Self-perceived general health at start of TNFi therapy predicts therapeutic response in patients with rheumatoid arthritis: analysis from the ATTRA registry

Lucie Nekvindová
Institute of Biostatistics and Analyses, Ltd., Brno
Jiří Vencovský
Department of Rheumatology, First Faculty of Medicine, Charles University, Prague
Karel Pavelka
Department of Rheumatology, First Faculty of Medicine, Charles University, Prague
Pavel Horák
Department of Internal Medicine III- Nephrology, Rheumatology, Endocrinology, Faculty of Medicine and Dentistry, Palacký University, Olomouc
Renata Rouhová
Institute of Biostatistics and Analyses, Ltd., Brno
Jakub Závada (zavada@revma.cz)
Department of Rheumatology, First Faculty of Medicine, Charles University, Prague

Research Article

Keywords: Registry, TNFi, SF-36, Rheumatoid arthritis, Propensity score, Remission, drug retention

Posted Date: May 17th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1643221/v1

Abstract

Background: Patient-reported outcomes (PROs) have been shown to predict various disease outcomes. One of the most widely used PRO instruments is the Short Form (SF) 36 questionnaire which evaluates the patient's health status. Our goal was to evaluate the association between therapeutic response and patients' self-perceived general health status at TNFi initiation based on answers to two selected questions (Qs) in the SF-36 questionnaire.

Methods: We included two separate datasets with RA patients (pts) initiating the first-line TNFi within the period 01/01/2001–31/12/2017 (primary dataset) and 01/01/2018–01/01/2020 (validation dataset) with at least one-year follow-up and filled SF-36 questionnaire at baseline. Patients were grouped according to their response ('definitely/mostly yes' vs 'definitely/mostly no') to Q11A and Q11C at baseline. The primary outcome was remission (REM) according to DAS28-ESR (<2.6) at the 12-month visit. REM rates were compared across patients' groups with Pearson's chi-squared test. Using logistic regression, crude and adjusted (to baseline DAS28-ESR and HAQ) odds ratios (ORs) were computed. Drug retentions were obtained through the Kaplan-Meier method. We repeated the analysis on propensity score-matched patients at baseline as a sensitivity analysis.

Results: Within the primary dataset (648/792 pts answering positively/negatively to Q11A; 730/580 pts answering positively/negatively to Q11C), patients answering '*yes*' to Q11A/Q11C had 1.5/1.4 times higher odds for REM at 12-month visit than patients answering '*no*'. The odds remained significantly different even after accounting for baseline DAS28-ESR and HAQ and within propensity score-matched datasets. Further, patients answering '*yes*' to Q11A had a 1.3 times higher risk of TNFi discontinuation than patients answering '*no*'. The validation dataset analysis (216/254 pts answering '*yes*'/'*no*' to Q11A; 231/201 answering '*yes*'/'*no*' to Q11C) gave similar results. Patients answering '*yes*' to Q11A/Q11C had 1.7 times higher odds of reaching REM at the 12-month visit than patients responding '*no*'. Even after accounting for baseline disease activity and functional status and within PS-matched datasets, the odds remained significantly higher. However, there was no statistically significant difference in drug retentions.

Conclusions: We provide strong evidence that self-perceived general health at TNFi initiation predicts reaching remission at 12 months in pts with RA.

Background

One of the main therapy targets in patients with rheumatoid arthritis (RA) is an optimisation of the quality of life. Several instruments were developed to evaluate patients' quality of life and functioning. Patient-reported outcomes (PROs) provide reports directly from patients about their own health, quality of life, or functional status associated with the health care or receiving treatment (1). One of the most widely used PRO instruments is the Short Form (SF) 36 questionnaire which evaluates the patient's health status using eight dimensions and includes 36 questions in total (2). PROs have been shown to predict various disease outcomes in a number of diseases (3–7).

For RA, multiple factors have been identified as predictors of remission, e.g., male sex, young age, short disease duration, or baseline lower disease activity (8, 9). Several studies have evaluated the predictive ability of PROs at baseline in patients with early RA (5, 10). So far, SF-36 dimensions have not yet been frequently studied as possible predictors for remission achievements in RA patients.

Our primary goal in this study was to evaluate the association between therapeutic response (achieving remission within the first year) and patients' self-perceived general health status at TNFi initiation based on answers to two selected questions from the *general health* dimension in the SF-36 questionnaire. We aimed to compare drug retentions between the studied groups as the secondary goal. We hypothesised that positive responses to questions (Q) 11A '*I seem to get sick a little easier than other people*' and 11C '*I expect my health to get worse*' from the general health (GH) domain of the SF36 questionnaire may correspond to a more fragile self-perceived GH status, and thus serve as possible predictors of future disease outcomes in patients with RA.

Methods

Study setting and data source

The ATTRA registry, established in 2001, is a non-interventional, prospective, national, observational cohort study. Its primary purpose is to evaluate the safety and effectiveness of bDMARDs/tsDMARDs in patients with chronic inflammatory rheumatic diseases. Patients with RA (and ankylosing spondylitis, psoriatic arthritis, juvenile idiopathic arthritis and systemic lupus erythematosus) starting bDMARDs or tsDMARDs are recruited from fifty-six practices sites (private or academic), and the registry captures more than 95% of patients with RA treated with bDMARDs/tsDMARDs in the Czech Republic (CZ).

At the start of therapy, baseline data are collected including demographics (gender, age at diagnosis, age at the start of 1st line treatment, height, weight, presence of comorbidities), disease characteristics (disease duration, presence of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), presence of joint erosions on X-ray), disease activity (swollen and tender joint count (0–28), patient global assessment (PtGA) of disease activity and physician global assessment of disease activity (MDGA) on a 100-mm visual analogue scale (VAS; 0 – best, 100 – worst), erythrocyte sedimentation rate (ESR, mg/h) and C-reactive protein (CRP, mg/L)) and 28-joint disease activity score index (DAS28; 0–10) (11), Health Assessment Questionnaire (HAQ) for patient function with values from 0 to 3 (the higher, the worse disability) (12), EuroQol EQ-5D questionnaire for quality of life with values from − 0.59 to 1 (the higher, the better quality of life) (13), and current or previous anti-rheumatic therapies and therapy with glucocorticoids (GCs). Follow-up data on disease activity, disease function and antirheumatic therapies are collected after three and six months, and then every six months for three years, with disease activity and anti-rheumatic therapy data collected annually after that.

Ethics approval

for ATTRA was granted by the Czech Multicentre Research Ethics Committee (no. 201611 S300) and Institutional Ethics Committee of Institute of Rheumatology, Prague, Czech Republic (no. 10113/2016). No additional ethical approval was required for the current analysis. All subjects provided their written consent for collecting and storing data before participation. All procedures were performed following the Declaration of Helsinki.

Study population

In this study, we used two separate datasets for analyses to validate our results – primary dataset (older cohort) and validation dataset (newer cohort). The primary dataset included all bio-naive adult patients diagnosed with RA starting TNFi therapy within a period from the registry data collection start (2001) until 31/12/2017. The validation dataset consisted of all bio-naive adult patients with RA diagnosis starting TNFi therapy between 01/01/2018 and 01/01/2020. Patients without filled SF36 questionnaire at baseline and without at least oneyear follow-up with available 6-month and 12month visits were excluded from the analysis (see flow charts Fig. 1).

Study design

We divided patients meeting the inclusion criteria according to their response (definitely/mostly yes, definitely/mostly no, do not know) to Q11A '*I seem to get sick a little easier than other people*', and Q11C '*I expect my health to get worse*' at baseline. We further analysed only patients who answered definitely/mostly yes/no, because we focused only on decisive patients. Therefore, patients who responded '*definitely yes*' and '*mostly yes*' were analysed together (as well as patients responding '*definitely no*' and '*mostly no*'). Patients' subgroups based on their responses are shown in pie charts **Supplementary Fig. 1**. We used two separate cohorts (primary and validation datasets) to validate our results. As part of a sensitivity analysis, we performed the whole analysis on the propensity-score matched datasets as well.

Objectives and Outcome measures

Our goal was to investigate whether the two selected SF-36 questions Q11A '*I seem to get sick a little easier than other people*' and Q11C '*I expect my health to get worse*', could predict therapeutic response in patients starting their first TNFi therapy. The therapeutic response was evaluated through remission achievements throughout the first year of TNFi therapy and drug retention.

Our primary outcome was remission (REM) achievement at 6 and 12 months since TNFi treatment initiation. Remission was defined through the disease activity index as DAS28-ESR < 2.6. Besides remission rates, odds ratios (ORs) of remission with '*no*' group as a reference were calculated. Our secondary outcome was drug retention, computed as the time from the first-line TNFi initiation until the date of drug discontinuation (for any reason) or the last update of patients in the registry. Primary and secondary outcomes were evaluated across studied subgroups ('*definitely/mostly yes*' vs

'*definitely/mostly no*') in both datasets (primary and validation) and propensity-score matched datasets afterwards.

Statistical methods

A descriptive summary of patients' demographic and treatment characteristics and disease activity measurements was performed for patients answering '*definitely/mostly yes'* and '*definitely/mostly no*' to Q11A and Q11C. For continuous variables, we calculated the median with interquartile range (IQR, 25th–75th percentiles). For a description of categorical variables, we used absolute and relative frequencies (i.e., percentages). We performed the non-parametric Mann-Whitney *U* test for continuous variables (after normality checks) and Pearson's chi-squared test for categorical variables to test differences between two patients' groups. In case the assumption of Pearson's chi-squared test was violated, Fisher's exact test was used instead. For all tests, P values < 0.05 were considered to be statistically significant.

We computed univariable logistic regression models to obtain odds ratios of remission achievement after 6/12 months of treatment for patients answering '*yes*' vs '*no*' to studied questions. Next, we performed multivariable logistic regression models with baseline HAQ and DAS28-ESR to obtain odds ratios adjusted for potential confounders.

Drug retention was computed through the Kaplan-Meier survival method. Drug survival probabilities were displayed through Kaplan-Meier curves and supplemented by numbers of patients at risk beneath the graphs. We also present numbers of discontinuations, one-year and two-year survival rates and median survival time with corresponding confidence intervals. The probabilities of drug discontinuations were compared across the studied groups through the Log-rank test. If the curves were crossing, we also computed the Breslow and Tarone-Ware tests. Finally, we employed Cox regression models to estimate hazard ratios (HRs) for treatment discontinuation for patients answering '*yes*' vs '*no*' to studied questions. Besides crude hazard ratios, we obtained adjusted versions with baseline HAQ and DAS28-ESR as confounders.

For the sensitivity analysis, we created balanced datasets for both subgroups (answering '*yes*' and '*no*'). We used propensity score matching to match patients answering '*yes*' to patients responding '*no*' within each studied question. We performed logistic regression with the outcome variable '*yes*' (= 1) vs '*no*' (= 0) and selected baseline covariates for matching. The covariates were chosen based on statistically significant differences in baseline characteristics with respect to clinical relevance and multicollinearity. We chose the matching ratio 1:1 and set the caliper to 0.2. The adequacy of the final propensity score model was checked through the balance diagnostics (standardised mean differences should be less than 0.1 to ensure balance in selected covariates). We used matching to make both groups comparable in baseline characteristics and to minimise confounding by other factors in evaluating REM achievements at the 6-/12-month visit and in the evaluation of drug retentions.

We did not impute missing data in this analysis and performed an availablecase analysis instead. We used IBM SPSS Statistics 25.0 to compute all descriptive statistics and comparisons. The propensity

score model was performed in R (version 3.5.3).

Results

Patients' characteristics at baseline

Within the primary dataset (older cohort), 648 (45.0%) / 792 (55.0%) patients responded positively/negatively to Q11A and 730 (55.7%) / 580 (44.3%) patients answered '*yes*'/'*no*' to Q11C. There was a statistically significantly higher percentage of women, higher frequency of comorbidities, a higher number of previous csDMARDs, more frequent GCs in previous therapy, and a higher percentage of csDMARDs and GCs in concomitant therapy in patients answering '*yes*' to Q11A compared to patients answering '*no*'. Further, patients answering '*yes*' had statistically significantly higher disease activity (DAS28-ESR), worse quality of life (lower EQ-5D, higher HAQ), but lower MDGA. Patients answering '*yes*' to Q11C had significantly longer disease duration, a bigger number of previous csDMARDs, worse quality of life (lower EQ 5D, higher HAQ), and lower MDGA compared to patients answering '*no*'. The summary of baseline characteristics can be found in Table 1.

Table 1
Baseline characteristics of patients answering '*yes*'/'*no*' to studied questions within primary dataset

	Q11A (*N*= 1440)		**Q11C (*N*= 1310)**	
Characteristic	Yes (*n* = 648)	No (*n* = 792)	Yes (*n* = 730)	No (*n* = 580)
Female	**539** (**83.2%**)	**612** (**77.3%**)	577 (79.0%)	468 (80.7%)
Age at diagnosis, years	43.0 (33.0–51.0)	42.0 (33.0–51.0)	42.0 (33.0–50.0)	43.0 (32.0–52.0)
Age at start of 1st line, years	52.0 (43.0–60.0)	52.0 (43.0–59.0)	52.0 (44.0–60.0)	52.5 (42.0–60.0)
Disease duration, years	7.3 (3.4–12.8)	6.8 (3.2–13.1)	**7.8** (3.8–13.4)	**6.1** (2.9–12.5)
RF positive	453/595 (76.1%)	499/689 (72.4%)	487/649 (75.0%)	374/511 (73.2%)
ACPA positive	377/548 (68.8%)	438/621 (70.5%)	405/588 (68.9%)	341/469 (72.7%)
Presence of comorbidities	**356 (54.9%)**	**377 (47.6%)**	374 (51.2%)	298 (51.4%)
BMI[a]	25.6 (22.9–29.4)	25.6 (22.6–28.8)	25.7 (22.8–29.4)	25.5 (22.9–28.7)
Previous csDMARDs				
0–1	**93/641 (14.5%)**	**173/784 (22.1%)**	**110/724 (15.2%)**	**140/576 (24.3%)**
2	**123/641 (19.2%)**	**193/784 (24.6%)**	**142/724 (19.6%)**	**157/576 (27.3%)**
3	**126/641 (19.7%)**	**174/784 (22.2%)**	**146/724 (20.2%)**	**118/576 (20.5%)**
4+	**299/641 (46.6%)**	**244/784 (31.1%)**	**326/724 (45.0%)**	**161/576 (28.0%)**

IQR interquartile range; *RF* rheumatoid factor; *ACPA* anti-citrullinated protein; TNFi tumour necrosis factor inhibitor; *csDMARDs* conventional synthetic disease-modifying anti-rheumatic drugs; *MTX* methotrexate; *DAS28-ESR* 28-joint disease activity score with ESR; *TJC* tender joint count; *SJC* swollen joint count; *ESR* erythrocyte sedimentation rate; *CRP* C-reactive protein; *PtGA* patient general assessment of disease activity; *MDGA* physician general assessment of disease activity; *HAQDI* Health Assessment Questionnaire; *EQ-5D* EuroQol 5 Dimension for measuring the quality of life

For continuous variables, the median (interquartile range) is presented. For categorical variables, absolute *(*relative) frequencies are presented. Statistical significant differences ($p < 0.05$) across patients' groups are marked in bold.

[a] BMI: *n* = 352 (Q11A '*yes*'), *n* = 392 (Q11A '*no*'), *n* = 510 (Q11C 'yes'), *n* = 398 (Q11C 'no')

[b] MDGA: *n* = 352 (Q11A '*yes*'), *n* = 392 (Q11A '*no*'), *n* = 365 (Q11C 'yes'), *n* = 305 (Q11C 'no')

	Q11A (*N* = 1440)		Q11C (*N* = 1310)	
GCs in previous history	**601/646 (93.0%)**	**701/787 (89.1%)**	669/726 (92.1%)	526/578 (91.0%)
Concomitant csDMARDs	**551** (**85.0%**)	**633** (**79.9%**)	604 (82.7%)	463 (79.8%)
Concomitant MTX	415 (64.0%)	522 (65.9%)	465 (63.7%)	384 (66.2%)
Concomitant GCs	**417** (**64.4%**)	**451** (**56.9%**)	459 (62.9%)	342 (59.0%)
DAS28-ESR (0–10)	**6.3** (5.8–6.8)	**6.2** (5.6–6.8)	6.3 (5.7–6.8)	6.3 (5.6–6.9)
TJC (28 joints)	13.0 (10.0–18.0)	13.0 (9.0–17.0)	13.0 (10.0–17.0)	13.0 (9.0–18.0)
SJC (28 joints)	10.0 (8.0–14.0)	10.0 (7.0–14.0)	10.0 (8.0–14.0)	10.0 (7.0–14.0)
ESR (mm/h)	**35.0** (22.0–50.0)	**32.0** (21.0–47.0)	35.0 (22.0–48.0)	32.0 (22.0–50.0)
CRP (mg/l)	**18.9** (9.3–34.0)	**15.5** (6.7–32.6)	17.4 (8.9–33.0)	16.9 (7.1–32.5)
PtGA (0–100)	70.0 (60.0–80.0)	70.0 (59.0–80.0)	70.0 (60.0–80.0)	70.0 (60.0–80.0)
MDGA (0–100) [b]	**60.0** (50.0–75.0)	**68.0** (52.0–80.0)	**60.0** (50.0–75.0)	**66.0** (52.0–78.0)
HAQ-DI (0–3)	**1.6** (1.3–2.0)	**1.5** (1.0–1.9)	**1.6** (1.3–2.0)	**1.5** (1.0–1.9)
EQ-5D (-0.59–1)	**0.1** (0.0–0.5)	**0.2** (0.1–0.7)	**0.1** (0.0–0.5)	**0.2** (0.1–0.7)
Year od administration				
2001–2011	**383 (59.1%)**	**452 (57.1%)**	455 (62.3%)	317 (54.7%)
2012–2013	**105 (16.2%)**	**99 (12.5%)**	97 (13.3%)	84 (14.5%)

IQR interquartile range; *RF* rheumatoid factor; *ACPA* anti-citrullinated protein; TNFi tumour necrosis factor inhibitor; *csDMARDs* conventional synthetic disease-modifying anti-rheumatic drugs; *MTX* methotrexate; *DAS28-ESR* 28-joint disease activity score with ESR; *TJC* tender joint count; *SJC* swollen joint count; *ESR* erythrocyte sedimentation rate; *CRP* C-reactive protein; *PtGA* patient general assessment of disease activity; *MDGA* physician general assessment of disease activity; *HAQDI* Health Assessment Questionnaire; *EQ-5D* EuroQol 5 Dimension for measuring the quality of life

For continuous variables, the median (interquartile range) is presented. For categorical variables, absolute *(*relative) frequencies are presented. Statistical significant differences ($p < 0.05$) across patients' groups are marked in bold.

[a] BMI: *n* = 352 (Q11A '*yes*'), *n* = 392 (Q11A '*no*'), *n* = 510 (Q11C 'yes'), *n* = 398 (Q11C 'no')

[b] MDGA: *n* = 352 (Q11A '*yes*'), *n* = 392 (Q11A '*no*'), *n* = 365 (Q11C 'yes'), *n* = 305 (Q11C 'no')

	Q11A (*N* = 1440)		Q11C (*N* = 1310)	
2014–2015	**93 (14.4%)**	**159 (20.1%)**	115 (15.7%)	111 (19.1%)
2016–2017	**67 (10.3%)**	**82 (10.4%)**	63 (8.6%)	68 (11.7%)
TNFi: adalimumab	**278 (42.9%)**	**348 (43.9%)**	311 (42.6%)	247 (42.6%)
TNFi: etanercept	**186 (28.7%)**	**162 (20.5%)**	186 (25.5%)	120 (20.7%)
TNFi: infliximab	**103 (15.9%)**	**175 (22.1%)**	147 (20.1%)	130 (22.4%)
TNFi: certolizumab	**33 (5.1%)**	**52 (6.6%)**	35 (4.8%)	40 (6.9%)
TNFi: golimumab	**48 (7.4%)**	**55 (6.9%)**	51 (7.0%)	43 (7.4%)
Bs ADA/ETA/INF	22/567 (3.9%)	30/685 (4.7%)	30/644 (4.7%)	28/497 (5.6%)

IQR interquartile range; *RF* rheumatoid factor; *ACPA* anti-citrullinated protein; TNFi tumour necrosis factor inhibitor; *csDMARDs* conventional synthetic disease-modifying anti-rheumatic drugs; *MTX* methotrexate; *DAS28-ESR* 28-joint disease activity score with ESR; *TJC* tender joint count; *SJC* swollen joint count; *ESR* erythrocyte sedimentation rate; *CRP* C-reactive protein; *PtGA* patient general assessment of disease activity; *MDGA* physician general assessment of disease activity; *HAQDI* Health Assessment Questionnaire; *EQ-5D* EuroQol 5 Dimension for measuring the quality of life

For continuous variables, the median (interquartile range) is presented. For categorical variables, absolute *(*relative) frequencies are presented. Statistical significant differences ($p < 0.05$) across patients' groups are marked in bold.

[a] BMI: *n* = 352 (Q11A '*yes*'), *n* = 392 (Q11A '*no*'), *n* = 510 (Q11C 'yes'), *n* = 398 (Q11C 'no')

[b] MDGA: *n* = 352 (Q11A '*yes*'), *n* = 392 (Q11A '*no*'), *n* = 365 (Q11C 'yes'), *n* = 305 (Q11C 'no')

Together 216 (46.0%) / 254 (54.0%) patients responded positively/negatively to Q11A in the validation dataset (newer cohort). Within Q11C, 231 (53.3%) / 201 (46.5%) patients responded '*yes*'/'*no*'. There was a statistically significantly higher number of previous csDMARDs, higher disease activity (e.g. DAS28ESR), worse quality of life (lower EQ-5D, higher HAQ) and higher frequency of biosimilars in patients answering '*yes*' to Q11A compared to patients responding '*no*'. Patients answering '*yes*' to Q11C had statistically significantly higher disease activity (e.g. DAS28-ESR), worse quality of life (lower EQ-5D, higher HAQ) and higher frequency of biosimilars than patients responding negatively. The overview of all baseline characteristics for each patients' group is presented in **Supplementary Table 1a**.

For a sensitivity analysis, we prepared propensity score-matched datasets. Within the primary dataset, 574 patients responding '*yes*' and 574 responding '*no*' to Q11A were matched based on the computed PS. Further, 550 from the group answering '*yes*' and 550 from the group answering '*no*' to Q11C were matched based on the computed PS. After the matching, patients only differed in the quality of life parameters (EQ-5D, HAQ). We did not include these parameters in the PS model as they correlated with the SF-36 questionnaire (and thus with our studied groups). Summary of baseline characteristics in each propensity score-matched group is presented in **Supplementary Table 1b**. In the validation dataset, both patients answering '*yes*'/'*no*' to Q11A included 185 patients after the matching. For patients answering

'*yes*'/'*no*' to Q11C, both groups included 169 patients. Patients only differed in EQ5D after the matching. Summary of baseline characteristics in each propensity scorematched group is presented in **Supplementary Table 1c**.

Comparison of remission achievement within the first year

Comparison of remission rates according to DAS28-ESR score after 3, 6 and 12 months of TNFi treatment between patients answering '*yes*' and '*no*' to Q11A and Q11C within the primary dataset (older cohort) is displayed in Fig. 2. We could observe a statistically significantly higher frequency of remission at all visits within the first year (e.g. 38.8% vs 30.1% at 12 months) in patients who seemed to get sick a little easier than other people at the treatment initiation than patients who did not think that. Similarly, remission was achieved statistically significantly more frequently after 3, 6 and 12 (37.3% vs 29.5%) months in patients who expected their health to get worse at the treatment initiation than patients who did not expect it. Remission rates remained significantly different even when computed within patients staying on the treatment through the Lundex index (not shown here) (14). Patients answering '*yes*' to Q11A had almost 1.5 × higher odds for remission both at the 6- and 12month visit than patients answering '*no*'. Patients answering '*yes*' to Q11C had 1.7 (1.4) × higher odds for remission at the 6-month (12month) visit than patients answering '*no*'. Both crude and adjusted odds ratios for reaching remission are shown in Table 2. Even after accounting for baseline disease activity and functional status, the odds for remission remained significantly different.

Table 2
Univariable and multivariable logistic regression models for reaching remission at 6/12 months – primary dataset. Patients are grouped based on answers to Q11A/Q11C at treatment initiation.

	Remission after 6 months		**Remission after 12 months**	
Parameter	OR (95% CI)	p	OR (95% CI)	*p*
Univariable models				
Q11A: Yes vs no	**1.46** (1.16; 1.83)	**0.001**	**1.47** (1.18; 1.83)	< **0.001**
Q11C: Yes vs no	**1.70** (1.33; 2.18)	< **0.001**	**1.42** (1.12; 1.80)	**0.003**
Multivariable model				
Q11A: Yes vs no	**1.82** (1.43; 2.33)	< **0.001**	**1.75** (1.39; 2.21)	< **0.001**
Baseline HAQ	**0.58** (0.48; 0.69)	< **0.001**	**0.63** (0.53; 0.74)	< **0.001**
Baseline DAS28-ESR	**0.57** (0.50; 0.64)	< **0.001**	**0.64** (0.56; 0.72)	< **0.001**
Multivariable model				
Q11C: Yes vs no	**1.91** (1.47; 2.47)	< **0.001**	**1.53** (1.20; 1.95)	< **0.001**
Baseline HAQ	**0.59** (0.49; 0.70)	< **0.001**	**0.65** (0.55; 0.77)	< **0.001**
Baseline DAS28-ESR	**0.57** (0.50; 0.65)	< **0.001**	**0.64** (0.57; 0.72)	< **0.001**
DAS28-ESR 28-joint disease activity score with ESR; *HAQDI* Health Assessment Questionnaire; OR – odds ratio; CI – confidence interval				
The outcome in the logistic regression model is DAS28-ESR < 2.6 (1 – yes; 0 – no).				
Q11A: '*I seem to get sick a little easier than other people*'; Q11C: '*I expect my health to get worse*'				

Within the validation dataset (newer cohort), remission was achieved statistically significantly more often after 6 and 12 months in patients answering '*yes*' to Q11A than patients answering '*no*'. At the 3-month visit, the difference was not statistically significant. Similarly, patients answering '*yes*' to Q11C achieved remission after 12 months statistically significantly more often than patients answering '*no*'. Even though the remission rates did not statistically significantly differ at 3- and 6-month visits, there were also tendencies for the more frequent occurrence of remission in patients answering '*yes*' to Q11C (see **Supplementary Fig. 2**). Both patients answering '*yes*' to Q11C and Q11A had significantly higher odds (1.7 times) of reaching remission at the 12-month visit than patients answering '*no*' to these questions. The odds remained significantly higher after accounting for baseline disease activity and functional status (see **Supplementary Table 2a**).

Concurrently, we evaluated remission achievements in PS-matched datasets. Within PS-matched primary dataset, patients who seemed to get sick a little easier than other people at the treatment initiation (Q11A)

achieved remission more often after six months (31.4% vs 24.2%; p = 0.007) and twelve months (36.3% vs 28.5%; p = 0.005) than patients who did not think that. Similarly, remission was achieved more often after six months (32.5% vs 23.0%; p < 0.001) and twelve months (36.6% vs 29.7%; p = 0.015) in patients who expected their health to get worse at the treatment initiation than patients who did not expect their health to get worse (Q11C). Patients answering '*yes*' to Q11A had 1.4 × higher odds for remission at both 6- and 12-month visits than patients answering '*no*'. Patients answering '*yes*' to Q11C had 1.6 (1.4) × higher odds for remission at the 6-month (12-month) visit than patients answering '*no*' (see **Supplementary Table 2b**). Within PS-matched validation dataset, patients who seemed to get sick a little easier than other people at the treatment initiation (Q11A) achieved remission more often after six months (36.1% vs 30.8%) and twelve months (47.8% vs 35.0%) than patients who did not think that. The difference was statistically significant only at the 12-month visit. Similarly, remission was achieved more often after six months (40.5% vs 35.7%) and twelve months (46.7% vs 36.7%) in patients who expected their health to get worse at the treatment initiation than patients who did not expect their health to get worse (Q11C). Patients answering '*yes*' to Q11A had 1.7 × higher odds for remission both at the 12-month visit than patients answering '*no*' (p = 0.013). Patients answering '*yes*' to Q11C had 1.5 × higher odds for remission at the 12-month visit than patients answering '*no*', but the result was only close to statistical significance (p = 0.066). See **Supplementary 2b** for an overview of logistic regression results.

Comparison of drug retentions

Comparison of probabilities of staying on the first-line TNFi in patients answering '*yes*'/'*no*' to Q11A and Q11C within the primary dataset (older cohort) is presented in Fig. 3. There was found a statistically significant difference in probabilities of staying on the first TNFi between patients who seemed to get sick a little easier than other people at the treatment initiation than patients who did not think that. Patients answering '*yes*' had a 1.3 times higher risk of treatment discontinuation than patients answering '*no*'. Even after adjustment for baseline DAS28-ESR and HAQ, the risk remained 1.3 times higher in the '*yes*' group. The estimated 1-year retention rate was 83.2% (95% CI 80.4–86.1) in the '*yes*' group and 86.4% (95% CI 84.0–88.8) in the '*no*' group. The estimated 2-year retention rate was 67.8% (95% CI 64.2–71.5) and 73.3% (95% CI 70.2–76.5) in patients answering '*yes*' and '*no*'. The numbers of discontinuations and median survival times are presented in Table 3. The median length of follow-up in patients answering '*yes*' was 61 months, and in patients answering '*no*', it was 68 months. The most frequent reason for discontinuation was a loss of effect and inefficacy. There was no statistically significant difference (p-values of Log-rank, Breslow and Tarone-Ware test > 0.05) in the probability of staying on the first TNFi between the patients who expected their health to get worse at treatment initiation and patients who did not expect their health to get worse (see Fig. 3).

Table 3
Number of TNFi discontinuations and median survival time of patients responding negatively/positively to Q11A/11C

		Discontinuations, *n* (%)	**Median survival time in months (95% CI)**
Primary dataset (older cohort)	*Q11A*		
	Definitely / mostly yes (*n* = 648)	417 (64.4%)	42.8 (37.4; 48.2)
	Definitely / mostly no (*n* = 792)	420 (53.0%)	66.0 (54.6; 77.4)
	Q11C		
	Definitely / mostly yes (*n* = 730)	462 (63.3%)	48.1 (41.6; 54.6)
	Definitely / mostly no (*n* = 580)	327 (56.4%)	49.9 (40.6; 59.2)
Validation dataset (newer cohort)	*Q11A*		
	Definitely / mostly yes (*n* = 216)	82 (38.0%)	Not reached
	Definitely / mostly no (*n* = 254)	101 (39.8%)	34.3 (–)
	Q11C		
	Definitely / mostly yes (*n* = 231)	81 (35.1%)	Not reached
	Definitely / mostly no (*n* = 201)	76 (37.8%)	Not reached
CI – confidence interval			
Q11A: 'I seem to get sick a little easier than other people'; Q11C: 'I expect my health to get worse'			

Within the validation dataset (newer cohort), there was no statistically significant difference in drug retentions between patients answering *yes* and *no* to Q11A/Q11C (see **Supplementary Fig. 3a**).

Drug retentions computed on the PS-matched datasets are presented in **Supplementary Fig. 3b**. Within the PS-matched primary dataset, there was a statistically significant difference in probabilities of staying on the first TNFi between patients who seemed to get sick a little easier than other people at the treatment initiation (Q11A) than patients who did not think that. The median survival was 42.8 (CI 36.0–49.6) months in the '*yes*' groups and 66.4 (CI 52.7–80.2) months in the '*no*' group. Within the PS-matched validation dataset, there was no statistically significant difference in TNFi retention probabilities between the studied groups.

Discussion

In this prospective observational cohort study from real clinical practice in the Czech Republic, we evaluated the predictive ability of two SF-36 questionnaire questions, specifically Q 11A '*I seem to get sick a little easier than other people*', and Q 11C '*I expect my health to get worse*'. We hypothesised that positive responses to these questions might correspond to more fragile, self-perceived general health status, thus serving as possible predictors of future patient disease outcomes. For each diagnosis, we used separate datasets to validate our hypothesis. Apart from univariable models to quantify odds and hazard ratios, we employed multivariable models adjusted for baseline disease activity and quality of life. Furthermore, we repeated the whole analysis within propensity scorematched patients to make both study groups (answering '*yes*'/'*no*' to Q11A and Q11C) comparable in baseline characteristics, thus reducing selection bias. By employing the propensity score matching at baseline, we have partially overcome missing randomisation in this study. Overall, we employed three ways to verify our results: 1) adjustment for baseline disease activity and functional status; 2) two separate datasets (primary and validation); 3) propensity-score matched datasets.

The results of the primary dataset were presented within the 62nd Annual Congress of Czech and Slovak Rheumatologists in 2018, Prague. We have shown that patients answering positively to Q11A and patients answering positively to Q11C have significantly higher odds of reaching remission at 6- and 12-month visits than patients answering to these questions negatively. This difference in remission rates and odds ratios remained statistically significant even when computed on propensity scorematched patients who were balanced in baseline characteristics. We obtained analogical results in the validation dataset of RA patients as well. Patients answering positively to Q11A (or Q11C) had significantly higher odds of remission achievement at the 12-month visit than patients responding to these questions negatively. Within the propensity score-matched dataset, patients responding 'yes' to Q11A had significantly higher odds of remission at the 12-month visit than patients answering 'no'. For Q11C, the difference was not statistically significant at the 12-month visit, but it was very close to the statistical significance ($p = 0.066$). Overall, we provided robust evidence that self-perceived general health at the start of TNFi therapy predicts reaching remission at 12 months in patients with RA. In terms of treatment discontinuation, patients answering '*yes*' to Q11A had a significantly higher probability of treatment discontinuation than patients answering '*no*' within the primary dataset (older cohort). In the validation dataset (newer cohort), there was no statistically significant difference in the probability of treatment discontinuation between patients answering positively/negatively to the studied SF-36 questions.

The predictive ability of SF-36 dimensions was not very investigated so far. A randomised clinical trial studied PROs as predictors of remission in early RA (5). At baseline, they measured eight SF-36 questionnaire dimensions, PGA, HAQ, and pain (VAS). Remission at two years was associated with SF36 dimensions: higher vitality (OR 2.0; 95% CI 1.2–3.4) and better emotional role functioning (OR 1.6; 95% CI 1.0–2.7). The general health dimension (to which our two studied questions belonged) was not associated with remission in this study. A three-year prospective observational study of a Brazilian early RA cohort evaluated whether baseline scores (HAQ and SF-36) can predict the achievement of remission

(DAS28 < 2.6) (10). Neither initial HAQ nor SF-36 scores were associated with clinical remission. The baseline general health score was not significantly different between patients achieving and not achieving remission. In the randomised controlled CareRA-trial, they studied how psychosocial aspects affect the probability of achieving sustained remission in early RA (15). Suboptimal psychosocial wellbeing and negative illness perceptions were associated with lower odds of sustained remission. The general health dimension of the SF-36 questionnaire was not investigated in this study. They only focused on mental dimensions.

Our results within the RA cohort are quite surprising because we assumed that patients who expected their health to get worse at treatment initiation and patients who seemed to get sick a little easier than other people at treatment initiation would have lower odds of treatment response (achieving remission within one year) than patients who did not think that. However, the results showed the exact opposite. Thus, it would be interesting to include a psychologist in future studies to get a deeper insight. Including more questions from different SF-36 dimensions is another point for further studies.

Conclusion

In conclusion, we provided robust evidence that self-perceived general health at the start of TNFi therapy predicts reaching remission at 12 months in patients with RA. Patients who seemed to get sick a little easier than other people at treatment initiation and patients who expected their health to get worse at treatment initiation had significantly higher odds of reaching REM within the first year than patients who did not think that.

Abbreviations

ACPA
anti-citrullinated protein antibodies
bDMARDs
biological disease-modifying anti-rheumatic drugs
CI
confidence interval
CRP
C-reactive protein
csDMARDs
conventional synthetic disease-modifying anti-rheumatic drugs
CZ
Czech Republic
DAS28-ESR
28-joint disease activity score using the erythrocyte sedimentation rate
DMARD
disease-modifying anti-rheumatic drugs

EQ-5D
EuroQol-5 Dimensions
ESR
erythrocyte sedimentation rate
GCs
glucocorticoids
HAQ-DI
health assessment questionnaire disability index
HR
hazard ratio
IQR
interquartile range
MDGA
physician global assessment of disease activity
MTX
methotrexate
OR
odds ratio
PROs
patient-reported outcomes
PtGA
patient global assessment of disease activity
Qs
questions
RA
rheumatoid arthritis
REM
remission
RF
rheumatoid factor
SF-36
36-item short form survey
SDAI
simplified disease activity index
TNFi
tumour necrosis factor inhibitor
tsDMARDs
targeted disease-modifying anti-rheumatic drugs
VAS
visual analogue scale

Declarations

Ethics approval and consent to participate

All procedures in this study were in accordance with the ethical standards of the institutional and national research committee (Czech Multicentre Research Ethics Committee, no. 201611 S300 and Institutional Ethics Committee of Institute of Rheumatology, Prague, Czech Republic, no. 10113/2016) and with the 1964 Helsinki declaration and its later amendments. All subjects provided their written consent for the collection and storage of data before participation.

Consent for publication

Not applicable

Availability of data and materials

The datasets analysed during the current study are available from the corresponding author on reasonable request. Requests will be considered by the Czeach Rheamatological Society.

Competing interests

The authors declare that they have no competing interests

Funding

This work was supported by the project (Ministry of Health, Czech Republic) for conceptual development of research organisation 00023728 (Institute of Rheumatology).

Authors' contributions

All authors were involved in drafting the manuscript or revising it critically for content. LN planned and performed the analysis, interpreted patients' data and wrote the manuscript. JV, KP and PH revised the manuscript. RR managed the project. JZ designed the project, supervised its conduct, and helped to write the manuscript. All authors read and approved the final manuscript.

Acknowledgements

Not applicable

References

1. Weldring T, Smith SMS. Patient-Reported Outcomes (PROs) and Patient-Reported Outcome Measures (PROMs). Health Serv Insights. 2013 Aug 4;6:61–8.
2. Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. BMJ. 1992 Jul

18;305(6846):160–4.

3. Jarnagin JX, Parikh AR, Van Seventer EE, Shah Y, Baiev I, Mojtahed A, et al. Changes in patient-reported outcomes (PROs) and tumor markers (TMs) to predict treatment response and survival outcomes in patients with metastatic gastrointestinal (GI) cancer. JCO. 2021 May 20;39(15_suppl):6560–6560.
4. Vámosi M, Lauberg A, Borregaard B, Christensen AV, Thrysoee L, Rasmussen TB, et al. Patient-reported outcomes predict high readmission rates among patients with cardiac diagnoses. Findings from the DenHeart study. International Journal of Cardiology. 2020 Feb 1;300:268–75.
5. Kuusalo L, Puolakka K, Kautiainen H, Karjalainen A, Malmi T, Yli-Kerttula T, et al. Patient-reported outcomes as predictors of remission in early rheumatoid arthritis patients treated with tight control treat-to-target approach. Rheumatol Int. 2017 May 1;37(5):825–30.
6. Wong ECL, Buffone E, Lee SJ, Dulai PS, Marshall JK, Reinisch W, et al. End of Induction Patient-reported Outcomes Predict Clinical Remission but Not Endoscopic Remission in Crohn's Disease. J Crohns Colitis. 2021 Jul 5;15(7):1114–9.
7. Schennach-Wolff R, Jäger M, Obermeier M, Schmauss M, Laux G, Pfeiffer H, et al. Quality of life and subjective well-being in schizophrenia and schizophrenia spectrum disorders: Valid predictors of symptomatic response and remission? The World Journal of Biological Psychiatry. 2010 Aug 1;11(5):729–38.
8. Katchamart W, Johnson S, Lin H-JL, Phumethum V, Salliot C, Bombardier C. Predictors for remission in rheumatoid arthritis patients: A systematic review. Arthritis Care & Research. 2010;62(8):1128–43.
9. Yu C, Jin S, Wang Y, Jiang N, Wu C, Wang Q, et al. Remission rate and predictors of remission in patients with rheumatoid arthritis under treat-to-target strategy in real-world studies: a systematic review and meta-analysis. Clin Rheumatol. 2019 Mar 1;38(3):727–38.
10. da Mota LMH, Dos Santos Neto LL, Oliveira ACV, Pereira IA, Burlingame RW, Ménard HA, et al. Baseline HAQ and SF-36 questionnaire scores cannot predict clinical remission, radiographic progression or the need for biological therapy in a three-year prospective study of a Brazilian early rheumatoid arthritis cohort. Rheumatol Int. 2012 Dec;32(12):3937–43.
11. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995 Jan;38(1):44–8.
12. Bruce B, Fries JF. The Health Assessment Questionnaire (HAQ). Clin Exp Rheumatol. 2005 Oct;23(5 Suppl 39):S14-18.
13. EuroQol Group. EuroQol–a new facility for the measurement of health-related quality of life. Health Policy. 1990 Dec;16(3):199–208.
14. Kristensen LE, Saxne T, Geborek P. The LUNDEX, a new index of drug efficacy in clinical practice: results of a five-year observational study of treatment with infliximab and etanercept among rheumatoid arthritis patients in southern Sweden. Arthritis Rheum. 2006 Feb;54(2):600–6.

15. Doumen M, De Cock D, Pazmino S, Bertrand D, Joly J, Westhovens R, et al. Psychosocial burden predicts sustained remission in early rheumatoid arthritis: unraveling the complex interplay of wellbeing and disease activity. Arthritis Care Res (Hoboken). 2021 Dec 20;

Figures

Figure 1

Flow chart showing individual steps to the final datasets.

(A) primary dataset (older cohort); (B) validation dataset (newer cohort)

Figure 2

Remission rates (DAS28-ESR<2.6) within the first year of TNFi treatment – primary dataset.

Patients answering '*yes*'/'*no*' to Q11A (upper graph) and Q11C (lower graph).

Figure 3

Kaplan-Meier survival plots showing drug retention in patients answering '*yes*'/'*no*' to Q11A (a) and Q11C (b). HR – hazard ratio; CI – confidence interval; primary dataset

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementary.docx