improvement of the quality of sleep.

Methods

We conducted a multicentre prospective study in RA patients requiring initiation or change of biologic therapy. The improvement in fatigue, sleep disorders and depression was assessed respectively by the FACIT fatigue scale, Spiegel scale and Beck Depression Inventory at inclusion (M0) and 3 months (M3) after the beginning of treatment. Potential confounders were assessed and adjusted for. The association between evolution of fatigue and other characteristics were evaluated by univariate (χ^2) then multivariate (logistic regression) analyses.

Results

We followed-up 99 patients. FACIT scores at M0 revealed frequently reported fatigue: 89%, high prevalence of sleep disorders: 95% and depression: 67%. Improvement of fatigue, sleep quality and depression was observed in 58.6%, 26.3% and 34.3% of cases, respectively. Significant factors associated with an improvement in fatigue at M3 were an elevated sedimentation rate at M0 (OR=5.7[2.0-16.0], p=0.001) and a favourable EULAR response at M3 (OR=4.8[1.6-14.8], p=0.006). Furthermore, a number of swollen joints > 5 at baseline (OR=0.3 [0.1-0.8]) and the use of psychotropic drugs (OR=0.2[0.04-0.9]) were predictive of an absence of improvement in fatigue. No significant association with the improvement in sleep disorders could be demonstrated.

Conclusion

Fatigue in RA is improved by effective treatment, via decreasing disease activity. Improvement of sleep disorders is more likely a surrogate of therapeutic efficiency rather than an independent outcome.

Key words

fatigue, arthritis rheumatoid, sleep disorders, biologics, depression

Marlène Genty, MD
Bernard Combe, MD, Prof.
Marie Kostine, MD
Elodie Ardouin, MD
Jacques Morel, MD, Prof.
Cédric Lukas, MD, Prof.

Please address correspondence to:
Prof. Cédric Lukas,
Département de Rhumatologie,
Hôpital Lapeyronie,
371, avenue du Doyen Gaston Giraud,
34295 Montpellier Cedex 5, France.
E-mail: c-lukas@chu-montpellier.fr

Received on February 18, 2016; accepted in revised form on July 11, 2016.

Competing interests: none declared

Introduction

The functional burden of disease in patients affected by rheumatoid arthritis (RA), mainly caused by pain and swelling of joints, is often worsened by extra-articular manifestations, among which fatigue remains the most frequently reported and probably the consequence of the disease the most difficult to deal with (1). It is usually reported that 40 to 90% of RA patients complain (2, 3) about fatigue, and they often consider it as an important symptom in terms of both severity and impact on daily life (4). Predicting which RA patient will be most concerned remains a difficult challenge, as the severity of fatigue experienced by a patient is a subjective appreciation, and can be entirely independent from the other domains of the disease like activity, severity or treatments.

Furthermore, efficiently treating fatigue by itself is illusory, and it is acknowledged that most efforts must be aiming at disentangling which underlying pathologic -and potentially treatable- processes are involved in the development and persistence of fatigue in a patient. Indeed, different and sometimes independent characteristics like disease activity, disability, pain or depression or the treatments themselves are known to potentially generate and worsen fatigue (3, 5-10). However whether improvement of those respective aspects results or is associated with a decrease in fatigue remains unknown.

One of the characteristics of the disease activity, the pain at rest and consequently the resulting sleeping disorders could intuitively be related to fatigue in a patient. Over the past few decades, several observational studies have shown a statistically significant association between the severity of fatigue in RA and sleep disorders (11), but concluding in a direct causal relationship between these two elements is hazardous, because they could also be considered correlated manifestations of a single underlying causative process. Indeed, patients describe this fatigue as persistent over time and only slightly improved by rest (1).

In terms of therapeutic approach, most biologics have shown overall efficacy on reported fatigue, yet with a limited effect in a systematic review (12), and whether this is due to overall improvement of disease or to more specific aspects of the disease like sleep disorders due to overnight pain and awakenings remains unknown.

To date, scarce multidimensional models of fatigue have been published (13, 14), conceptualising the different aspects and origins of the concept of fatigue but none has investigated which factors could predict an improvement or persistency of fatigue in treated patients. Therefore, in view of these etiologic and therapeutic difficulties, it is crucial to identify modifiable risk factors that can impact on evolution of fatigue in RA.

We therefore prospectively examined the association between baseline characteristics of patients and disease and further evolution of reported fatigue in RA patients newly receiving biologic therapy, and more specifically the potential influence of the improvement in sleep disorders.

Methods

Study population

Eligibility criteria for study participants were: 1. having a diagnosis of RA, with fulfillment of the 2010 ACR/EULAR criteria (15); 2. being over the age of 18 at the time of inclusion; 3. requiring the initiation of a new biologic treatment, either because of the severity and activity of their disease or because of their dependence on a high dose of corticoids even if their disease activity is low; 4. having no contra-indication to the use of a biologic therapy.

Patients with active endocrinopathy, sleep apnea or unstable diagnosed psychiatric disease were excluded in order to limit interference with fatigue of other causes than RA disease. Therefore, a thyroid stimulating hormone (TSH) rate stable with normal triiodothyronine (T3) and thyroxine (T4) permitted inclusion, as well as patients with psychotropic drugs unmodified for 3 months.

Finally, also fibromyalgic patients were excluded. Patients were considered fibromyalgic only if the prescriber wrote it in the medical record.

Study design

This multicentre (French University Hospitals of Bordeaux, Clermont-Ferrand Limoges, Montpellier and Toulouse) prospective study included consecutive RA patients requiring initiation or change of biologic therapy, meeting study inclusion criteria and having given their informed consent. The study was performed from December 2011 up to March 2013, in accordance with the standards of the responsible local committee.

All patients underwent the same investigations at inclusion or month zero (M0) and 3 months (M3) after the beginning of biologic treatment: medical history (gender, age, duration of disease, smoking status, disease-modifying anti-rheumatic drugs (DMARDs) already used and currently prescribed, intake of corticosteroids, psychotropic drugs and analgesics); physical examination (numbers of tender and swollen joints, visual analogue score (VAS) for pain, VAS for disease activity, disease activity score calculated with sedimentation rate (DAS28 ESR), Health Assessment Questionnaire (HAQ); biologic tests (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), presence or absence of anti-citrulinated proteins (ACPA), rheumatoid factor (RH), haemoglobin level, TSH and iron balance).

Fatigue, sleep disorders and depression were assessed by the means of 3 validated different scales, at both time points M0 and M3, in order to numerically assess their baseline values and change over the 3 months after initiation of biologic treatment.

Fatigue was assessed by the FACIT fatigue scale (16). Sleep disorders and evaluation of depression were respectively evaluated by the Spiegel scale (17) and the shortened Beck Depression Inventory (BDI) (13 items) (18-20).

These 3 scales are self-administered questionnaires, graduated respectively from 0 (severe fatigue) up to 52 (no fatigue) for the FACIT scale, 0 (bad sleep quality) up to 30 (good sleep quality) for the Spiegel scale and 0 (no depression) up to 39 (severe depression). An increase of three or four point in FACIT fatigue scale is clinically relevant to consider an fatigue improvement (16), and we used a cut-off value of 4 to consider a change present. Moreover, general healthy population has score ≥44/52. Using Spiegel scale, sleep is considered normal if the score is between 25 and 30, disturbed between 15 and 24 and pathologic below. The shortened BDI has a discriminant validity (20). The cut-off to distinguish the severity of depression symptoms is this: 0–3 no depression, 4–7 mild depression, 8–15 moderate depression and 16-39 major depression.

Primary objective

The primary objective was to evaluate the potential influence of improvement of sleep disorders on reported fatigue in RA patients newly receiving biologic therapy.

The secondary objectives were to assess the overall efficacy of biologics on fatigue and evaluate potential predictive factors on improvement in reported fatigue, besides sleep disorders.

Sample size determination

Number needed to treat (NNT) is a key notion in clinical research, less in epidemiology. A good practice is to compute this NNT in a virtual therapeutic trial, given that the calculation is not rigorously possible in a situation of multivariate analysis. In our situation, we consider sleep improvement as the treatment and degradation of fatigue as the outcome.

For a power of 80%, with an alpha risk of 5%, the NNT was 78.

To estimate the effect size, we relied on the data from the literature (8, 21-25).

- 28% of 316 patients treated with rituximab improved their fatigue
- 31% of 222 patients treated with etanercept improved their fatigue
- 37% of 30 patients treated with anti-TNF-α improved their fatigue
- 49% of 898 patients treated with certolizumab improved their fatigue
- 62% of 610 patients treated with tocilizumab improved their fatigue
- 53% of 13 patients treated with tocilizumab improved their sleep

We recruited 100 patients to allow for patients dropping out when treatment had started.

Statistical analysis

Analyses were conducted with software SPSS V.15.

Potential confounders like presence of anaemia, thyroid dysfunctions, iron deficiency, psychotropic or corticosteroids medications were assessed and adjusted for. The association between evolution of fatigue (improvement/no improvement according to predefined validated cut-offs (16)) and other characteristics were evaluated by univariate (Chi2) then multivariate (logistic regression) analyses, using a significance level of 0.05. Numeric values (except for those like DAS28 with a validated relevant cut-off) were dichotomised according to the observed median value.

Results

Demographic and clinical data for RA patients at inclusion (M0)

• *Characteristics of the population*

Ninety-nine RA patients were included and followed up in the study.

The mean ± SD age of the patients was 58.2±12.1 years, of which 72.7% were women. The mean duration of disease was 11.3±9.6 years, ranging from less than 1 year to 40 years.

Approximatively half of the patients (52.2%) had never been smoking. Among smokers, 25.6% were in smoking-cessation and 22.2 % were currently active smokers.

• *Characteristics of the disease*

Regarding the characteristics of the disease, 79.8% and 78.8% were RF and ACPA positive (14% double-seronegative) respectively; 72% had radiographic erosions at inclusion.

Disease activity according to DAS28 ESR was high (>5.1) in 51%, moderate (3.2–5.1) in 39% and low (≤3.2) in 6% of the patients, respectively. Table I presents other clinical and biological characteristics of the RA patients at baseline.

Treatments

With regard to the treatments, 50.5% of patients were receiving methotrexate before inclusion, 53% prednisone (mean dose: 5.9 mg/day) and 14% psychotropic drugs (benzodiazepines and SSRIs mainly). Most patients required daily use of analgesics (71%), with

Table I. Clinical and biological characteristics of the RA patients at inclusion.

	unit	number of patients	mean	standard deviation	median	min	max
Age	year	99	58.2	12.1	61	18	84
Disease duration	year	99	11.3	9.6	9.0	0.0	40.0
HAQ-DI		66	1.45	0.81	1.56	0	3
Haemoglobin	g/dL	99	12.9	1.4	12.9	9.5	15.9
Iron	µmol/l	95	13.8	10.4	11.4	2.0	84.0
Ferritin	µg/ml	96	165.9	149.1	118.0	7.0	635.0
TSH	mUI/l	96	1.65	1.08	1.47	0.03	8.09
Rheumatoid factor		99	313	520	122	0.0	3.300
ACPA		97	308.6	511.7	250.0	0.0	3.200

HAQ-DI: Health Assessment Quality Disability Index; TSH thyroid stimulating hormone; ACPA: antibodies against cyclic citrullinated peptides; min: minimum; max: maximum.

23% and 47% taking acetaminophen and grade II analgesics, respectively. One patient was receiving morphine.

The biologic initiated in this study was the first line biologic in 37.7% of patients, for 17.2% of them it was the second biologic, the third for 21.2%, the fourth for 8.1%, the fifth for 2%, up to the sixth biologic for one patient. Anti-TNF drugs were started in 50 patients, other biologics in 49 patients (tocilizumab n=19, abatacept n=16, rituximab n=14).

• *Patient-reported outcomes on fatigue sleep quality and depression*

The included patients frequently reported fatigue: 89% had scores more severe than expected in general healthy population (<44/5) (26). The mean FACIT scores at inclusion was 27.9/52 SD (range of observed values: 6–50).

A high prevalence (95%) of sleep disorders was also revealed: abnormal in 68% of patients, pathologic in 27%. Only 5% of patient had a normal sleep quality according to the Spiegel scale.

Only one-third of included patients did not exhibit depressive features: 67% reported various levels of depression (mild 31%, moderate 24%, severe 11%) according to the shortened BDI scale.

Demographic and clinical data for RA patients after 3 months of biologic therapy (M3)

Table II shows the clinical and biological characteristics of the RA patients which changed between M0 and M3.

• *Characteristics of the disease*

After three month of biologics treatment, clinical response was beneficial in most patients: 36% showed good EULAR response, 40% moderate, with however 24% having no relevant therapeutic response.

• *Treatments*

Fifty-seven percent of patients were still on prednisone (with a reduced mean dose of 3.8 mg/day) and 15% on psychotropic drugs. Compared to 29% before treatment, 44% no longer require daily use of analgesics, although 18% and 37% were still receiving acetaminophen and grade II analgesics, respectively. No patient took morphine.

• *Evolution of patient-reported outcomes at 3 months*

Improvement of fatigue, sleep quality and depression according to predefined cut-offs was observed in 58.6%, 26.3% and 34.3% of patients respectively.

Table II. Changes in parameters between M0 and M3.

	unit	number of patients		mean		standard deviation		median		minimum		maximum	
		M0	M3	M0	M3	M0	M3	M0	M3	M0	M3	M0	M3
Tender joints		99	99	8.4	3.8	7.7	5.1	6.0	2.0	0.0	0.0	28.0	24.0
Swollen joints		99	99	6.2	2.4	4.9	3.3	5.0	2.0	0.0	0.0	23.0	23.0
Pain (VAS)	/10	99	98	56.9	34.0	22.4	22.2	60.0	30.0	0.0	0.0	100.0	90.0
Patient global (VAS)	/10	99	99	61.6	35.7	20.9	23.0	60.0	30.0	0.0	0.0	100.0	100.0
DAS28 ESR		99	99	5.1	3.41	1.4	1.42	5.1	3.25	2.4	0.48	8.2	8.2
ESR	mm/1H	99	99	35.2	20.0	28.0	19.8	32.0	13.0	2.0	2.0	127.0	100.0
CRP	mg/L	99	99	21.3	9.8	21.9	22.3	14.0	4.0	0.0	0.0	98.0	190.0

VAS: visual analogue scale; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Table III. Outcome of patient-reported outcomes at 3 months.

	number of patients		mean		standard deviation		median		minimum		maximum		normal condition (%)		slight disturbance (%)		moderate disturbance (%)		severe disturbance (%)	
	M0	M3	M0	M3	M0	M3	M0	M3	M0	M3	M0	M3	M0	M3	M0	M3	M0	M3	M0	M3
Fatigue (FACIT)	99	99	27.9	33.8	11.0	11.3	28.0	36.0	6.0	10.0	50.0	52.0	11	25						
Sleep (Spiegel)	99	99	17.5	19.5	4.6	4.4	18.0	20.0	8.0	7.0	27.0	28.0	5.0	12.1	67.7	75.7			27.3	12.1
Depression (Beck)	99	99	7.2	5.6	6.0	5.6	5.0	4.0	0.0	0.0	27.0	35.0	33.0	44.4	31.0	30.3	24.0	20.2	12.0	5.1

Prevalence of sleep disorders was still high (88%; abnormal 76%, pathologic 12%), as well as depression (mild, 30%; moderate, 20%; severe, 5%) (Table III).

Univariate analyses

Unexpectedly, no association with the improvement in sleep disorders could be demonstrated: of 29 patients showing relevant improvement in sleep quality, 17 (58.6%) considered their level of fatigue had decreased, while exactly the same proportion 41/70 (58.6%) among those without correction of sleep disorders did so (p=0.9).

The risk of improving fatigue depending on each variable are presented in Table IV.

With univariate analyses, several variables were significantly associated with an improvement in fatigue at 3 months including: pain (VAS) >60mm (p=0.039), DAS28>5.1 at M0 (p=0.046), EULAR response at M3 (p=0.002) and abnormal baseline C-reactive protein (p=0.004) and sedimentation rate at M0 (p=0.003).

Multivariate analysis

Multivariate analysis was conducted with all original variables except anaemia and tobacco use because missing data were frequent (12 patients) and no relevant association in univariate analyses have been observed.

Results of the multivariable analysis are shown in Table V.

Significant factors associated with an improvement in fatigue at 3 months after controlling for the covariates listed above were an elevated sedimentation rate at M0 and a favourable EULAR response at M3. Furthermore, a number of swollen joints >5 at baseline and the use of psychotropic drugs were predictive of an absence of relevant improvement in fatigue.

Table IV. Association between improvement of asthenia and different variables.

		n/N patients with improvement in FACIT	p-value
Age (year)	<61	32/55 (58.2%)	0.927
	> 61	26/44 (59.1%)	
Sex	male	17/27 (63.0%)	0.588
	female	41/72 (56.9%)	
Disease duration (year)	<9	30/50 (60.0%)	0.773
	>9	28/49 (57.1%)	
Smokers	no	41/70 (58.7%)	0.281
	yes	90/20 (45.0%)	
Improvement in sleep	no	41/70 (58.6%)	0.996
	yes	17/29 (58.6%)	
Improvement in depression	no	20/39 (51.3%)	0.234
	yes	38/60 (63.3%)	
Tender joints at M0	≤6	32/56 (57.1%)	0.739
	>6	26/43 (60.5%)	
Swollen joints at M0	≤5	34/54 (63.0%)	0.333
	>5	24/45 (53.3%)	
Pain at M0 (VAS mm)	≤60	29/58 (50.0%)	0.039
	>60	29/41 (70.7%)	
Moderate activity at M0	≤3.2	3/10 (30.0%)	0.087
	>3.2	55/89 (61.8%)	
Severe activity at M0	≤5.1	25/51 (49.0%)	0.046
	>5.1	33/48 (68.8%)	
EULAR response	no	7/23 (30.4%)	0.002
	yes	51/76 (67.1%)	
Erosion at M0	no	15/27 (55.6%)	0.747
	yes	42/71 (59.2%)	
RF + or ACPA +	no	10/14 (71.4%)	0.293
	yes	48/85 (56.5%)	
Abnormal CRP at M0	no	11/30 (36.7%)	0.004
	yes	47/69 (68.1%)	
Abnormal ESR at M0	no	18/43 (41.9%)	0.003
	yes	40/56 (71.4%)	
Steroids at baseline	no	27/46 (58.7%)	0.984
	yes	31/53 (58.5%)	
Methotrexate at baseline	no	28/49 (57.1%)	0.773
	yes	30/50 (60.0%)	

M0: at baseline; VAS: visual analogue scale; RF: rheumatoid factor; ACPA: antibodies against cyclic citrullinated peptides; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

Discussion

Fatigue is a frequent aspect of the disease in RA, considered as frequent and severe as pain from the patient perspective, especially in periods of active disease (flares or persistent activity) (10). Therefore OMERACT (Outcome Measures in Rheumatology) suggested fatigue should be a therapeutic priority for patients and should be measured in all clinical trials about RA (27) (28) in order to continuously improve quality care for patients.

Sleep disturbances, also common in rheumatoid arthritis (29), have been associated with an increased prevalence of fatigue (10, 30, 31) but no study could demonstrate thus far that improvement in sleep quality would result in a decrease in fatigue.

The main aim of this study was to evaluate potential predictive factors of improvement in reported fatigue in RA patients, and more specifically the potential influence of the improvement in sleep disorders. Since most biologics are efficient on reported fatigue (12), we performed our study in patients newly receiving biologic therapy, with the objective of disentangling respective influences of disease activity and others investigated factors, especially reported sleep quality.

This study assessed fatigue by the means of a validated scale (27). The FACIT fatigue scale is a short and simple self-reported questionnaire, well described in published reports (16) and considered to have a good sensitivity

Table V. Variables significantly associated with asthenia improvement in the multivariate analysis.

Variables	OR	Confidence Interval 95% lower limit - upper limit	*p*-value
Swollen joints >5 at M0	0.254	[0.085;0.753]	0.014
EULAR response	4.803	[1.562;14.766]	0.006
Use of psychotropics at M0	0.196	[0.043;0.905]	0.037
Abnormal sedimentation rate at M0	5.656	[2.001;15.985]	0.001

to change. Regarding the assessment of fatigue, Wolfe (32) reviewed available fatigue scales of suitable length or previously used for rheumatic diseases and concluded that the fatigue measure (VAS) was just as suitable for a simple assessment of fatigue as more extensive scales. However, when it is of interest, a greater understanding of fatigue may be expected by evaluating and comparing different domains of fatigue, thus requiring a multi-domain fatigue instrument like the FACIT fatigue scale.

The choice of Spiegel scale and shortened BDI is also criticisable, as they are also respectively one of several available instruments designed to assess sleep disorders and depression, but both were chosen because they have formerly been shown to have good psychometric properties (17, 20, 33).

Our results suggest that fatigue in RA is frequent (89%) and even more severe than reported in a population of patients suffering from oncologic conditions (34). Sleep disorders were also extremely frequent in our study population (94%) as well as depression (66%), and without obvious differences in observed frequencies across the 4 centres where patients have been recruited (data not shown). Although apparently striking, our results remain in accordance with previously published studies (11, 16, 35), except however for the rate of depressed patient which is usually lower, reported from 13% to 45% in others studies (36-40). This remarkably high prevalence of patient-reported outcomes (PROs) globally revealing bad health assessments might be due to the severity of our population, as 71% of patients had erosive disease, and a substantial part of the patients were starting a second or third-line biologic therapy.

After three months of treatment, we could observe 76% patients having a favourable clinical response according to EULAR definition, and an improvement of fatigue according to predefined cut-offs in 58.6% of patients, which is somewhat higher than what is reported in other studies (improvement of fatigue usually between 28 and 62% (8, 21-24). A potential explanation of this inconsistency might be related to the scale used across different studies, as well as the open design and use of efficient drugs in our observational study. However, if we focus on clinical trials having used FACIT fatigue scale to assess fatigue in a RA population treated by biologics, we can observe a more limited improvement in absolute values in our study (+5.9 *vs*. +8.5;+8.6 and +9.1 in studies by Cohen, Smolen and Weinblatt *et al*. (41–43)). Another potential reason for this is an earlier data collection (3 months *vs*. 6 months in other studies), knowing that a further improvement can be expected in a substantial part of patients.

We were not able to identify an association between change in sleep disorders and related fatigue, though it was our primary outcome. Most previous studies have examined fatigue or improvement in fatigue according to sleep disorders at baseline, but not to their change. To our knowledge, only one recent study (25) based on a limited number (n=13) of patients treated by tocilizumab has examined fatigue and sleep disorders improvement with a longitudinal follow-up: despite an improvement in sleep quality in 53% of the population (versus 26% in our trial) and a follow-up of 6 months, they found similar results, namely no significant link between these two aspects of the disease. The absence of association might also be due to a lack of power in the statistical analysis, and further studies with more patients are needed to further investigate the question, although the exactly equal observed crude proportions of patients with and without improvement in sleep quality in the subsets of patients having or not having improved fatigue make this assumption unlikely.

We found that patients with a higher sedimentation rate before treatment are significantly more likely to improve their fatigue, as well as patients who have a favourable clinical response (by EULAR definition) after three months of biologics.

The validity of our results is supported in multivariate analysis by the strong associations between the improvement of FACIT scale and the abnormal sedimentation rate at inclusion, or the clinical response at M3 (odds ratio ≈ 5). This apparently high value remains however a relatively unprecise appreciation, with a quite large confidence interval, due to the limited number of participants that were included in our study. Analogous results were already reported in several studies (5, 44-46), confirming that treating disease activity rapidly and efficiently is essential (3), not only for functional prognosis but also for other aspects of the disease and its impact on quality of life in a patient.

We also found in multivariate analysis a significant association between the number of swollen joints and the change in fatigue. Indeed, a higher disease activity is consensually considered a bad prognostic factor, and the analysis revealed a significant association (odds ratio = 0.254), implying that a RA patient with six or more swollen joints at inclusion is four times less likely to improve his fatigue despite introduction of biologic therapy. Those results are in agreement with previously reported data (8, 31) with higher biologic markers and thus disease activity having a substantial impact on fatigue insufficiently reverted after a period of three months, a too short time to observe an optimal and stabilised response in this population with severe disease and high disease activity.

Finally, no significant association between depression and change in fatigue was found, whereas many studies pre-

viously reported a relationship between those features (5, 8, 47, 48). Again, this could be explained by our too short time of analysis.

However in multivariate analysis taking psychotropic treatment was associated with a decreased likelihood of showing an improvement of fatigue (odds ratio = 0.196). This result is more consistent because depressed patients receiving drug therapy have usually more severe depressive disease than untreated depressed patients. As fatigue is a clear symptom of depression, these patients usually feel more tired and improvement of their fatigue is less likely to occur or be detected by a self-reported questionnaire (46). These data probably suggest a psychiatric follow-up should be discussed in a patient reporting persistent fatigue despite apparently good therapeutic response from the "strictly rheumatologic" point of view.

Our study has several strengths, including the prospective design which reduces biases inherent to cross-sectional studies, the relatively large number of patient (n=99) and the exhaustivity in collected data. Moreover, using a multidomain fatigue instrument like FACIT fatigue permits the evaluation of different domains of fatigue and above all to perform a dynamic analysis of the latter. This measure remains innovative.

There are, however, several limitations. Firstly, our population of patients has substantially severe disease, as they were requiring a new biologic, but for this reason cannot be considered representative of the whole RA population. Secondly, we can regret the lack of a control group and above all the short time of follow-up. This probably explains some divergences in results with other studies, as previously exposed.

We believe the implications of this study in routine clinical rheumatology practice are twofold. First, our results indicate that improvement of sleep disorders is more likely a "surrogate marker" of therapeutic efficiency rather than an independent outcome. Then, these results do not encourage a referral of our persistently and refractory asthenic patients to a dedicated sleep centre, but preferably to a psychiatric evaluation in order to optimise the use of psychotropic treatment or therapies in case persistent fatigue is observed in a patient despite favourable response to treatment regarding his disease activity. Second, the analysis we describe points out the efficiency of biologics in treating RA extra-articular symptoms, as a substantial part of them do show a parallel improvement in reported mood or sleep quality, which is of course yet another argument for gaining patient adherence.

In summary, our results suggest that biologics may altogether improve fatigue, sleep quality and depression in patients with RA, but it seems unlikely that the reported amelioration in fatigue can be predominantly related to a better sleep quality that is expected by controlling aspects of disease activity like pain at night and awakenings in patients. Whether this effect is directly associated with a central role of biologics on each symptoms' regulation or is merely due to improvement in disease activity warrants further investigation. In any event, fatigue and sleep disturbance assessments should be included in evaluation of the efficacy of treatments in patients with RA, in order to further investigate these important aspects of disease with clearly reported impact on quality of life of the patients.

Significance and innovations

- Fatigue and sleep disorders are frequent among RA patients
- These patient-reported outcomes are improved after 3 months of biotherapy
- The more disease activity decreases, the more fatigue is improved.

References

1. MAYOUX-BENHAMOU M-A: Fatigue and rheumatoid arthritis. *Ann Readapt Med Phys* 2006; 49: 301-4, 385-8.
2. REPPING-WUTS H, VAN RIEL P, VAN ACHTERBERG T: Fatigue in patients with rheumatoid arthritis: what is known and what is needed. *Rheumatology* (Oxford) 2009; 48: 207-9.
3. VAN STEENBERGEN HW, TSONAKA R, HUIZINGA TW, BOONEN A, VAN DER HELM-VAN MIL AH: Fatigue in rheumatoid arthritis; a persistent problem: a large longitudinal study. *RMD Open* 2015; 1: e000041.
4. CARR A, HEWLETT S, HUGHES R *et al*.: Rheumatology outcomes: the patient's perspective. *J Rheumatol* 2003; 30: 880-3.
5. HUYSER BA, PARKER JC, THORESON R, SMARR KL, JOHNSON JC, HOFFMAN R: Predictors of subjective fatigue among individuals with rheumatoid arthritis. *Arthritis Rheum* 1998; 41: 2230-7.
6. IBN YACOUB Y, AMINE B, LAATIRIS A, WAFKI F, ZNAT F, HAJJAJ-HASSOUNI N: Fatigue and severity of rheumatoid arthritis in Moroccan patients. *Rheumatol Int* 2012; 32: 1901-7.
7. MANCUSO CA, RINCON M, SAYLES W, PAGET SA: Psychosocial variables and fatigue: a longitudinal study comparing individuals with rheumatoid arthritis and healthy controls. *J Rheumatol* 2006; 33: 1496-502.
8. POLLARD LC, CHOY EH, GONZALEZ J, KHOSHABA B, SCOTT DL: Fatigue in rheumatoid arthritis reflects pain, not disease activity. *Rheumatology* (Oxford) 2006; 45: 885-9.
9. RIEMSMA RP, RASKER JJ, TAAL E, GRIEP EN, WOUTERS JM, WIEGMAN O: Fatigue in rheumatoid arthritis: the role of self-efficacy and problematic social support. *Br J Rheumatol* 1998; 37: 1042-6.
10. WOLFE F, HAWLEY DJ, WILSON K: The prevalence and meaning of fatigue in rheumatic disease. *J Rheumatol* 1996; 23: 1407-17.
11. BELZA BL, HENKE CJ, YELIN EH, EPSTEIN WV, GILLISS CL: Correlates of fatigue in older adults with rheumatoid arthritis. *Nurs Res* 1993; 42: 93-9.
12. CHAUFFIER K, SALLIOT C, BERENBAUM F, SELLAM J: Effect of biotherapies on fatigue in rheumatoid arthritis: a systematic review of the literature and meta-analysis. *Rheumatology* (Oxford) 2012; 51: 60-8.
13. HEWLETT S, CHALDER T, CHOY E *et al*.: Fatigue in rheumatoid arthritis: time for a conceptual model. *Rheumatology* (Oxford) 2011; 50: 1004-6.
14. NICASSIO PM, ORMSETH SR, CUSTODIO MK, IRWIN MR, OLMSTEAD R, WEISMAN MH: A multidimensional model of fatigue in patients with rheumatoid arthritis. *J Rheumatol* 2012; 39: 1807-13.
15. LE LOËT X, NICOLAU J, BOUMIER P *et al*.: Validation of the 2010-ACR/EULAR -classification criteria using newly EULAR-defined erosion for rheumatoid arthritis on the very early arthritis community-based (VErA) cohort. *Jt Bone Spine Rev Rhum* 2015; 82: 38-41.
16. CELLA D, YOUNT S, SORENSEN M, CHARTASH E, SENGUPTA N, GROBER J: Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. *J Rheumatol* 2005; 32: 811-9.
17. SPIEGEL R: Sleep and Sleepness in advanced age. In WEITZMAN ED (Ed.) *Advances in Sleep Research*, vol 5. Spectrum publications, MTP Press, Jamaica, 1981.
18. RICHTER P, WERNER J, HEERLEIN A, KRAUS A, SAUER H: On the validity of the Beck Depression Inventory. A review. *Psychopathology* 1998; 31: 160-8.
19. SCHOTTE CK, MAES M, CLUYDTS R, DE DONCKER D, COSYNS P: Construct validity of the Beck Depression Inventory in a depressive population. *J Affect Disord* 1997; 46: 115-25.
20. COLLET L, COTTRAUX J: [The shortened Beck depression inventory (13 items). Study of the concurrent validity with the Hamilton

scale and Widlöcher's retardation scale]. *L'Encéphale* 1986; 12: 77-9.
21. EMERY P, FLEISCHMANN R, FILIPOWICZ-SOSNOWSKA A *et al*.: The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. *Arthritis Rheum* 2006; 54: 1390-400.
22. MORELAND LW, GENOVESE MC, SATO R, SINGH A: Effect of etanercept on fatigue in patients with recent or established rheumatoid arthritis. *Arthritis Rheum* 2006; 55: 287-93.
23. STRAND V, MEASE P, BURMESTER GR *et al*.: Rapid and sustained improvements in health-related quality of life, fatigue, and other patient-reported outcomes in rheumatoid arthritis patients treated with certolizumab pegol plus methotrexate over 1 year: results from the RAPID 1 randomized controlled trial. *Arthritis Res Ther* 2009; 11: R170.
24. GOSSEC L, STEINBERG G, ROUANET S, COMBE B: Fatigue in rheumatoid arthritis: quantitative findings on the efficacy of tocilizumab and on factors associated with fatigue. The French multicentre prospective PEPS Study. *Clin Exp Rheumatol* 2015; 33: 664-70.
25. FRAGIADAKI K, TEKTONIDOU MG, KONSTA M, CHROUSOS GP, SFIKAKIS PP: Sleep disturbances and interleukin 6 receptor inhibition in rheumatoid arthritis. *J Rheumatol* 2012; 39: 60-2.
26. CELLA D, LAI J-S, CHANG C-H, PETERMAN A, SLAVIN M: Fatigue in cancer patients compared with fatigue in the general United States population. *Cancer* 2002; 94: 528-38.
27. KIRWAN JR, MINNOCK P, ADEBAJO A *et al*.: Patient perspective: fatigue as a recommended patient centered outcome measure in rheumatoid arthritis. *J Rheumatol* 2007; 34: 1174-7.
28. KIRWAN JR, HEWLETT S: Patient perspective: reasons and methods for measuring fatigue in rheumatoid arthritis. *J Rheumatol* 2007; 34: 1171-3.
29. DREWES AM, NIELSEN KD, HANSEN B, TAAGHOLT SJ, BJERREGÅRD K, SVENDSEN L: A longitudinal study of clinical symptoms and sleep parameters in rheumatoid arthritis. *Rheumatology* (Oxford) 2000; 39: 1287-9.
30. VAN HOOGMOED D, FRANSEN J, BLEIJENBERG G, VAN RIEL P: Physical and psychosocial correlates of severe fatigue in rheumatoid arthritis. *Rheumatology* (Oxford) 2010; 49: 1294-302.
31. REPPING-WUTS H, FRANSEN J, VAN ACHTERBERG T, BLEIJENBERG G, VAN RIEL P: Persistent severe fatigue in patients with rheumatoid arthritis. *J Clin Nurs* 2007; 16: 377-83.
32. WOLFE F: Fatigue assessments in rheumatoid arthritis: comparative performance of visual analog scales and longer fatigue questionnaires in 7760 patients. *J Rheumatol* 2004; 31: 1896-902.
33. UHER R, FARMER A, MAIER W *et al*.: Measuring depression: comparison and integration of three scales in the GENDEP study. *Psychol Med* 2008; 38: 289-300.
34. SPICHIGER E, MÜLLER-FRÖHLICH C, DENHAERYNCK K, STOLL H, HANTIKAINEN V, DODD M: Prevalence of symptoms, with a focus on fatigue, and changes of symptoms over three months in outpatients receiving cancer chemotherapy. *Swiss Med Wkly* 2011; 141: w13303.
35. POUCHOT J, KHERANI RB, BRANT R *et al*.: Determination of the minimal clinically important difference for seven fatigue measures in rheumatoid arthritis. *J Clin Epidemiol* 2008; 61: 705-13.
36. HYRICH K, SYMMONS D, WATSON K, SILMAN A, BSRBR CONTROL CENTRE CONSORTIUM: British Society for Rheumatology Biologics Register. Baseline comorbidity levels in biologic and standard DMARD treated patients with rheumatoid arthritis: results from a national patient register. *Ann Rheum Dis* 2006; 65: 895-8.
37. DICKENS C, MCGOWAN L, CLARK-CARTER D, CREED F: Depression in rheumatoid arthritis: a systematic review of the literature with meta-analysis. *Psychosom Med* 2002; 64: 52-60.
38. TEKAYA R, SAADI F, MAHMOUD I *et al*.: [Assessment of depression in rheumatoid arthritis: a cross sectional study on 60 patients]. *Presse Med* 2012; 41: e220-5.
39. KATZ PP, YELIN EH: Prevalence and correlates of depressive symptoms among persons with rheumatoid arthritis. *J Rheumatol* 1993; 20: 790-6.
40. ISIK A, KOCA SS, OZTURK A, MERMI O: Anxiety and depression in patients with rheumatoid arthritis. *Clin Rheumatol* 2007; 26: 872-8.
41. COHEN SB, EMERY P, GREENWALD MW *et al*.: Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum* 2006; 54: 2793-806.
42. SMOLEN JS, BEAULIEU A, RUBBERT-ROTH A *et al*.: Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet* 2008; 371: 987-97.
43. WEINBLATT ME, KEYSTONE EC, FURST DE *et al*.: Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum* 2003; 48: 35-45.
44. DHIR V, LAWRENCE A, AGGARWAL A, MISRA R: Fibromyalgia is common and adversely affects pain and fatigue perception in North Indian patients with rheumatoid arthritis. *J Rheumatol* 2009; 36: 2443-8.
45. THYBERG I, DAHLSTRÖM O, THYBERG M: Factors related to fatigue in women and men with early rheumatoid arthritis: the Swedish TIRA study. *J Rehabil Med Off J UEMS Eur Board Phys Rehabil Med* 2009; 41: 904-12.
46. TREHARNE GJ, LYONS AC, HALE ED, GOODCHILD CE, BOOTH DA, KITAS GD: Predictors of fatigue over 1 year among people with rheumatoid arthritis. *Psychol Health Med* 2008; 13: 494-504.
47. STEBBINGS S, HERBISON P, DOYLE TCH, TREHARNE GJ, HIGHTON J: A comparison of fatigue correlates in rheumatoid arthritis and osteoarthritis: disparity in associations with disability, anxiety and sleep disturbance. *Rheumatology* (Oxford) 2010; 49: 361-7.
48. STONE AA, BRODERICK JE, PORTER LS, KAELL AT: The experience of rheumatoid arthritis pain and fatigue: examining momentary reports and correlates over one week. *Arthritis Care Res* 1997; 10: 185-93.