Treatment with the first TNF inhibitor in rheumatoid arthritis patients in the Hellenic Registry of Biologic Therapies improves quality of life especially in young patients with better baseline functional status

N. Boubouchairopoulou[1], I. Flouri[2], A.A. Drosos[3], K. Boki[4], L. Settas[5], D. Zisopoulos[6], F.N. Skopouli[7], I. Papadopoulos[8], A. Iliopoulos[9], J. Kyriopoulos[1], D.T. Boumpas[10], K. Athanasakis[1], P. Sidiropoulos[2]

[1]Department of Health Economics, National School of Public Health, Athens, Greece; [2]Rheumatology, Clinical Immunology and Allergy, Medical School, University of Crete, Greece; [3]Rheumatology Clinic, Department of Internal Medicine, Medical School, University of Ioannina, Greece; [4]Rheumatology Department, Sismanoglio Hospital, Athens, Greece; [5]First Department of Internal Medicine, Rheumatology Section, AHEPA Hospital of the Aristotle University Medical School, Thessaloniki, Greece; [6]Department of Rheumatology, 424 General Army Hospital, Thessaloniki, Greece; [7]Department of Nutrition and Diebetics, Harokopio University, Athens, Greece; [8]Rheumatology Clinic, General Hospital of Kavala, Greece; [9]Department of Rheumatology, Veterans Administration Hospital, Athens, Greece; [10]Joint Academic Rheumatology Program, Faculty of Medicine, National and Kapodestrian University of Athens, Greece.

Abstract

Objective

To assess in daily practice in patients with rheumatoid arthritis (RA) the effect of treatment with first tumour necrosis factor-α inhibitor (TNFi) in quality of life (Qol), disease activity and depict possible baseline predictors for gains in Qol.

Methods

Patients followed prospectively by the Hellenic Registry of Biologic Therapies were analysed. Demographics were recorded at baseline, while RA-related characteristics at baseline and every 6 months. Paired t-tests were used to detect divergences between patient-reported (Health Assessment Questionnaire (HAQ), EuroQol (EQ-5D)) and clinical tools (Disease Activity Score-28 joints (DAS28)). Clinical versus self-reported outcomes were examined via cross-tabulation analysis. Multiple regression analysis was performed for identifying baseline predictors of improvements in QALYs.

Results

We analysed 255 patients (age (mean±SD) 57.1±13.0, disease duration 9.2±9.1 years, prior non-biologic disease-modifying anti-rheumatic drugs 2.3±1.2). Baseline EQ-5D, HAQ and DAS28 were 0.36 (0.28), 1.01 (0.72) and 5.9 (1.3), respectively, and were all significantly improved after 12 months (0.77 (0.35), 0.50 (0.66), 3.9 (1.5), respectively, $p<0.05$ for all). 90% of patients who improved from high to a lower DAS28 status (low-remission or moderate) had clinically important improvement in Qol (phi-coefficient=0.531,$p<0.05$). Independent predictors of gains in Qol were lower baseline HAQ, VAS global and younger age (adjusted $R^2=0.27$).

Conclusion

In daily practice TNFi improve both disease activity and Qol for the first 12 months of therapy. 90% of patients who improved from high to a lower DAS28 status had clinically important improvement in Qol. Younger patients starting with lower HAQ and VAS global are more likely to benefit.

Key words

rheumatoid arthritis, TNF inhibitors, quality of life, Disease Activity Index-28 (DAS28), HAQ, EQ-5D

*Nadia Boubouchairopoulou**
*Irini Flouri, MD**
Alexandros A. Drosos, MD, FACR
Kyriaki Boki, MD
Loukas Settas, MD, PhD
Dimitrios Zisopoulos, MD
Fotini N. Skopouli, MD, PhD
Ioannis Papadopoulos, MD
Alexios Iliopoulos, MD
John Kyriopoulos, MD, PhD
Dimitrios T. Boumpas, MD, PhD
Konstantinos Athanasakis, BSc Econ, Msc Econ, PhD
Prodromos Sidiropoulos, MD, PhD

**These authors contributed equally to this study.*

Please address correspondence to:
Prodromos I. Sidiropoulos, MD,
Rheumatology,
Clinical Immunology and Allergy,
University of Crete Medical School,
Voutes, 71110 Heraklion, Greece
E-mail: sidiropp@uoc.gr

Received on February 15, 2016; accepted in revised form on March 7, 2016.

Funding: this work was supported in part by the Hellenic Rheumatology Society through unrestricted grants from Shering-Plough, Abbott, Wyeth, Bristol Myers Squibb and Roche.
These companies had no role in the study design, collection, analysis or interpretation of the data, the writing of the manuscript or in the decision to submit it for publication.

Competing interests: none declared.

Introduction

In the recent Global Burden of Disease Study, musculoskeletal conditions including rheumatoid arthritis (RA), represented the second highest burden of diseases globally, when expressed as years lived with disability (1). RA is a chronic autoimmune inflammatory disease causing musculoskeletal pain, disability and reduced life expectancy. Its prevalence in Western Europe is estimated to 0.63% in females and 0.24% in males, while it increases significantly up to 2% in the adult population aged over 60 years (2).

The treatment paradigm of RA has significantly improved and novel therapies have been introduced since the last 15 years. Early diagnosis, treatment with disease-modifying anti-rheumatic drugs (DMARDs) and recognition of the importance of comorbidities are important gains in the management of the disease. Moreover, introduction of targeted biologic therapies, like TNFi and other biologic agents is a step further in improving the quality of life of the more aggressive cases. Data from patient's registries (3-5) have added significant knowledge about long-term efficacy and safety, while treatment guidelines aim to improve everyday clinical practice (6). Application of patient's reported outcomes as well as cost analysis are of great importance to analyse the impact of novel expensive therapies in every day clinical practice.

In that context, economic evaluations of new treatments have gained ground in many healthcare systems, even as a prerequisite for reimbursement, in order to assess their effectiveness but also their cost and to enable the comparison between alternative options for the same disease, and even between drugs of different diseases. The main outcome of such an analysis is the cost per quality-adjusted life year (QALY) gained.

In light of the above, the present study aimed to investigate the association between clinical and patient-reported outcomes for RA, as well as at detecting the variables that could significantly influence the number of QALYs gained, in a Greek real life medical setting. We sought to investigate changes in patient reported outcomes and how improvements in clinical characteristics may modify QALYs gained.

Materials and methods

Patients and data collection

The sample consisted of patients with a diagnosis of RA followed within the Hellenic Registry for Biologic Therapies (HeRBT) cohort. All patients from 7 university and state rheumatology clinics (4) who according to their physician opinion and based on national guidelines were eligible to receive a TNFi (adalimumab, etanercept or infliximab) were prospectively registered. The diagnosis of RA was based on physician's clinical judgment. Demographic data were collected at baseline, whereas clinical and patient-reported data were obtained, at baseline, 6 and 12 months of follow-up. For the current study we analysed patients for whom relevant infosmation required for the present analysis, was available for the first year of treatment.

Recorded data included general demographic information such as the patients' gender and age, while RA-related data such as disease duration (DD), the number of non-biologic DMARDs (nb-DMARDs) used prior to biologic TNFi therapy initiation, were also recorded. Disease activity was based on the composite Disease Activity Score of 28 joints (DAS28) (7), while patient-reported data were collected through two health-related quality of life questionnaires, the Health Assessment Questionnaire for Rheumatoid Arthritis (HAQ) (8) and the EuroQol EQ-5D, both having previously been adapted and validated into Greek (9). Moreover, data on ongoing treatments (steroids, DMARDs), dose of the treatments as well as events while on follow-up were recorded.

Outcome measures

The DAS28 is an instrument used in clinical practice for measuring rheumatoid arthritis' disease activity through a composite score. There are cutoff values to categorise patients in low, moderate, or high disease activity, while it is also used as a tool to define response to therapy (EULAR response categories) (7, 10).

The Health Assessment Questionnaire (HAQ) is a patient-reported tool providing information on patients' physical function, reflecting the degree of difficulty that patients encounter in performing their daily activities, and detecting the changes perceived. The full HAQ questionnaire consists of 20 questions assessing all 5 dimensions of health outcomes: disability, discomfort, drug toxicity, health care utilisation and cost and death. Nevertheless, HAQ has been subjected to several modifications in order to improve its reliability and sensitivity. The participants of the present study were asked to fill in this shorter form of the HAQ questionnaire.
The EuroQol EQ-5D is the most widely used instrument for assessing quality of life. It includes five questions on mobility, self-care, pain, usual activities and psychological status, each of which can be characterised by three severity levels (no problems, moderate problems and severe problems. These five dimensions result in a total of 243 possible health states ranging from worst (score 0) to total health (score 1), which through specific valuations result in utility values. The EQ-5D scores, are widely used for estimating the Quality Adjusted Life Years (QALYs) gained (11), which represent the main technique used nowadays for measuring the health benefits of an intervention. Each health state is associated with a utility value at a particular point of time. A gain in QALYs for a given period of time reflects an improvement or response to the intervention.

Statistical analysis

Paired *t*-tests were used in order to detect possible significant differences in EQ-5D, HAQ, DAS28 scores, the number of swollen and tender joints, global VAS, and CRP levels at 6 and 12-months of follow-up compared to previous visits, with *p*-value <0.05 being considered as statistically significant.
In order to examine the clinical versus self-reported outcomes, patients were sub-grouped in four categories according to changes in DAS28 scores obtained at 6 and 12-months of follow-up compared to baseline scores. The first category included patients who remained in the same disease state, the second subjects who improved from high to moderate or low disease activity (or remission), while accordingly, in the third group were patients who improved from moderate to low disease activity (and remission) at 6 or 12 months. Finally, the fourth group included patients characterised by disease progression with RA disease activity increasing from lower to moderate or from moderate to higher levels.
A cross-tabulation analysis of the aforementioned subgroups versus the EQ-5D responses was then performed, considering as minimally important differences changes in EQ-5D scores of more than 0.05 (the cut-off for clinically important differences). In literature MIDs ranging from 0.05 to 0.13 have been proposed for RA; due to the lack of Greek specific data the MID used in the present study was that used in previous studies (12, 13).
We then grouped changes in DAS28 categories 2 and 3 as "$DAS28_{regression}$", DAS28 groups 1 and 4 as "$DAS28_{no\ regression}$" and accordingly MID scores over 0.05 as "$EQ\text{-}5D_{response}$" and MID scores below 0.05 as "$EQ\text{-}5D_{no\ response}$", and four possible combinations emerged. These combinations were subsequently used for performing ANOVA tests, in order to investigate the association of each DAS28 component with the following DAS28/EQ-5D combinations: 1) $DAS28_{no\ regression}$/$EQ\text{-}5D_{no\ response}$, 2) $DAS28_{no\ regression}$/$EQ\text{-}5D_{response}$, 3) $DAS28_{regression}$/ $EQ\text{-}5D_{no\ response}$, 4) $DAS28_{regression}$/ $EQ\text{-}5D_{response}$.
Multiple regression models were adapted for detecting the variables that could predict the change in QALYs after one year of treatment. Age, gender, disease duration, CRP, the components of DAS28, were included as possible independent variables. Possible associations between these variables were firstly examined in order to avoid multicollinearity. The remaining independent variables were then included in the analysis, and the final model resulted by removing the insignificant variables (*p*-value >0.05) with stepwise backward selection.
All the aforementioned statistical analyses were performed with IBM SPSS Statistics v. 20.0 software package.

Table I. Baseline characteristics of patients. Values are mean±SD except for the gender.

Characteristic	Valid cases	Values
Women, %	255	78
Age at the disease's onset (yrs)	255	48.0 ± 13.9
Age at the inclusion date (yrs)	255	57.1 ± 13.0
Disease duration (yrs)	255	9.2 ± 9.1
DMARDs previously administered	254	2.3 ± 1.2
DMARDs administered at baseline	255	1.0 ± 0.5

Results

Patients' baseline characteristics

A total of 255 patients for whom available data for the first year of treatment with the first TNFi were available from the Hellenic Registry for Biologic Therapies were analysed. In Table I are the baseline characteristics of the patients. A total of 255 patients were included, 78% of whom were women. The mean DD at the time of recruitment was 9.2±9.1 years, with mean age at baseline and at the disease's onset being 57.1±13.0 years and 48.0±13.9 accordingly. On average, the participants have been previously administered 2.3 nb-DMARDs. TNFi treatments included adalimumab, etanercept and infliximab, and were administered to 53, 57 and 111 patients accordingly. Notably, when we compared baseline characteristics (demographics and disease characteristics) of the patients analysed herein with the total cohort (n=1017) analysed on 2014, no significant differences were found (data non shown)(4).

Clinical and self-reported data

The mean (SD) values of EQ-5D, HAQ and DAS28 at baseline were 0.36 (0.28), 1.01 (0.72) and 5.9 (1.3) accordingly, while the number of swollen and tender joints being on average 8.7 and 10.6 for the study population (Table I). An average of 65.8 mm was obtained

on the global VAS at baseline, while the mean levels of CRP for the same time point were 2.4 mg/l.

All the aforementioned indexes were significantly improved after 6 months of follow-up compared to the baseline values (Table II). Accordingly, these clinical parameters remained statistically significant improved compared to baseline at 12 months of follow-up (Table II). Moreover, 72% and 83 % of the patients on therapy at 6 or 12 months respectively had a response according to the EULAR criteria (good or moderate).

Table II. EQ-5D, HAQ, and DAS28 mean scores (SD) at baseline, 6 months and 1 year and significant differences from baseline visits.

Measure	Valid Cases	Baseline	Valid Cases	6 months	Valid Cases	1 Year
EQ-5D	251	0.36 (0.28)	229	0.77 (0.35)*	177	0.77 (0.35)
HAQ	249	1.01 (0.72)	238	0.49 (0.61)*	189	0.50 (0.66)
DAS28	248	5.9 (1.3)	236	4.1 (1.4)*	191	3.9 (1.5)*
Swollen joints	251	8.7 (6.1)	243	4.3 (4.7)*	197	3.7 (4.3)*
Tender joints	251	10.6 (7.3)	243	4.9 (5.7)*	197	3.7 (5.3)*
Global VAS	252	65.8 (22.5)	243	37.8 (26.3)*	197	36.1 (27.4)
CRP	240	2.4 (3.1)	218	0.9 (3.2)*	183	0.9 (1.6)

Values are mean (±SD). *Indicates statistically significant difference from baseline visit according to paired *t*-tests (p-value <0.05).

Association between clinical and self-reported outcomes at 6 months and 1 year

An interesting question is to assess whether upon treatment clinical improvements associate to gains in quality of life. Thus we then analysed responses based on QALYs (MID) across different groups of response to therapy at 6 and 12 months of treatment, as described in the Statistical analysis section. As aforementioned, participants were classified into four categories according to DAS28 scores achieved at 6 or 12 months as compared to baseline DAS28, in combination to EQ-5D changes. In total, among the study population (*i.e.* 233 patients out of the initial 255 for the cross tabulation analysis), 59.2% transitioned to a lower disease activity state after 6 months of treatment, and 72.1% achieved MID according to the EQ-5D index. After 6 months of treatment, 89.3% of the patients who improved from high to moderate, low diseaseactivity or remission achieved MID response while the respective value for patients who improved from moderate to low disease activity was 76.5%. Interestingly 47.7% of the patients who remained in the same state presented no MID response, as compared to 77.8% of the patients who experienced disease progression. The phi-coefficient, measuring the effect size, thus the extent at which the clinical and self-reported results are related, was estimated at 0.443, highlighting a moderate but significant correlation between the aforementioned variables (p-value <0.05). At that point it must be mentioned that when examining the association between gains in quality of life and response to therapy based on EULAR response categories instead of DAS28 status, the aforementioned figures were comparable and reflected the same relationship (data not shown).

The same analysis for 165 patients was performed for the clinical and self-reported outcomes recorded after 1 year of treatment. In total, considering the whole population included in the analysis (*i.e.* 165 patients), 73.4% changed to lower DAS28 category and 78.8% achieved MID according to the EQ-5D index. 91.9% of the patients who improved DAS28 from high to a lower status had also significant improvement in QALYs gained. Importantly, 61 out of 68 patients (89.7%) who after 12 months improved from high to moderate disease activity status, also had significant improvement in EQ-5D (MID>0.05). The respective value for those improved from moderate to low disease activity was 90.0% (Table III). Among patients who remained in the same state 58.5% had no MID response. Finally, regarding the patients who after 1 year of treatment presented a disease progression, no conclusions can be drawn as only three patients experienced such transition. An also moderate relationship between the two variables was outlined after one year of treatment, according to the phi-coefficient, estimated at 0.531 (p-value <0.05), being nevertheless higher than the coefficient calculated after 6 months as mentioned above.

Association of the DAS28 components with the DAS28/EQ-5D combinations

Among the components of DAS28 index, swollen joint count is considered as the most important contributor to disease process. Moreover, upon treatment a differential improvement of the 4 different components of DAS28 may occur. Thus, we questioned whether changes in individual components of the DAS28 index correlate to changes in quality of life. For that purpose we analysed changes of the individual DAS28 components according to EQ-5D category. The mean reduction in swollen joints ranged from 1.3 in the $DAS28_{no\ regression}$/$EQ\text{-}5D_{no\ response}$ group to 6.5 in the $DAS28_{regression}$/$EQ\text{-}5D_{response}$ group after 6 months of treatment, whereas the respective values after 1 year of treatment were 2.3 and 7.3. Significant differences in swollen joints' reduction were noticed between $DAS28_{regression}$/$EQ\text{-}5D_{response}$as compared to $DAS28_{no\ regression}$/$EQ\text{-}5D_{no\ response}$or $DAS28_{no\ regression}$/$EQ\text{-}5D_{response}$groups for 6 months of treatment; considering outcomes after 1 year, the mean difference was significant between group $DAS28_{no\ regression}$/$EQ\text{-}5D_{no\ response}$ compared to $DAS28_{regression}$/$EQ\text{-}5D_{response}$ and $DAS28_{no\ regression}$/$EQ\text{-}5D_{response}$groups (p<0.05).

Accordingly, the mean reductionin tender joints in the aforementioned groups ranged from 0.5 to 8.3 after 6 months and from 1.7 to 9.0 after 1 year. Significantly smaller reductions were observed in the $DAS28_{no\ regression}$/$EQ\text{-}5D_{no\ response}$ category as compared to$DAS28_{regression}$/$EQ\text{-}5D_{no\ response}$and $DAS28_{regression}$/$EQ\text{-}5D_{response}$groups, and in between $DAS28_{no\ regression}$/$EQ\text{-}5D_{response}$and $DAS28_{regression}$/$EQ\text{-}5D_{response}$ groups after 6 months (p<0.05). Outcomes after 12 months of treatment slightly differed as significant differences were discerned between $DAS28_{no\ regression}$/$EQ\text{-}5D_{no\ response}$and $DAS28_{no\ regression}$/$EQ\text{-}5D_{response}$or $DAS28_{regression}$/$EQ\text{-}5D_{response}$ groups.

Table III. DAS28 disease progression classification versus minimally important differences according to EQ-5D after 6 months and 1 year.

Response according to DAS 28	Minimally important differences according to EQ-5D		Total
	No response	Response	
Clinical versus self-reported outcomes after 6 months (n=233)			
Remaining in the same state (no response)	41 (47.7%)	45 (52.3%)	86
Disease progression (no response)	7 (77.8%)	2 (22.2%)	9
Transition from high to lower disease activity states (response)	13 (10.7%)	108 (89.3%)	121
Transition from moderate to lower disease activity states (response)	4 (23.5%)	13 (76.5%)	17
Total	65	168	233
Clinical versus self-reported outcomes after 1 year (N=165)			
Remaining in the same state (no response)	24 (58.5%)	17 (41.5%)	41
Disease progression (no response)	1 (33.3%)	2 (66.7%)	3
Transition from high to lower disease activity states (response)	9 (8.1%)	102 (91.9)	111
Transition from moderate to lower disease activity states (response)	1 (10.0%)	9 (90.0%)	10
Total	35	130	165

Similarly, the same methodology was followed in order to investigate the relationship between the reduction in global VAS and the possible DAS28/EQ5D combinations. However, as according to the Levene's test the variances among the different groups did not differentiate significantly (p-value <0.05) for the analysis concerning the data at 6 months of treatment, the ANOVA test could only be applied to the outcomes observed after 6 months of follow-up. Therefore, the mean reduction in global VAS ranged from -1.4 to 47.4mm, while statistically significant differences were observed among all groups except when comparing mean reductions of $DAS28_{no\ regression}$/$EQ\text{-}5D_{no\ response}$ and $DAS28_{regression}$/$EQ\text{-}5D_{no\ response}$ groups.

Regarding CRP levels, for the same reasons described above, only reduction after 6 months of therapy was considered. The mean reduction of CRP levels ranged from -0.2 to 1.9 mg/l, while significant differences were detected only between $DAS28_{no\ regression}$/$EQ\text{-}5D_{no\ response}$ and $DAS28_{regression}$/$EQ\text{-}5D_{response}$ groups.

Table IV. Multiple linear regression with quality-adjusted life years as dependent variables; adjusted R^2=0.27.

Independent variables	Coefficient (95% CI)
Age	-0.002 (-0.004; 0.000)
Gender	-0.031 (-0.086;0.024)
HAQ	-0.099 (-0.135; -0.064)
No of swollen joints	-0.003 (-0.007; 0.002)
No of tender joints	0,000 (-0.003; 0.004)
Global VAS	-0.002 (-0.003; 0,000)
CRP levels	-0.003 (-0.010; 0.005)

Baseline predictors of gains in QALYs at first year

The mean gain in QALYs after one year of treatment for the total study population was 0.49±0.21. We finally analysed which of the baseline parameters (clinical, demographics, drugs) could predict gains in QALYs after 1 year of treatment. For this we applied the regression linear model, after checking for possible multi collinearities, included age, gender, HAQ, number of swollen and tender joints, global VAS and CRP levels, as independent variables which could possibly be associated with the observed changes in QALYs gained after one year of treatment. The analysis resulted in highlighting HAQ, global VAS and patients' age as the significant variables correlating with QALYs' changes at 1 year. These data suggest that QALYs' gain after 1 year of therapy increases with lower baseline HAQ and global VAS for younger patients (Table IV).

Discussion

Studies have shown that among 291 medical conditions RA is ranked as the 42nd highest contributor to global disability, just below malaria and just above iodine deficiency (2). Thus we consider of great importance data, as those of the present study, assessing the effect of high cost biologic treatments on quality of life in every day clinical practice. Quality of life measures have gained ground as a supplement outcome to the objective clinical measures of several diseases, including RA. Their increasing use reflects the extent at which nowadays, clinicians are taking into account patients' perspective of their disease and treatment. The outcomes resulting from these assessments should therefore be considered not only for evaluating the benefits of new treatments, but also for improving treatment adherence and patients' health state as supported by scientific evidence.

Our main findings are that in RA patients with established, long lasting and resistant to non-biologics DMARDs, clinical outcomes correlated with patient-reported outcomes with almost 90% of the patients who improve disease activity also showing a clinically significant improvement in quality of life. Interestingly, 89.7% of patients with improvements in disease activity but who still at 12 months had residual disease activity (moderate DAS28) had clinically important improvement in QALYs. Moreover, low baseline HAQ, patient's global VAS for disease activity and younger age, were independent predictors of QALYs' gain after 1 year of therapy.

We performed the present analysis in a sub-group of 255 patients followed by the Hellenic Registry of Biologic Therapies, for whom available data for the first year of treatment with the first TNFi were available. This group is rep-

resentative of the whole cohort since baseline demographic and disease characteristics were comparable (4). In the herein reported group, mean values of disease activity (DAS28), functional ability (HAQ) and quality of life (QALYs) improved significantly, while 72% and 83% of the patients at 6 and 12 months of therapy respectively were responders according to EULAR criteria. Accordingly, these data are comparable to the data of the 1028 patients analysed on 2014, which have shown a 72% response rate at 6 months (4).

It is an important clinical question to assess whether clinical improvements are associated with gains in quality of life, especially in a real word setting. In this group of established (mean DD: 9.2 years) and difficult to treat (mean number of previous nb-DMARDs: 2.3) RA patients, we depicted a mean gain in QALYs of 0.49±0.21 after one year of treatment. Our data corroborate data of Gulfe *et al*. who have shown a mean (95% CI) increase of 0.21 (0.19, 0.23) in QALYs (14), and an earlier study in which gains in quality of life at 1 year (increase of EQ-5D from 0.56 (SD 0.3) to 0.70 (SD 0.2)) remained for the 5 years of follow-up (15). Interestingly, approximately 90% of our patients with improvement in disease activity from high to lower DAS28 status, had also clinically important improvements in QALYs gained. This was evident both at 6 and 12 months of treatment. On the contrary, almost 50% and 80% of those with stable or deteriorated disease activity respectively, experienced no improvement in quality of life. The above data support the "value" of therapy in the responders group, since clinical improvement was accompanied by important improvement in quality of life and function.

An interesting finding of our cohort was that even patients with improvement but still residual moderate disease activity after 12 months, 90% of them had a clinically significant improvement in quality of life. This is a substantial group of patients in clinical practice, since in the cohort of the HeRBT moderate disease activity group represents approximately 48%–54% of the patients at 6 or 12 months of therapy. As rheumatologists we know that although according to the EULAR guidelines the aim of treatment is remission or low disease activity, we all confront with patients who although improved, still have moderate disease activity and are satisfied with current status. The present data, showing that patients who had a substantial improvement in quality of life albeit moderate residual disease activity, could support the practice of conditionally remaining on active treatment than switching to another biologic therapy.

Rheumatoid arthritis is considered as a heterogeneous disease, and thus we analysed the correlation of responses according to EULAR and EQ5D categories, to changes in several clinical parameters. Of note it has been shown that RA disease activity affects Qol in all domains (16). We found that improvements in swollen joint counts and patients' global scores associated to improvements in EULAR/EQ5D scores, while there was a weaker correlation to tender joint counts and no correlation to inflammatory markers (CRP). Although this could represent the correlation of the aforementioned individual parameters with the DAS28 index, it may also underscore that those parameters also drive quality of life. An interesting finding though was that swollen joint counts was the parameter with the highest correlation. Our data corroborate data from Danish patients showing that the gain in QALYs increased with increasing patient global score and number of swollen joints (12).

A clinical important issue is to predict which of the patients are those who are going to be benefited the most from biologics. In our patients, the multivariate analysis showed that baseline HAQ, global VAS and patients' age were independent predictors of gains in quality of life at 12 months. These data suggest that QALYs gained after 1 year of therapy were higher in younger patients with better baseline functional status. Comparing to the predictors for better response in patients of daily practice, data from the HeRBT have shown that younger age, male sex, lower VAS pain and SJC were independent predictors for low DAS28 at 18 months. These data support that those patients who are generally profited from TNFi agents are younger patients with a better baseline status.

In conclusion, our data support that in a real word setting, 72% of patients with established RA have clinically important gain in quality of life after 1 year of treatment with the first TNFi. The majority of patients with clinical responses, even those who still on moderate disease activity, had concomitant clinically significant improvements in quality of life.

Acknowledgement

We would like to thank the Hellenic Rheumatology Society for the support. We are grateful to Pierre Geborek, MD, University of Lund, for providing us with the software of the database, the protocol and for continuous support for the organisation of the HeRBT.

References

1. VOS T, FLAXMAN AD, NAGHAVI M *et al*.: Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380: 2163-96.
2. CROSS M, SMITH E, HOY D *et al*.: The global burden of rheumatoid arthritis: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis* 2014; 73: 1316-22.
3. DIXON WG, SYMMONS DP: What effects might anti-TNFalpha treatment be expected to have on cardiovascular morbidity and mortality in rheumatoid arthritis? A review of the role of TNFalpha in cardiovascular pathophysiology. *Ann Rheum Dis* 2007; 66: 1132-6.
4. FLOURI I, MARKATSELI TE, VOULGARI PV *et al*.: Comparative effectiveness and survival of infliximab, adalimumab, and etanercept for rheumatoid arthritis patients in the Hellenic Registry of Biologics: Low rates of remission and 5-year drug survival. *Semin Arthritis Rrheum* 2014; 43: 447-57.
5. VAN DEN BERG R, VAN DER HEIJDE D, LANDEWÉ R, VAN LAMBALGEN K, HUIZINGA T: The METEOR initiative: the way forward for optimal, worldwide data integration to improve care for RA patients. *Clin Exp Rheumatol* 2014; 32 (Suppl. 85): S-135-40.
6. SMOLEN JS, LANDEWÉ R, BREEDVELD FC *et al*.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014; 73: 492-509.
7. 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; 38: 44-8.

8. PINCUS T, SUMMEY JA, SORACI SA, JR., WALLSTON KA, HUMMON NP: Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. *Arthritis Rheum* 1983; 26: 1346-53.
9. KONTODIMOPOULOS N, PAPPA E, NIAKAS D, YFANTOPOULOS J, DIMITRAKAKI C, TOUNTAS Y: Validity of the EuroQoL (EQ-5D) instrument in a Greek general population. *Value Health* 2008; 11: 1162-9.
10. VAN GESTEL A, PREVOO M, VAN 'T HOF M, VAN RIJSWIJK M, VAN DE PUTTE L, VAN RIEL P: Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/ International League Against Rheumatism Criteria. *Arthritis Rheum* 1996; 39: 34-74.
11. HURST NP, KIND P, RUTA D, HUNTER M, STUBBINGS A: Measuring health-related quality of life in rheumatoid arthritis: validity, responsiveness and reliability of EuroQol (EQ-5D). *Br J Rheumatol* 1997; 36: 551-9.
12. LINDE L, SORENSEN J, OSTERGAARD M, HETLAND ML: Gain in quality-adjusted life-years in patients with rheumatoid arthritis during 1 year of biological therapy: a prospective study in clinical practice. *J Rheumatol* 2013; 40: 1479-86.
13. MARRA CA, WOOLCOTT JC, KOPEC JA *et al*.: A comparison of generic, indirect utility measures (the HUI2, HUI3, SF-6D, and the EQ-5D) and disease-specific instruments (the RAQoL and the HAQ) in rheumatoid arthritis. *Soc Sci Med* 2005; 60: 1571-82.
14. GULFE A, KRISTENSEN LE, SAXNE T, JACOBSSON LT, PETERSSON IF, GEBOREK P: Utility-based outcomes made easy: the number needed per quality-adjusted life year gained. An observational cohort study of tumor necrosis factor blockade in inflammatory arthritis from Southern Sweden. *Arthritis Care Res* (Hoboken) 2010; 62: 1399-406.
15. KIEVIT W, FRANSEN J, ADANG EM *et al*.: Long-term effectiveness and safety of TNF-blocking agents in daily clinical practice: results from the Dutch Rheumatoid Arthritis Monitoring register. *Rheumatology* (Oxford) 2011; 50: 196-203.
16. CHIU YM, LAI MS, LIN HY, LANG HC, LEE LJ, WANG JD: Disease activity affects all domains of quality of life in patients with rheumatoid arthritis and is modified by disease duration. *Clin Exp Rheumatol* 2014; 32: 898-903.