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ORIGINAL ARTICLE

Health-related quality of life and utility in patients receiving biological and non-biological treatments in rheumatoid arthritis

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Abstract Biological treatments earn increasing significance in the treatment of rheumatoid arthritis (RA) but are associated with high incremental cost-effectiveness ratio compared to conventional antirheumatic treatments such as disease-modifying antirheumatic drugs. As the most important objective of medical technologies should be to increase life years and/or patients' health-related quality of life (HRQoL), measuring QoL and utility in RA patients treated with biological therapies is crucial. The objective of this study is to compare the utility and QoL of patients treated with biological ($n = 85$) and non-biological ($n = 168$) antirheumatic drugs in Hungary in a cross-sectional non-interventional study. A measure of impairment (Disease Activity Score (DAS)-28), QoL measure (EuroQol five Dimension (EQ-5D) Visual Analogue Scale (VAS), Rheumatoid Arthritis Quality of Life (RAQoL)) and utility measures (indirect: EQ-5D index, direct: time trade-off (TTO)) were applied using an interview method. The Pearson correlation was used to assess the strength of the relationship of different measures in the total study group ($n = 253$). The EQ-5D index (biological treatment: 0.608, non-biological treatment: 0.483; $P = 0.012$) and DAS-28 (biological treatment: 3.8, non-biological treatment: 4.5; $P = 0.003$) showed statistically significant difference between the two subcohorts after adjusting data by age, gender and disease duration. Our results indicate that patients on biological treatment have lower disease activity and higher utility; however, it was not statistically significant in all cases. According to our knowledge, TTO was not used previously in Hungarian RA patients. Utility data concerning biological treatments are essential for cost-utility models in health technology assessment reports for public reimbursement.

Keywords Rheumatoid arthritis · Health-related quality of life · Utility · Biological therapies · Disease-specific quality of life · Time trade-off

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Introduction

Improvement in a clinical parameter results in health gain only if it increases life expectancy and/or patients' health-related quality of life (HRQoL). HRQoL is a broad theoretical term; in the medical literature, quality of life (QoL) is often used as a simple, shorter meaning of HRQoL [1]. It explains measures concerned with the evaluation of health status, attitudes, values and perceived levels of satisfaction and general well-being [2]. Although a patient's QoL is multidimensional and subjective [3], standardised and validated questionnaires are used for QoL measurement, developed to meet psychometric principles. Generic QoL measures such as EuroQol five Dimension [4] (EQ-5D) are designed to be applicable across all diseases or conditions; thus, broad experience has been accumulated with them, although they are less sensitive. Disease-specific measures such as the Rheumatoid Arthritis Quality of Life [5] (RAQoL) questionnaire in rheumatoid arthritis (RA) cannot be used for the comparison of different diseases, but are designed to be relevant to a particular health condition or population; they are more sensitive and preferred in clinical

studies. RA is a chronic autoimmune disease that has a significant impact on a patient's QoL [6, 7].

The last 25 years have seen major developments in the management of RA, most notably since the introduction of the tumour necrosis factor-α (TNF-α) inhibitors in Europe in 1999 [8]. Although today's first-line therapies are disease-modifying antirheumatic drugs (DMARDs) in RA, the so-called biological therapies (such as TNF-α inhibitors) are becoming more and more important [9]. However, these therapies are associated with very high drug costs and a high incremental cost-effectiveness ratio compared to conventional DMARDs [10, 11]. Expensive treatments could be widely available if their cost-effectiveness for public reimbursement is justified [12]. Cost-utility analysis in reimbursement dossiers applies the quality-adjusted life year (QALY) as the health benefit outcome [13]. The QALY combines gains or losses in both quantity of life (mortality) and QoL (morbidity)/utility in a single measure [14, 15]. Utility has two fix anchors: 1 for the perfect health and 0 for dead [16]. As utility is based on preference, states worse than dead can have negative weights [17, 18]. A patient with a utility level of 0.6 for a duration of 2 years accumulates $2 \times 0.6 = 1.2$ QALYs. Utility can be measured with direct (standard gamble (SG), time trade-off [19, 20] (TTO) and Rating Scale [21] (RS)) and indirect (EQ-5D index) utility measures. Measuring utility in RA patients treated with biological drugs is crucial for cost-utility models.

Objectives

The aim of this study is to compare QoL and utility of two RA subcohorts: patients receiving biological treatments and patients on non-biological antirheumatic therapy. The other main goal of this paper is to define the strength of correlation between disease activity (Disease Activity Score (DAS)-28), disease-specific QoL (RAQoL), direct (TTO) and indirect (EQ-5D index) utility measures.

Methods

Two hundred fifty-three patients were interviewed in a cross-sectional, non-interventional study with the authorisation of Semmelweis University Regional and Institutional Committee of Science and Research Ethics. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All patients fulfilled the 1987 revised American College of Rheumatology criteria [22] for RA and gave their informed consent prior to their inclusion in the study. Two cross-sectional cohorts of consecutive patients with RA (aged over 18) were recruited from the outpatient clinic of Rheumatology Unit of Polyclinic of the Hospitaller Brothers of St. John of God in Budapest from April 2009 until July 2009. One subgroup of patients received traditional DMARDs ($n = 168$), whilst the other, the severe destructive subgroup of RA patients, were on biological therapy for at least 6 months ($n = 85$). The Hungarian guidelines [23] recommend the start of TNF-α inhibitors if the patients' response is inadequate to optimal dose of methotrexate (20 mg/week) or leflunomide (20 mg/day) for 3 months, with active or evolving disease (DAS-28 $\geq$ 5.1), or in case of the presence of progression of structural lesions on radiography.

A number of instruments can be used to assess QoL and utility in RA [24]. In this study, the EQ-5D Visual Analogue Scale (VAS) was used to measure generic QoL, and RAQoL was applied as a disease-specific QoL instrument, whilst the TTO and the EQ-5D index were used as utility measures. The questionnaires were previously adapted to Hungary [25–27] and were used with the previous authorisation of their owners.

RAQoL is an RA-specific QoL measure [28] that comprises 30 statements answered with 'yes' or 'no' about activities relevant to patients. The higher the final score, ranging between 0 and 30, represents a worse QoL.

In the TTO method, patients express their preference by choosing between two alternatives: maintaining the actual health state for time T or living for a shorter X time period in perfect health. The duration X would then be varied until the individual was indifferent between the two choices. The utility value of a patient's current health state is calculated as X/T, on a scale where immediate death is 0 and perfect health for lifetime duration is 1 [29]. According to empirical data, TTO indicates a higher utility compared to VAS utility measures or the EQ-5D index, because of the potential loss expressed during the preference choice as a reduction in healthy life expectancy.

The EQ-5D index is a widely used instrument to assess general QoL, focusing on 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 1 item, and each item provides 3 levels with level 1 denoting no problems and level 3 denoting extreme problems [30]. Utility values derived from a UK population survey [31] using the TTO method can be assigned to the $3^5 = 243$ theoretically possible outcomes. The EQ-5D VAS (also known as EQ-5D Thermometer) is a visual scale, calibrated from 0 (worst imaginable health state) to 100 (best imaginable health state).

Statistical analysis

Comparison of demographic parameters between the two different subgroups was made using a two-sample t-test and Fisher's exact test. The levels of significance were set

to 0.05 unless stated otherwise. QoL (RAQoL, EQ-5D VAS), utility (EQ-5D index and TTO) and disease activity (DAS-28) variables were adjusted by age, gender and disease duration in statistical regression models. Normality and homoscedasticity were tested. Pearson correlation coefficient (r) was used to observe the strength of the relation of different measures. Data were analysed using SPSS 15.0 (Statistical Package of Social Sciences) and STATA 10.1 (Data Analysis and Statistical Software).

Results

According to Table 1, a statistically significant difference could be observed within patients with non-biological treatment versus biological treatment in demographic and base characteristics concerning age ($P = 0.003$), patient opinion on disease activity ($P < 0.0001$), patient's pain ($P < 0.0001$) and disease activity score ($P < 0.001$).

Statistically significant row differences could be observed in EQ-5D VAS (difference: 5.73, $P = 0.0391$) and EQ-5D index (difference: 0.124, $P = 0.0035$) indicating a better QoL and higher utility in the biological subgroup. After adjusting the row difference by age, gender and disease duration, the difference of EQ-5D index between the two subgroups remained statistically significant ($P = 0.012$). The utility derived from the TTO was also higher in the biological treatment group. Normality and homoscedasticity were tested. Disease-specific QoL (RAQoL) was slightly better in the non-biological drug group; however, the difference was not significant. Each patient's DAS-28 score was also measured in the biological treatment subgroup at the administration of the first biological drug dose. The mean initial DAS-28 score was 5.9, indicating an average 2.1 DAS-28 score decrease in the biological treatment subgroup. The average duration of biological drug therapy was 2.3 years.

In Table 2, we compared the results of our non-biological treatment subgroup with the observations of Péntek et al. [27, 32, 33] (2004). In that multicenter study, patients with biological treatments were excluded. Concerning the demographic and baseline characteristics, a statistically significant difference was found in disease duration ($P = 0.02$), physician's global assessment ($P < 0.0001$) and DAS-28 (difference 0.6, $P = 0.0001$). Statistically significant differences could be observed concerning QoL measures in EQ-5D VAS (difference: 6.4, $P = 0.0015$) and RAQoL (difference: 4.1, $P < 0.0001$).

Table 3 presents the correlation matrix of DAS-28 and the different QoL (EQ-5D VAS, RAQoL) and utility (EQ-5D index, TTO) measures. Moderate correlation ($0.2 < r < 0.7$) was observed in all cases at the 0.01 significance level. The highest correlation was found between

Table 1 Main characteristics of the observed patients. No biological treatment versus biological treatment

General characteristics, mean (SD)	Total	Biological treatment	Not receiving biological therapy within previous 6 months	Row difference (95% CI)	P-value	Adjusted difference (95% CI)	P-value
N	253	85	168				
Age, year	56.2 (12.6)	52.9 (12.9)	57.8 (12.2)	−4.96 (−8.21; −1.70)	0.0030		
Women, n (%)	220 (87)	75 (88)	145 (86)		0.844		
Disease duration, year	11.5 (9.6)	11.9 (7.0)	11.26 (10.6)	0.69 (−1.84; 3.22)	0.5916		
Physician's global assessment	25.2 (19.3) $n = 170$	24.0 (16.4) $n = 78$	26.1 (21.6) $n = 92$	−2.13 (−8.03; 3.77)	0.4774		
Patient's opinion on disease activity	44.9 (26.3)	34.7 (23.8)	50.0 (26.1)	−15.28 (−21.93; −8.63)	0.0000		
Patient's pain	44.3 (25.5)	34.8 (23.1)	49.1 (25.4)	−14.23 (−20.70; −7.77)	0.0000		
DAS28	4.29 (1.5) $n = 248$	3.8 (1.3) $n = 84$	4.5 (1.6) $n = 164$	−0.70 (−1.09; −0.30)	0.0006	−0.61 (−1.01; −0.20)	0.003
Eq-5D index	0.525 (0.32)	0.608 (0.25)	0.483 (0.35)	0.12 (0.04; 0.21)	0.0035	0.11 (0.02; 0.19)	0.012
Eq-5D VAS	60.1 (20.8)	63.9 (20.6)	58.1 (20.7)	5.73 (0.29; 11.18)	0.0391	4.27 (−1.37; 9.91)	0.137
RAQoL	12.4 (7.5)	12.9 (7.4)	12.1 (7.5)	0.88 (−1.10; 2.85)	0.3846	1.15 (−0.86; 3.15)	0.261
TTO	0.769 (0.21)	0.795 (0.20)	0.755 (0.22)	0.04 (−0.02; 0.10)	0.1863	0.039 (−0.023; 0.100)	0.216

Row difference was adjusted by age, gender and disease duration

RAQoL and EQ-5D index ($r = -0.637$). The results are comparable to those of Péntek et al. According to our knowledge, the TTO method was not used previously in RA patients in Hungary.

Discussion

Both TTO and EQ-5D instruments demonstrated improved QoL in the biological treatment group compared with the non-biological treatment subgroup. Because of the significant age difference of the two subgroups, row difference in QoL and utility was adjusted by age, gender and disease duration, to achieve comparable demographic data. The higher utility (EQ-5D index) of patients in the biological treatment group remained statistically significant after amending data. This suggests that the difference cannot be ascribed to demographic characteristics.

Interestingly, the mean DAS-28 score was 3.8 in the biological treatment subgroup, indicating an average decrease of 2.1 DAS-28 score if comparing it to baseline (average initial DAS-28 was 5.9 when starting biological treatments). These data suggest that patients in the biological subgroup represent a more severe initial health status than patients treated with DMARDs only. The statistically significant DAS-28 advantage compared to the conventional treatment group remains stable after adjusting row results ($P = 0.003$), underlining the significance of the utility advantage of the biological group.

As our research was of single-centre design, we compared our results to a previous Hungarian study by Péntek et al. The differences may originate from different study design: the previous research (2004) was conducted at six locations; thus, it represents a wider Hungarian practice. Data indicate that the study population of Péntek et al. represents patients with more severe health status (higher DAS-28, lower QoL and utility values in all measures) compared to the non-biological treatment subgroup of our study. This subgroup in our study was the comparator for the biological drug subgroup, and additional utility advantage of biological drugs has been proved against this group of patients. This also highlights the value of our findings concerning the utility advantage of biological drugs.

Our findings of the TTO method (mean score: 0.769) supported the hypothesis that it results in higher utility than the Visual Analogue Scales or EQ-5D index (0.525). We compared our QoL and utility results with previous RA-QoL studies in the literature (Table 4). Ariza-Ariza et al. [29] found likewise a higher mean TTO score (0.81) than EQ-5D index (0.53), whilst mean EQ-5D VAS was 55.95. Tijhuis et al. [20] found a median TTO score of 0.77 which is similar to our results and a median RAQoL score of 16. Mean utility values derived from the TTO (0.86) and EQ-5D index (0.52) by Witney et al. [34] are also comparable to our findings and indicate that the TTO may overestimate utility compared with indirect utility measures (EQ-5D index). Scott et al. [35] reported an EQ-5D index of 0.45 in a cross-sectional observational study, with higher mean age (60 years) but shorter mean disease duration (9 years), whilst the mean DAS score was 4.7. These results show an older patient population with higher disease activity and consequently lower utility (EQ-5D index). In the study by Marra et al. [36], mean disease duration was longer (13.87 years), and average age was higher (61.5 years); they found an EQ-5D index value of 0.66, indicating better general QoL than in our study. However, the RAQoL score of 12.82 is comparable to our results. EQ-5D VAS was also found to be better (65.02) than in the two Hungarian studies.

Table 2 The comparison of patients not receiving biological therapy with the previous RA study (2004) in Hungary

General characteristics, mean (SD)	Péntek et al. [27, 32, 33] Non-biological treatment	This study Not receiving biological therapy within previous 6 months	Row difference (95% CI)	*P*-value
N	255	168		
Age, year	55.5 (12.3)	57.8 (12.2)	−2.3 (−4.69; 0.09)	0.0597
Women, *n* (%)	218 (86)	145 (86)		0.887
Disease duration, year	9.0 (9.3)	11.26 (10.6)	−2.26 (−4.18; −0.34)	0.0212
Physician's global assessment	39.2 (22.9)	26.1 (21.6) $n = 92$	13.1 (7.70; 18.50)	0.0000
Patient's opinion on disease activity	47.0 (22.8)	50.0 (26.1)	−3 (−7.72; 1.72)	0.2122
Patient's pain	48.7 (24.0)	49.1 (25.4)	−0.4 (−5.20; 4.40)	0.8699
DAS28	5.1 (1.4)	4.5 (1.6) $n = 164$	0.6 (0.31; 0.89)	0.0001
Eq-5D index	0.46 (0.33)	0.483 (0.35)	−0.023 (−0.089; 0.043)	0.4939
Eq-5D VAS	51.7 (19.8)	58.1 (20.7)	−6.4 (−10.34; −2.46)	0.0015
RAQoL	16.2 (8.1)	12.1 (7.5)	4.1 (2.56; 5.64)	0.0000
TTO	–	0.755 (0.22)		

Table 3 Pearson *r* correlation values between generic disease-specific quality of life measures and disease activity

Measures	This study					Péntek et al. [27, 32, 33]			
	TTO	DAS28	EQ5D index	EQ5D VAS	RAQoL	DAS28	EQ5D index	EQ5D VAS	RAQoL
TTO	1	−0.279 $n = 214$	0.299 $n = 217$	0.252 $n = 217$	−0.302 $n = 217$	–	–	–	–
DAS28		1	−0.523 $n = 247$	−0.367 $n = 247$	0.471 $n = 247$	1	−0.494 $n = 243$	−0.336 $n = 243$	0.37 $n = 243$
EQ5D index			1	0.561 $n = 252$	−0.637 $n = 252$		1	0.419 $n = 249$	−0.654 $n = 249$
EQ5D VAS				1	−0.465 $n = 252$			1	−0.389 $n = 245$
RAQoL					1				1

Level of significance in all cases: 0.01

Table 4 International comparison with other quality of life studies in rheumatoid arthritis

Mean values	This study	Tijhuis et al. [20]	Ariza-Ariza et al. [29]	Whitney et al. [34]	Scott et al. [35]	Marra et al. [36]
TTO score	0.77	0.77 (median)	0.81	0.86		
EQ-5D index	0.525		0.53	0.52	0.45	0.66
EQ-5D VAS	60.1		55.95			65.02
RAQoL	12.4	16				12.82

Although the strength of correlation of instruments was also observed within each subgroup in our study, no connection between the r values and the use of biological treatment could be identified. Correlation values among different impairment (DAS-28), QOL (EQ-5D VAS, RAQoL) and utility (EQ-5D index, TTO) measures were also compared with the previous studies. Our correlation values with TTO support the previous findings in the medical literature: Ariza-Ariza et al. [29] reported significant but poor correlation between TTO and the EQ-5D index (Pearson's product-moment correlation, $r = 0.29$), an $r = -0.28$ between TTO and DAS-28 and $r = -0.47$ between DAS-28 and EQ-5D. In our study, we found r values in these relations of $r = 0.299$, $r = -0.279$ and $r = -0.523$, respectively. Tijhuis et al. [20] identified Spearman's correlation coefficients between TTO–RAQoL and TTO–DAS-28 (-0.34 ($P < 0.01$) and -0.19 ($P < 0.05$), respectively). We found Spearman's correlation coefficients in these cases of -0.308 ($P < 0.001$) and -0.263 ($P < 0.001$), respectively. However, Bejia et al. [37] did not find any correlation between TTO and DAS. These previous findings support the validity of our correlation results.

Conclusion

Although patients having biological treatment are supposed to be a subgroup with more severe initial health status and worse QoL than patients treated with DMARDs only, according to our results, they showed higher utility; however, the advantage was not significant in all cases. As our comparator subgroup (the non-biological treatment group) had lower disease activity, better QoL and higher utility according to all measures, compared with a previous multicenter Hungarian study group, the utility advantage of the biological subgroup is even more meaningful. According to our knowledge, the TTO was not used previously in Hungarian RA patients. Our data confirmed that the TTO approach results in higher utility scores compared with the EQ-5D index. All observed instruments correlated moderately in our study.

Conflict of interest The authors declare that they have no conflict of interest. This study was not funded by a pharmaceutical company/medical device manufacturer or any other profit-making stakeholders.

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