

# Relationship between beliefs about medicines, adherence to treatment, and disease activity in patients with rheumatoid arthritis under subcutaneous anti-TNF $\alpha$ therapy

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**Objective:** In patients with rheumatoid arthritis (RA), nonadherence to treatment is often related to patients' beliefs and concerns regarding their medication. This study aimed to analyze the correlations regarding patients' medication beliefs, medication adherence, and objective measures of disease activity and safety in patients with RA established on subcutaneous (SC) anti-tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) therapy.

**Methods:** This Phase IV, noninterventional, non-drug-specific study enrolled patients with RA being treated with stable-dose SC anti-TNF $\alpha$  (adalimumab, etanercept, golimumab, and certolizumab pegol). At initial visit and 6 and 12 months later, patients completed the Beliefs about Medicines Questionnaire-Specific section, assessing perceptions of personal need for anti-TNF $\alpha$  therapy (anti-TNF $\alpha$ -Necessity) and concerns (anti-TNF $\alpha$ -Concerns), Medication Adherence Rating Scale (MARS), mean Disease Activity Score in 28 joints (DAS28), and other scales. Longitudinal data were analyzed by linear mixed models.

**Results:** A total of 460 patients were included. At initial visit, anti-TNF $\alpha$ -Necessity beliefs were high (mean  $\pm$  SD:  $4.3 \pm 0.55$ ) vs anti-TNF $\alpha$ -Concerns ( $2.8 \pm 0.78$ ). Medication adherence (MARS) was high ( $4.8 \pm 0.39$ ). All scores remained stable over the 1-year follow-up period. Anti-TNF $\alpha$ -Necessity beliefs and anti-TNF $\alpha$ -Concerns were not related to each other, but strongly correlated with medication adherence. While concerns worsened with disease activity, clinical status, and low quality of life, necessity beliefs remained unaffected.

**Conclusion:** In patients with RA established on stable-dose SC anti-TNF $\alpha$ , anti-TNF $\alpha$ -Necessity beliefs persistently outweighed anti-TNF $\alpha$ -Concerns, but both correlated with adherence. These findings may be of use in subsequent studies looking to predict adherence in patients starting treatment with SC anti-TNF $\alpha$ .

**Keywords:** arthritis, rheumatoid, biological therapy, tumor necrosis factor- $\alpha$ , medication adherence

## Plain-language summary

Rheumatoid arthritis (RA) is a chronic, long-term condition that causes pain, swelling, and stiffness in the joints. Tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) is one of the components of the immune system that causes joint inflammation in RA. A class of biological disease-modifying antirheumatic drugs binding to TNF $\alpha$  prevent it from causing the symptoms of RA. However, these drugs can have side effects. Worries about side effects are one of the reasons patients stop taking their medication. This study was designed to investigate the beliefs patients have about their RA medication over a year of taking it. At the beginning of the year, after 6 months, and at the end of the year, patients were asked questions about the necessity of taking their medication,

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their concerns about their medication, and how closely they adhered to their medication schedule. Patients' beliefs in the necessity of taking their medication outweighed their concerns regarding their medication throughout the year. While concerns grew as patients' disease and quality of life worsened, beliefs regarding the necessity of the treatment remained unaffected. Patients with a strong belief in the necessity of their medication and low concerns regarding their medication had higher treatment adherence.

## Introduction

Rheumatoid arthritis (RA) is a chronic multisystem disease with a global estimated prevalence of 0.35% in women and 0.13% in men.<sup>1</sup> Disease-modifying antirheumatic drugs (DMARDs) are important for the successful treatment of RA and can be classified into biological and nonbiological agents. Nonbiological DMARDs are widely used as first-line treatments for RA.<sup>2</sup> Current clinical practice guidelines recommend that clinicians start biological DMARDs if patients have suboptimal responses or are intolerant to one or two nonbiological DMARDs.<sup>2</sup> TNF $\alpha$  inhibitors are the largest group of biological DMARDs available to treat RA, and include adalimumab, etanercept, infliximab, golimumab, and certolizumab pegol.<sup>3,4</sup> Clinical trials of these medications consistently show excellent and comparable efficacy in improving clinical, functional, and radiological disease outcomes in patients with RA.<sup>5</sup>

The ultimate goal of DMARD treatment is to achieve remission.<sup>6</sup> With improving treatment strategies and an increasing number of available effective treatments, the proportion of patients reaching sustained remission has grown.<sup>5</sup> If complete remission cannot be achieved, the management goals are to control disease activity and maximize the patient's quality of life.<sup>7</sup>

In patients with RA who are established on anti-TNF $\alpha$  therapy, optimal patient outcomes depend on continued adherence to treatment. Studies across long-term conditions, including RA, show that adherence to treatment tails off over time.<sup>8,9</sup> It is estimated that in developed countries, adherence to long-term therapy for chronic illnesses averages 50%.<sup>8</sup> Nonadherence is often related to patients' beliefs regarding their medication, doubts about continued need, and concerns, even when patients are doing well on treatment.<sup>10</sup> A recent meta-analysis of 94 peer-reviewed studies spanning 18 countries and involving over 25,000 patients across 24 long-term conditions, including RA, consistently showed that nonadherence was related to doubts about medication necessity and concerns about potential adverse effects.<sup>11</sup> Investigating beliefs about medication is especially important

in RA, as it is a chronic disease, and patients are often advised to take potentially toxic drugs, including anti-TNF $\alpha$ .<sup>12</sup> Being able to identify patients with RA who are at risk of medication nonadherence could assist in the design and appropriately timed delivery of interventions to support optimal adherence, thus improving patients' health.<sup>12</sup>

There is a relative lack of information regarding the beliefs about anti-TNF $\alpha$  medication held by patients with RA who are established on anti-TNF $\alpha$  therapy. Only one cohort study has evaluated the beliefs about anti-TNF $\alpha$  medicines in patients with RA, and that study was restricted to patients receiving adalimumab.<sup>13</sup>

The aim of this study was to assess patients' beliefs about the necessity of and concerns regarding subcutaneous (SC) anti-TNF $\alpha$  therapy, and to analyze the correlations regarding medication beliefs and self-reported adherence to medication, objective measures of RA disease activity, and safety profiles over a 12-month follow-up period – in particular the correlation between belief in the necessity of treatment and the Disease Activity Score in 28 joints (DAS28), which was the study primary objective. It also purposed to identify factors influencing patients' beliefs and concerns regarding SC anti-TNF $\alpha$  therapy.

## Methods

### Study design

This was a 4-year, open-label, multicenter, Phase IV, noninterventional, non-drug-specific study conducted in patients with RA who were being treated with stable-dose SC anti-TNF $\alpha$  (adalimumab, etanercept, golimumab, and certolizumab pegol) prior to enrollment. Patients were recruited from 34 treatment centers in Belgium. The study was initiated on October 1, 2010, and the last patient was enrolled on December 30, 2013. The last follow-up visit took place on January 14, 2015. This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki, and the protocol adhered to the International Conference on Harmonisation Guidelines for Good Clinical Practice. Patients provided written informed consent before participating in the study. The protocol and informed consent documents were reviewed and approved by the institutional review board/independent ethics committee of the main institution (approving board AZ St Jan Brugge Oostende AV Ethics Committee, site number OG 065/049, date of approval August 6, 2010) and all other study centers before patient enrollment. This study was registered on [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01432366) (NCT01432366). Each participating study center is listed in Table S1.

At the initial study visit, patient demographics, duration of disease and treatment, and details of current medication and comorbidities were recorded, with several questionnaires and scales completed. Patients were assessed 6 and 12 months after the initial visit; the same questionnaires were completed and details of current medication and anti-TNF $\alpha$  and DMARD-related adverse events (AEs) were recorded at these follow-up visits. The primary objective of the study was to estimate the correlation between patient beliefs about the necessity of SC anti-TNF $\alpha$  and DAS after a 1-year follow-up.

The Beliefs about Medicines Questionnaire (BMQ) – Specific (BMQ-S11, © R Horne) comprises two scales: Specific-Necessity and Specific-Concerns.<sup>14</sup> The two scales together include eleven statements (five Necessity, six Concerns). Details regarding these can be found in the Supplementary material. Patients indicated their level of agreement with each statement on a 5-point Likert scale where 1 = strongly disagree and 5 = strongly agree. Both BMQ Necessity and Concerns scores were scaled to range from 1 to 5, with higher scores indicating stronger beliefs regarding medicine. The BMQ-Specific Necessity scale was used to assess patients' beliefs about their personal need for anti-TNF $\alpha$  therapy, with higher scores indicating stronger beliefs in medication necessity. The BMQ-Specific Concerns scale assessed patients' concerns about the potential adverse effects of using anti-TNF $\alpha$ , based on beliefs about the potential for harm now and in the future, and other concerns, such as being dependent on medicines. A Necessity-Concerns differential (NCD) was calculated as a numerical indicator of how each individual judged their personal need for anti-TNF $\alpha$  treatment relative to their concerns about taking it (range –4 to 4). Patients with missing BMQ items were excluded from all BMQ-score calculations.

The Medication Adherence Rating Scale (MARS) is a 5-item scale in which the patient himself/herself assesses how often he/she engages in nonadherent behavior. Each item is rated on a 5-point Likert scale where 1 = always and 5 = never. The total score is scaled to range from 1 to 5, with higher scores indicating higher levels of self-reported adherence.<sup>15</sup> Details regarding the items of the MARS can be found in the Supplementary material.

Other instruments used to document patients' health included the DAS28 (either erythrocyte-sedimentation rate or C-reactive protein could be used to calculate the DAS28 score, and the mean score was used if both were available for an individual patient),<sup>16</sup> DAS28 remission (score <2.6), Health Assessment Questionnaire (HAQ),<sup>17</sup> pain visual

analog scale (VAS),<sup>18</sup> fatigue VAS,<sup>19</sup> European Quality of Life-5 Dimensions (EQ5D),<sup>20</sup> physician and patient satisfaction regarding medication using a 0–100 VAS where 0 = absolutely not satisfied and 100 = extremely satisfied, and the Patient Health Questionnaire (PHQ-9) depression questionnaire (DQ).<sup>21</sup> Safety was categorized and scored as 1 = absence of AEs, 2 = presence of nonserious AEs only, and 3 = presence of one or more serious AEs for each patient.

## Patients

Patients were eligible to participate in this study if they were  $\geq 18$  years of age with a diagnosis of active RA. Patients had to be receiving stable SC anti-TNF $\alpha$  therapy for  $\geq 1$  consecutive year, to ensure that treatment was well established and disease activity well managed. SC anti-TNF $\alpha$  therapies were administered at the recommended labeled dose (etanercept 50 mg/week once or 25 mg/week twice, adalimumab 40 mg/once every other week, golimumab 50 mg once a month, and certolizumab pegol at 200 mg/once every other week). Any other therapies for RA also had to be taken at stable doses for defined periods (DMARDs, including methotrexate, for  $\geq 12$  weeks before the initial visit; oral corticosteroids for  $\geq 4$  weeks before the initial visit and maximum dose 10 mg/day; intravenous or intra-articular corticosteroids for  $\geq 4$  weeks before the initial visit). Patients had to provide written informed consent and be capable of understanding and completing the study questionnaires. Patients were excluded from the study if they had a current or former psychiatric illness that would interfere with their ability to comply with protocol requirements or give informed consent, or if they were participating in other clinical or observational trials.

## Statistical analyses

Results are expressed as mean  $\pm$  SD for quantitative data, median and interquartile range (IQR) for lifetime data, and frequency tables for categorical findings. Correlation coefficients were used to measure association between two quantitative variables. Mean values were compared by one-way analysis of variance, while for proportions the  $\chi^2$  test was used. The time evolution of each study variable was analyzed by a generalized linear mixed-effect model in which patients were considered as random and time the only fixed covariate. The same method was used to test the relationship between BMQ scores (Necessity and Concerns) and each variable separately (adherence and clinical parameters) over the 12 months by accounting for repeated data within patients. Results were expressed as regression coefficients with associated standard error (SE).

Calculations were always done on the maximum number of data available. Results were considered significant at the 5% critical level ( $P < 0.05$ ). Data analysis was carried out using SAS version 9.4 for Windows and R version 3.2.2.

## Results

### Patient disposition

A total of 477 patients were screened for this study, and 17 were found to be ineligible to participate (Figure 1). Of the 460 patients included, 427 (92.8%) had one or more follow-up visits and 392 (91.8%) completed all study visits.

### Demographics and patient history

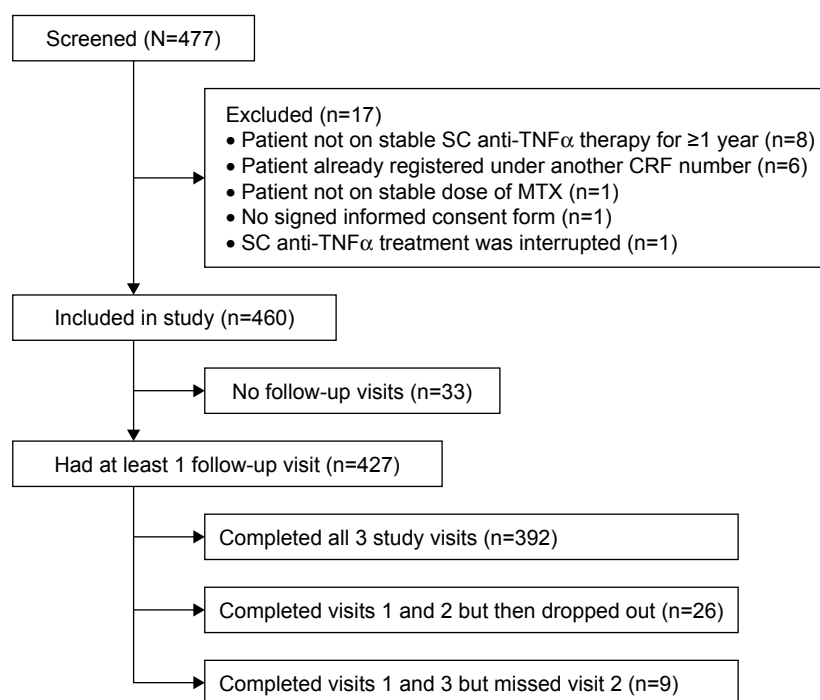
Demographic and clinical characteristics of the study population are shown in Table 1. Among the 460 patients, there was a majority of women (73.0%) and the average age was 59.3 years. A total of 437 patients had previously been taking one or more DMARDs, with over half (58.6%) taking two. Most patients (84.3%) were taking one SC anti-TNF $\alpha$  medication and had not previously taken any other biological treatments for RA (89.7%).

### Patients' initial beliefs, adherence, clinical status, and safety

Patients' beliefs about medicines (anti-TNF $\alpha$ -Necessity and anti-TNF $\alpha$ -Concerns), self-reported adherence, clinical status,

and safety parameters were assessed throughout the study (Table 2). At the initial visit, the average NCD was positive (1.46), although 26 of 408 (6.4%) patients had a negative NCD. The average MARS total score was 4.76, and less than 1% of patients scored at or below the MARS midpoint, indicating high levels of self-reported adherence to treatment. Figure 2 provides a profile of the beliefs held about RA medication and reasons for nonadherence in this patient population.

Table 3 shows patients' responses to the individual BMQ items at the initial visit. Less than 2% of patients scored at or below the anti-TNF $\alpha$ -Necessity scale midpoint ( $\leq 3$  on a scale of 1–5), indicating a high level of belief in the need for their RA medication. The percentage of patients scoring below the scale midpoint (totally disagree/disagree) for the anti-TNF $\alpha$ -Necessity items ("N" in Table 3) ranged from 0.9% (My health at present depends on my medicines) to 3.5% (My medications protect me from becoming worse). Almost half (48%) of the patients, however, scored at or above the anti-TNF $\alpha$ -Concerns scale midpoint, indicating increased concerns about their RA medication. The percentage of patients scoring above the scale midpoint (agree/totally agree) for the anti-TNF $\alpha$ -Concerns items ("C" in Table 3) ranged from 15.7% (My medications disrupt my life) to 61.8% (I sometimes worry about the long-term effects of my medications). At the initial visit, no correlation was seen between anti-TNF $\alpha$ -Necessity and anti-TNF $\alpha$ -Concerns



**Figure 1** Patient disposition.

**Abbreviations:** CRF, case report form; MTX, methotrexate; SC, subcutaneous.

**Table 1** Patient demographics and medical history at initial visit (n=460)

Characteristics	Summary statistics
Sex, n (%)	
Male	124 (27.0)
Female	336 (73.0)
Age, years	
Mean (SD)	59.3 (12.4)
BMI, kg/m <sup>2</sup>	
Mean (SD)	25.3 (4.3)
Professional status, n (%)	
Professional activity	130 (28.6)
Full-time	87 (69.0)
Part-time	39 (31.0)
No professional activity	80 (17.6)
Retired	172 (37.8)
Incapacity for work	73 (16.0)
Time since first RA symptoms, months	
Median (IQR)	167 (98–252)
Time since first RA diagnosis, months	
Median (IQR)	146 (90–228)
Comorbidities, n (%)	
Yes	217 (47.2)
No	243 (52.8)
Previous SC anti-TNF $\alpha$ medications, n (%)	
One	387 (84.3)
Two or more	72 (15.7)
Other previous biologics, n (%)	
None	408 (89.7)
One or more	47 (10.3)
Previous DMARDs, n (%)	
One	50 (11.4)
Two	256 (58.6)
Three	80 (18.3)
Four	51 (11.7)
Time since starting first anti-TNF $\alpha$ therapy, months	
Median (IQR)	71 (32–91)
Time since starting current SC anti-TNF $\alpha$ therapy, months	
Median (IQR)	60 (26–84)

**Abbreviations:** BMI, body-mass index; DMARDs, disease-modifying antirheumatic drugs; IQR, interquartile range; RA, rheumatoid arthritis; SC, subcutaneous; SD, standard deviation; TNF $\alpha$ , tumor necrosis factor  $\alpha$ .

scores ( $r=-0.056$ ,  $P=0.26$ ). Anti-TNF $\alpha$ -Necessity scores were correlated with MARS, patient-satisfaction, and safety scores, while anti-TNF $\alpha$ -Concerns scores were correlated with all clinical and quality-of-life parameters, but not with safety scores (Table S2).

## Evolution of patients' beliefs and clinical parameters over 12 months

After the initial visit (Table 2, Figure S1), mean anti-TNF $\alpha$ -Necessity, anti-TNF $\alpha$ -Concerns, MARS, and DAS28 scores remained stable during the entire 1-year follow-up.

In particular, the NCD was maintained at a positive mean level of about 1.44 points and generalized linear mixed-effect model analysis showed no time effect. The number of patients with a negative NCD did not change over the course of the year. This was also the case for the other instrument scores, except safety, where a small increase in incidence of AEs was noted at 6 months ( $P=0.012$ ). Remission patterns were also fairly stable, with the status of almost two-thirds of patients not changing over the 12 months: 126 (41.2%) patients were constantly in remission and 66 (21.6%) were never in remission.

Given the stable evolution pattern, the relationship between BMQ scales (dependent variable) and each individual parameter (covariate) was assessed by linear mixed-effects models accounting for repeated values over 12 months (Table 4). Results shown in Table 4 confirmed the lack of correlation between anti-TNF $\alpha$ -Necessity and anti-TNF $\alpha$ -Concerns ( $P=0.062$ ) observed at initial visit, the strong positive associations of adherence and patient satisfaction with anti-TNF $\alpha$ -Necessity, and the negative associations with anti-TNF $\alpha$ -Concerns (all  $P<0.0001$ ). Neither anti-TNF $\alpha$ -Necessity nor anti-TNF $\alpha$ -Concerns were related to safety. More importantly, while anti-TNF $\alpha$ -Concerns was found to be significantly correlated with disease activity (DAS28), clinical status (HAQ, pain and fatigue VAS, PHQ-9-DQ), and quality of life (EQ5D), no association was found between anti-TNF $\alpha$ -Necessity beliefs and these parameters. Specifically, the study's primary objective of estimating correlation between anti-TNF $\alpha$ -Necessity and the DAS28 showed that there was none after a 1-year follow-up.

## Discussion

This study of beliefs about SC anti-TNF $\alpha$  treatment (adalimumab, etanercept, golimumab, and certolizumab pegol) in patients with persistent RA is the first to investigate the relationship between these beliefs and disease activity and self-reported treatment adherence. In this study of patients with stable and generally well-managed disease, most had positive views about anti-TNF $\alpha$  treatment and agreed that anti-TNF $\alpha$  medication was necessary to maintain health now and in the future. However, some harbored concerns about the potential adverse effects of treatment. More than a fifth (22.4%) of patients agreed that their anti-TNF $\alpha$  medication caused unpleasant side effects, and 61.8% were concerned about long-term effects, but concerns went beyond the experience of side effects; patients also reported worrying about having to take medication (46.0%) and becoming too dependent on their medication (36.3%). However,



**Table 2** Patient beliefs and clinical characteristics at each visit

Characteristics (score range)	Initial visit		6-month visit		12-month visit		P-value
	N	Mean (SD)*	N	Mean (SD)*	N	Mean (SD)*	
Anti-TNF $\alpha$ -Necessity score (1–5)	422	4.30 (0.55)	372	4.23 (0.58)	357	4.28 (0.59)	0.19
Anti-TNF $\alpha$ -Concerns score (1–5)	409	2.83 (0.78)	364	2.81 (0.77)	356	2.84 (0.78)	0.83
NCD (–4 to 4)	408	1.46 (0.97)	361	1.43 (1.00)	352	1.44 (1.02)	0.93
Patients with negative NCD, n (%)	408	26 (6.4)	361	29 (8.0)	352	20 (5.7)	0.43
MARS total score (1–5)	415	4.76 (0.39)	372	4.78 (0.39)	355	4.78 (0.36)	0.79
DAS28 (0–10)	424	2.5 (1.1)	374	2.4 (1.1)	345	2.6 (1.2)	0.14
Remission (DAS28 <2.6), n (%)	424	242 (57.1)	374	234 (62.6)	345	198 (57.4)	0.23
Physician satisfaction (0–100)	456	75.2 (25.2)	409	75.2 (24.7)	385	74.0 (25.1)	0.72
Patient satisfaction (0–100)	427	83.8 (19.9)	377	83.8 (19.2)	365	81.7 (21.5)	0.26
HAQ (0–60)	435	11.3 (10.7)	371	11.6 (10.9)	353	12.6 (11.7)	0.21
Pain VAS (0–100)	428	32.2 (25.5)	376	30.8 (24.0)	364	34.7 (26.6)	0.11
Fatigue VAS (0–100)	429	42.1 (26.8)	376	40.5 (26.3)	362	41.4 (26.1)	0.70
PHQ-9-DQ (5–20)	422	8.1 (2.9)	374	7.7 (2.5)	360	8.1 (2.9)	0.10
EQ5D total (–1.0 to +1.0)	420	0.64 (0.26)	374	0.65 (0.24)	357	0.65 (0.25)	0.78
Safety, n (%) <sup>#</sup>	460		418		401		
No AEs		425 (92.4)		367 (87.8) <sup>‡</sup>		361 (90.0)	0.012
Nonserious AE(s) only		31 (6.7)		36 (8.6) <sup>‡</sup>		26 (6.5)	
One or more serious AEs		4 (0.9)		15 (3.6) <sup>‡</sup>		14 (3.5)	
Safety score (1–3) <sup>§</sup>	460	1.08 (0.31)	418	1.16 (0.45)	401	1.13 (0.43)	0.022

**Notes:** \*Unless otherwise stated. <sup>#</sup>AE categories were mutually exclusive. Patients experiencing both unserious and serious AEs were classified according to their worst AE category (ie, included in the “one or more serious AEs” category). <sup>‡</sup>Six-month distribution was significantly different from the initial visit. <sup>§</sup>Safety score: 1 = no AEs, 2 = nonserious AE(s) only, 3 = one more serious AEs.

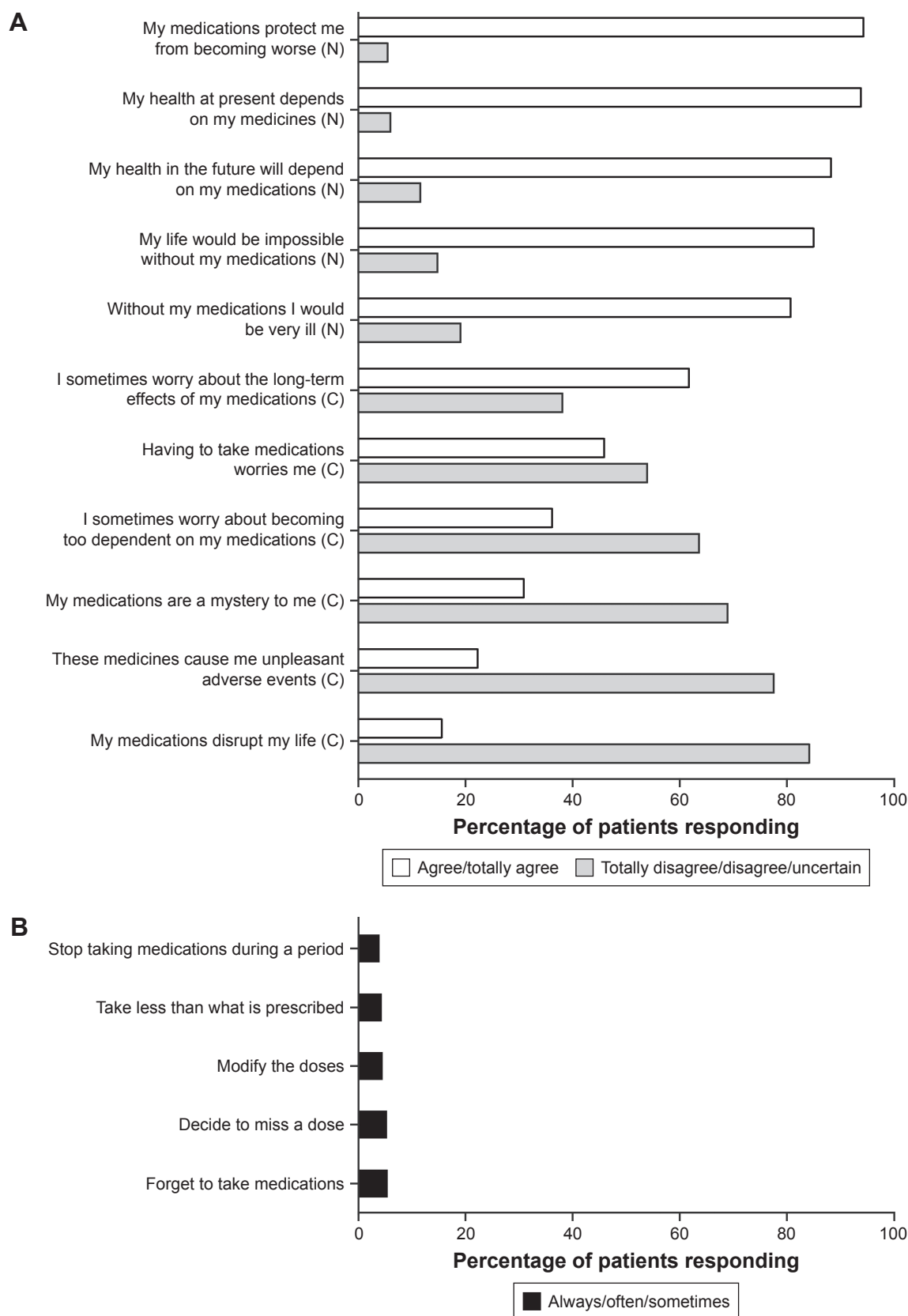
**Abbreviations:** AE, adverse event; DAS28, Disease Activity Score (28 joints); EQ5D, European Quality of Life-5 Dimensions; HAQ, Health Assessment Questionnaire; MARS, Medication Adherence Rating Scale; NCD, Necessity-Concerns Differential; PHQ-9-DQ, Patient Health Questionnaire-9 items-Depression Questionnaire; SD, standard deviation; TNF, tumor necrosis factor; VAS, visual analog scale.

patients generally considered their RA medication necessary (ie, average scores were greater than the scale midpoint) and tended to disagree that potential adverse consequences of taking their medication were a cause for concern. The NCD was consistently positive, indicating that patients generally rated their need to take SC anti-TNF $\alpha$  more highly than their concerns about the potential disadvantages. The positive association between anti-TNF $\alpha$ -Necessity and time since RA symptoms and diagnosis suggests that patients with longer duration of disease were more likely to consider their medication necessary for controlling their RA. The significantly lower anti-TNF $\alpha$ -Concerns scores for patients in remission suggest that patients with lower disease burdens were less concerned about the potential side effects of their medication. The average BMQ scores (Necessity and Concerns) in this study were similar to those reported in the only other study of beliefs about SC anti-TNF $\alpha$  treatment published to date.<sup>13</sup> Studies of other RA medications have also reported similar BMQ Necessity<sup>12,22,23</sup> and Concerns<sup>12,22–24</sup> scores, although one had lower Necessity scores than have been reported here and elsewhere.<sup>24</sup>

The patients in the present study had mostly high self-reported adherence to treatment, which was strongly correlated with a belief in the necessity of treatment. Concerns regarding AEs correlated with poor clinical status and were

inversely correlated with adherence. A previous study of adalimumab in the treatment of RA has also found that patient beliefs impacted treatment adherence; the importance of medication necessity for adalimumab users (regardless of the level of concern) predicted increased adherence.<sup>13</sup> However, that study focused on patients who were beginning biological DMARD treatment with adalimumab as their first anti-TNF $\alpha$  medication, while the study reported here involved persistent patients. This suggests that belief in the importance of the medication could be indicative of high levels of adherence, regardless of how long the patient has been receiving anti-TNF $\alpha$  medication; however, a study with a direct comparison between groups (patients who recently started receiving anti-TNF $\alpha$  vs those established on this medication) would be required to confirm this. Studies of nonbiological therapies for RA,<sup>22,24,25</sup> as well as studies involving patients with other chronic conditions,<sup>10,11,26–30</sup> have also shown the important effect of patient beliefs on medication adherence.

In the study reported here, significant ( $P < 0.05$ ) correlations were seen regarding Necessity and Concerns scores and several other variables. Some of these correlations are similar to those seen in a previous study of beliefs about medications in patients with RA.<sup>12</sup> Neame and Hammond<sup>12</sup> reported significant correlations between Necessity scores



**Figure 2** Patient responses to BMQ and MARS items at initial visit.

**Notes:** (A) Percentage of patients endorsing (agree/totally agree) or expressing doubts (totally disagree/disagree/uncertain) about each item of the BMQ at study baseline; (B) Percentage of patients reporting nonadherence to treatment (MARS).

**Abbreviations:** BMQ, Beliefs about Medicines Questionnaire; C, anti-TNF $\alpha$ -Concerns; MARS, Medication Adherence Rating Scale; N, anti-TNF $\alpha$ -Necessity.

**Table 3** Responses to BMQ at initial visit

BMQ statement (subscale)	N	Totally disagree, n (%)	Disagree, n (%)	Uncertain, n (%)	Agree, n (%)	Totally agree, n (%)
1: My health at present depends on my medicines (N)	426	0	4 (0.9)	22 (5.2)	190 (44.6)	210 (49.3)
2: Having to take medications worries me (C)	422	57 (13.5)	92 (21.8)	79 (18.7)	150 (35.5)	44 (10.4)
3: My life would be impossible without my medications (N)	424	4 (0.9)	9 (2.1)	50 (11.8)	175 (41.3)	186 (43.9)
4: I sometimes worry about the long-term effects of my medications (C)	424	31 (7.3)	56 (13.2)	75 (17.7)	172 (40.6)	90 (21.2)
5: Without my medications, I would be very ill (N)	427	2 (0.5)	12 (2.8)	68 (15.9)	183 (42.9)	162 (37.9)
6: My medications are a mystery to me (C)	419	48 (11.5)	156 (37.2)	85 (20.3)	88 (21.0)	42 (10.0)
7: My health in the future will depend on my medications (N)	426	0	8 (1.9)	42 (9.9)	214 (50.2)	162 (38.0)
8: My medications disrupt my life (C)	426	106 (24.9)	200 (46.9)	53 (12.4)	57 (13.4)	10 (2.3)
9: I sometimes worry about becoming too dependent on my medications (C)	424	49 (11.6)	141 (33.3)	80 (18.9)	125 (29.5)	29 (6.8)
10: My medications protect me from becoming worse (N)	427	5 (1.2)	10 (2.3)	9 (2.1)	186 (43.6)	217 (50.8)
11: These medicines cause me unpleasant adverse events (C)	428	82 (19.2)	153 (35.7)	97 (22.7)	72 (16.8)	24 (5.6)

**Abbreviations:** BMQ, Beliefs about Medicines Questionnaire; C, anti-TNF $\alpha$ -Concerns; N, anti-TNF $\alpha$ -Necessity.

and disease duration (as seen in our study), but they also found significant correlations between Necessity scores and Pain VAS, Fatigue VAS, and HAQ, which our study did not. Differences between these results could reflect the different treatments being assessed (SC anti-TNF $\alpha$  in this study vs DMARDs in the earlier study) and the different study populations (patients in our study were selected on the basis of receiving stable treatment, while no such selection was applied in the other study).

This study followed a cohort of persistent patients with RA, who were recruited after they had been receiving anti-TNF $\alpha$  treatment for a median of 5 years. The data did not vary significantly over the 12-month study period and can thus be viewed as a profile of the clinical and psychological characteristics of persistent and stable patients with RA. It would be useful to see if the belief profile observed in this

persistent and adherent population (anti-TNF $\alpha$ -Necessity outweighing anti-TNF $\alpha$ -Concerns) can help predict which patients starting treatment are likely to become nonpersistent (discontinue treatment before 12 months) or have lower self-reported treatment adherence. Beliefs about medicines in patients with RA have previously been shown to predict side effects over 6 months.<sup>31</sup> More detailed studies of patients' beliefs in other long-term conditions<sup>32–34</sup> have found that doubts about treatment necessity are often linked to logical but potentially misplaced beliefs about the illness (eg, perceiving that regular treatment is less important in the absence of symptoms). Likewise, concerns about specific medicines are often linked to mistrust of pharmaceuticals as a class of treatment. Addressing these beliefs in negotiated approaches to treatment (where the patient is involved in making treatment decisions) can support informed treatment choices and

**Table 4** Individual relationship of anti-TNF $\alpha$ -Necessity and anti-TNF $\alpha$ -Concerns scores with adherence, disease activity, and other clinical parameters assessed over 12 months

Covariate	Anti-TNF $\alpha$ -Necessity		Anti-TNF $\alpha$ -Concerns	
	Regression coefficient (SE)	P-value	Regression coefficient (SE)	P-value
Anti-TNF $\alpha$ -Concerns	–0.042 (0.023)	0.062	–	–
MARS total score	0.22 (0.044)	<0.0001	–0.28 (0.058)	<0.0001
DAS28	–0.0064 (0.016)	0.69	0.060 (0.021)	0.0046
Physician satisfaction	0.0013 (0.00063)	0.043	–0.0013 (0.00080)	0.10
Patient satisfaction	0.0038 (0.00077)	<0.0001	–0.0054 (0.0010)	<0.0001
HAQ	0.0023 (0.0018)	0.20	0.0067 (0.0024)	0.0052
Pain VAS	0.00042 (0.00066)	0.52	0.0042 (0.00088)	<0.0001
Fatigue VAS	0.0011 (0.00065)	0.089	0.0048 (0.00085)	<0.0001
PHQ-9-DQ	0.0027 (0.0063)	0.67	0.074 (0.0082)	<0.0001
EQ5D	–0.094 (0.069)	0.18	–0.57 (0.090)	<0.0001
Safety	–0.045 (0.034)	0.19	0.028 (0.044)	0.53

**Abbreviations:** DAS28, Disease Activity Score (28 joints); EQ-5D, European Quality of Life-5 Dimensions; HAQ, Health Assessment Questionnaire; MARS, Medication Adherence Rating Scale; PHQ-9-DQ, Patient Health Questionnaire-9 items-Depression Questionnaire; SD, standard deviation; TNF, tumor necrosis factor; VAS, visual analog scale.



help ensure that nonadherence does not result from misplaced beliefs.<sup>35,36</sup> If (as we expect) treatment necessity beliefs and concerns are shown to influence persistence and long-term adherence, then adherence-support programs could take account of these beliefs, as recommended by the National Institute for Health and Care Excellence.<sup>37</sup>

This study did have some limitations. Given that patients were on stable SC anti-TNF $\alpha$  for  $\geq 1$  year at the initial study visit and had a median treatment duration of 5 years before enrollment, the study population could be biased toward positive beliefs regarding their study medication. Also, a stable study population means that it is not possible to test whether beliefs about medicines can predict treatment outcome (such as remission, discontinuing therapy, or the occurrence of AEs), and there was no cohort of patients starting anti-TNF $\alpha$  therapy included to allow such predictions to be made. Another limitation is that accurately measuring self-reported adherence to medication is difficult and self-reported measures tend to overestimate adherence compared with other assessment approaches.<sup>38</sup> This study utilized a patient-reported measure of adherence that is open to some interpretation. As the anti-TNF $\alpha$  therapies covered in this study are self-injectable and the study protocol did not include other measures of adherence, such as the collection of used self-injection devices, there was no way of independently verifying levels of medication adherence.

## Conclusion

This study found that beliefs about medicines strongly correlated with medication adherence. Beliefs about medicines and medication adherence did not change over the 12-month follow-up period, giving a clinical and psychological profile of a persistent, stable RA population being treated with SC anti-TNF $\alpha$ . These findings may be of use in subsequent studies looking to predict adherence in patients starting treatment with SC anti-TNF $\alpha$ .

## Acknowledgments

This study was funded by Pfizer. Medical writing support for this manuscript was provided by Lorna Forse, PhD, and Samantha Forster, PhD, of Engage Scientific Solutions and was funded by Pfizer.

## Disclosure

RH was supported by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care (CLAHRC) North Thames at Bart's Health NHS Trust. He has undertaken speaker

engagements with honoraria with AbbVie, Amgen, Biogen Idec, Gilead Sciences, GlaxoSmithKline, Janssen, Pfizer, Roche, Shire Pharmaceuticals, MSD, Astellas, AstraZeneca, DRSU, Erasmus, and Novartis. He is founder and shareholder of an UCL-business spin-out company (Spoonful of Sugar), providing consultancy on medication-related behavior to health care policy makers, providers, and industry. AA is professor emeritus of biostatistics and adviser at the University Hospital of Liège and was funded by Pfizer for the statistical analysis of this study. CB was employed by Pfizer at the time of the study and owns stock in Pfizer. The authors report no other conflicts of interest in this work.

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## Supplementary materials

**Table S1** Participating study centers

1. AZ Sint-Jan, 10 Rudderhove, Brugge 8000, Belgium	18. 17 Anne Frankplein, Hasselt 3500, Belgium
2. AZ Turnhout, 44 Steenweg op Merkplas, Turnhout 2300, Belgium	19. Heilig Hart Ziekenhuis, 105 Naamsestraat, Leuven 3000, Belgium
3. CHU de Liège, Sart Tilman, Liège 4000, Belgium	20. 242 Hendrik Heymanplein, St-Niklaas 9100, Belgium
4. CHU Tivoli, 34 Av M. Buset, La Louvière 7100, Belgium	21. OLV Ziekenhuis, 164 Moorselbaan, Aalst 9300, Belgium
5. CH Jolimont, 159 Rue Ferrer, Haine-St-Paul 7100, Belgium	22. 237 Plezantstraat, Sint-Niklaas 2100, Belgium
6. 12 Albert Dineurlaan, Schoten 2900, Belgium	23. 21C Nederen Heirweg, Gistel 8470, Belgium
7. 137 Rue des Déportés, Arlon 6700, Belgium	24. ASZ, 80 Merestraat, Aalst 300, Belgium
8. CHPLT, 29 Rue du Parc, Verviers 4800, Belgium	25. 123 Weg naar As, Genk 3600, Belgium
9. CH Jolimont, 159 Rue Ferrer, Haine-St-Paul 7100, Belgium	26. 13 Hubert van de Vijverstraat, Lokeren 9160, Belgium
10. CH Epicura, 1 Rue M Thomée, Ath 7800, Belgium	27. 646 Bredabaan, Merksem 2170, Belgium
11. CHU Mont-Godinne, 1 Avenue Dr G Therasse, Yvoir 5530, Belgium	28. 88 Grand Route, Plainevaux 4122, Belgium
12. 248 Grand Route, Flemalle 4400, Belgium	29. 9 Rue Linette, Plainevaux 4122, Belgium
13. CNDG, 212 Chaussée de Nivelles, Gosselies 6041, Belgium	30. AZ St-Lucas, 1 Greone Briel, Ghent 9000, Belgium
14. 38 Schuttersvert, Mechelen 2800, Belgium	31. 18 Louizastraat, Mechelen 2800, Belgium
15. 24 Rue de Marcinelle, Charleroi 6000, Belgium	32. 119 Molenstraat, Schelderode 9820, Belgium
16. 8 Rue des Tilleuls, Grand-Manil 5030, Belgium	33. AZ Alma, 132 Gentse Steenweg, Sijsele 8340, Belgium
17. Hôpital Erasme, 808 Route de Lennik, Brussels 1070, Belgium	34. AZ Sint-Lucas, 29 Sint-Lucaslaan, Assebroek 8310, Belgium

## Beliefs about Medicines Questionnaire items: BMQ-Specific

The BMQ-Specific consists of two scales assessing the patient's beliefs about the Necessity (N) of the currently prescribed medications for controlling the disease (BMQ-Necessity) and his/her Concerns (C) about potential adverse consequences of taking them (BMQ-Concerns).

The items are:

1. My health at present depends on my medicines (N)
2. Having to take medications worries me (C)
3. My life would be impossible without my medications (N)
4. I sometimes worry about the long-term effects of my medications (C)
5. Without my medications I would be very ill (N)
6. My medications are a mystery to me (C)
7. My health in the future will depend on my medications (N)
8. My medications disrupt my life (C)
9. I sometimes worry about becoming too dependent on my medications (C)
10. My medications protect me from becoming worse (N)
11. These medicines cause me unpleasant adverse events (C).

Respondents indicate their degree of agreement with each statement on a 5-point Likert scale, ranging from 1 = strongly disagree to 5 = strongly agree. Scores obtained for individual items within both scales are summed and divided by the total number of items in the scale to give a scale score of 1–5. Higher scores indicate stronger beliefs.

## Medication Adherence Report Scale items

This five-item scale asks the patient to rate the frequency with which he/she engages in each of the five aspects of nonadherent behavior:

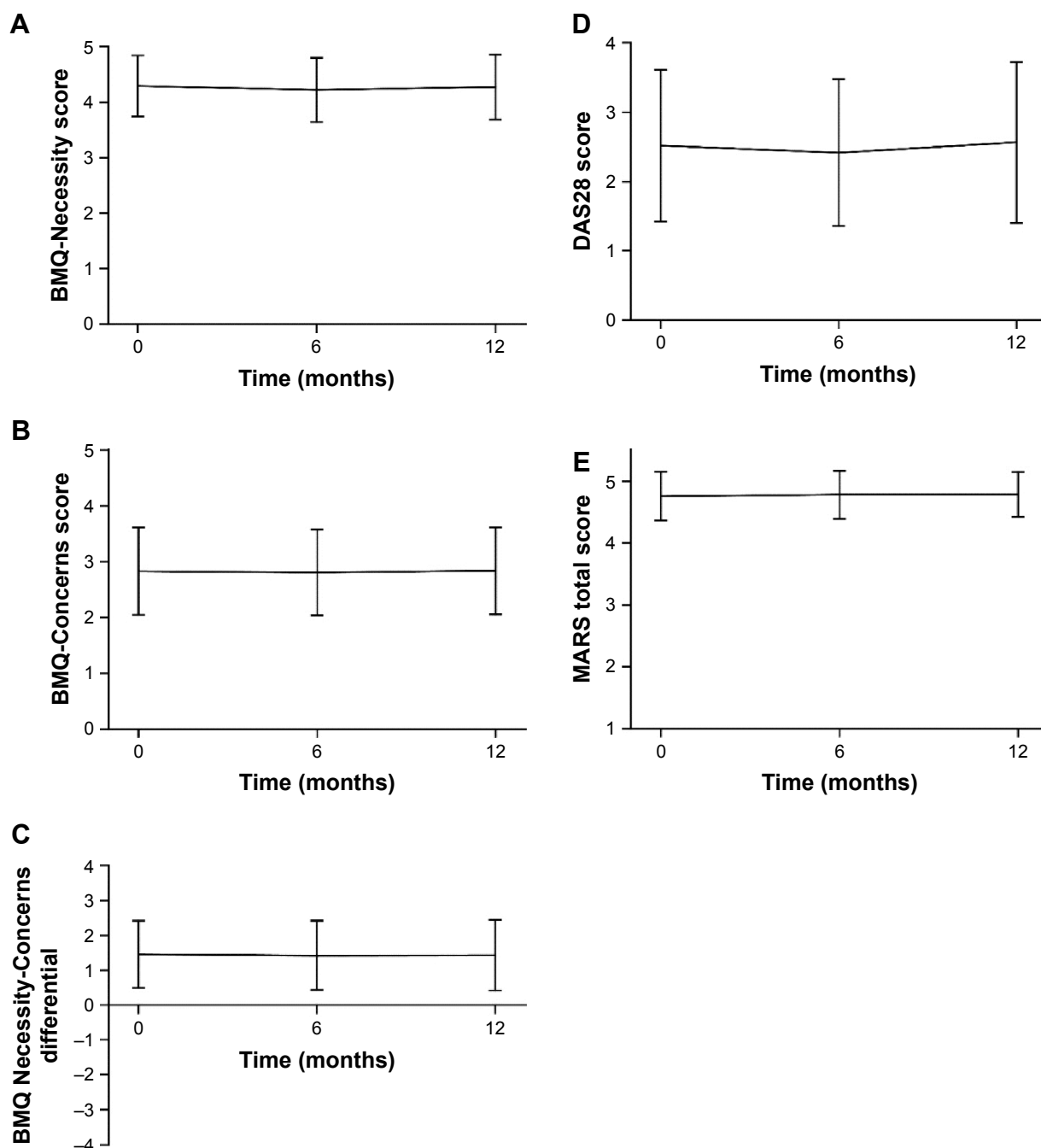
1. Forget to take medications
2. Modify doses
3. Stop taking medications during a certain period
4. Decide to miss a dose
5. Take less than what is prescribed.

Each item is rated on a 5-point Likert scale, where 1 = always, 2 = often, 3 = sometimes, 4 = rarely, and 5 = never. Scores for each of the five items are summed and divided by five to give a scale score of 1–5, where higher scores indicate higher levels of reported adherence.

**Table S2** Correlations regarding anti-TNF $\alpha$ -Necessity and anti-TNF $\alpha$ -Concerns scores and clinical and quality-of-life parameters at initial visit

Parameters	Anti-TNF $\alpha$ -Necessity			Anti-TNF $\alpha$ -Concerns		
	N	Pearson correlation (r)	P-value	N	Pearson correlation (r)	P-value
Anti-TNF $\alpha$ -Concerns	408	−0.056	0.26	–	–	–
MARS total score	409	0.13	0.0082	400	−0.18	0.0003
DAS28	392	−0.038	0.46	379	0.11	0.034
Physician satisfaction	418	0.012	0.80	405	−0.13	0.0073
Patient satisfaction	420	0.12	0.011	407	−0.21	<0.0001
HAQ	397	0.066	0.19	384	0.14	0.0066
Pain VAS	421	−0.025	0.61	408	0.23	<0.0001
Fatigue VAS	422	0.048	0.33	409	0.28	<0.0001
PHQ-9-DQ	416	0.01	0.76	405	0.32	<0.0001
EQ5D	414	−0.024	0.62	403	−0.31	<0.0001
Safety	422	0.10	0.036	409	0.010	0.85

**Abbreviations:** DAS28, Disease Activity Score (28 joints); EQ5D, European Quality of Life-5 Dimensions; HAQ, Health Assessment Questionnaire; MARS, Medication Adherence Rating Scale; PHQ-9-DQ, Patient Health Questionnaire-9 items-Depression Questionnaire; VAS, visual analog scale.



**Figure S1** BMQ, DAS28, and MARS scores throughout the study (mean  $\pm$  SD).

**Notes:** (A) BMQ-Necessity score over 12 months; (B) BMQ-Concerns score over 12 months; (C) BMQ Necessity-Concerns differential over 12 months; (D) DAS28 score over 12 months; (E) MARS total score over 12 months.

**Abbreviations:** BMQ, Beliefs about Medicines Questionnaire; DAS28, Disease Activity Score (28 joints); MARS, Medication Adherence Rating Scale.

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