Clinical and quality of life improvements with golimumab or infliximab in a real-life ankylosing spondylitis population: the QUO-VADIS study

F. Van den Bosch[1], R.M. Flipo[2], J. Braun[3,4], N. Vastesaeger[5], S. Kachroo[6], M. Govoni[7]

[1]Ghent University Hospital, Belgium and VIB Center for Inflammation Research, Ghent, Belgium; [2]University Hospital of Lille, France; [3]Rheumazentrum Ruhrgebiet, Herne, Germany; [4]Ruhr-Universität Bochum, Bochum, Germany; [5]MSD Belgium, Brussels, Belgium; [6]Merck & Co., Inc., Kenilworth, NJ, USA; [7]MSD Italy, Rome, Italy.

Abstract

Objective

The QUO VADIS study evaluated disease activity and health-related quality-of-life (HRQoL) in ankylosing spondylitis (AS) patients treated with golimumab (GLM) or infliximab (IFX, originator) during routine clinical care.

Methods

This prospective observational study followed biologics-naïve AS patients newly treated with GLM or IFX for 6 months. Disease activity (BASDAI, BASFI, ASAS, and ASDAS) and HRQoL improvement (≥5 points of SF-36 Physical Component Summary [PCS] score; PCS response) were measured. A Classification and Regression Trees (CART) analysis evaluated association of baseline parameters with PCS response at 6 months.

Results

963 patients (mean age 43 years, 61% male, 64% HLA-B27 positive) received ≥1 dose of medication (78% GLM; 22% IFX). Disease activity was reduced; mean (SD) changes from baseline at month 6 of -2.7 (BASDAI) and -2.1 (BASFI) and 40% and 35% achievement of BASDAI50 and ASAS40 response, respectively, were observed. PCS response was achieved at month 6 in 52% of patients. Using CART analysis, baseline parameters (cut-off values) associated with HRQoL improvement were ASDAS (≥3.48), C-reactive protein (≥8.55 mg/L), age (≤35.5 years), and BASFI (≥1.15). This algorithm correctly identified 57.5% (sensitivity) of PCS responders (≥5 points) and 61.0% (specificity) of PCS non-responders (<5points) with ROC-AUC=0.61. Serious adverse events (AEs) occurred in 1.8% of patients; the most common AEs were infections (7.7%).

Conclusion

We demonstrated clinical and HRQoL improvements over 6 months in a large, real-world population of AS patients newly treated with GLM or IFX; higher ASDAS, elevated CRP, and younger age were associated with improvements in HRQoL and an overall more robust response.

Key words

ankylosing spondylitis, anti-TNF treatment, golimumab, infliximab, prospective observational studies

Filip Van den Bosch, MD
Rene Marc Flipo, MD
Jürgen Braun, MD
Nathan Vastesaeger, PhD
Sumesh Kachroo, PhD
Marinella Govoni, PhD

Please address correspondence to:
Dr Marinella Govoni,
MSD Italia,
Via Vitorchiano 151,
00189 Rome, Italy.
E-mail: marinella.govoni@merck.com

Received on February 26, 2018; accepted in revised form on May 7, 2018.

Funding: this work was supported by a grant by Merck & Co., Inc, Kenilworth, NJ, United States. Authors from Merck & Co., Inc. and subsidiaries of Merck & Co., Inc. were involved in the design of the study and analysis of data.

Competing interests: F. Van den Bosch received speaker and/or consultancy fees from Abbvie, Celgene, Elil Lilly, Janssen, Novartis, Pfizer, Sanofi and UCB. R.M. Flipo has received grants for research support from Roche and Pfizer and honoraria from Roche, Pfizer, AbbVie, Bristol Meyers Squibb, Merck & Co., Inc., and Nordic Pharma. J. Braun has received honoraria for talks, advisory boards, paid consultancies and grants for studies from Abbvie (Abbott), Amgen, Biogen, BMS, Boehringer, Celgene, Celltrion, Centocor, Chugai, EBEWE Pharma, Hospira, Janssen, Medac, Merck & Co., Inc., Mundipharma, Novartis, Pfizer (Wyeth), Roche, Sanofi-Aventis and UCB. N. Vastesaeger, S. Kachroo, and M. Govoni are employees of MSD Belgium, Merck Sharp & Dohme Corp., and MSD Italy, respectively, which are subsidiaries of Merck & Co., Inc., Kenilworth, NJ, USA; M. Govoni also owns stock and restricted stock units in the company.

Introduction

Ankylosing spondylitis (AS) is a chronic, painful, debilitating disorder that leads to structural and functional impairment of the axial skeleton (1). The detrimental effects on spinal mobility and physical function can have a profound impact on health-related quality-of-life (HRQoL) (1, 2). Importantly, functional disability in AS is a major contributor to economic costs based on direct medical costs and indirect costs from missed work days or permanent work disability (3)

The development anti-tumour necrosis factor (TNF)-α treatments represented a major advance in the treatment of AS. Golimumab (GLM) and infliximab (IFX) are two anti-TNF treatments that have demonstrated efficacy for AS. IFX is a chimeric (human-murine) monoclonal IgG_1 antibody against TNF-α that has been available since 1998 and is administered as a 2-hour intravenous infusion. GLM, a human $IgG_1κ$ monocolonal antibody against TNF-α, has been available since 2009. GLM has demonstrated efficacy in patients with AS with maintenance of efficacy up to 5 years under continuous treatment and a high rate of survival-on-drug, particularly for AS (4-8). The AE profile of GLM is similar to that of other anti-TNF agents. GLM has demonstrated greater treatment persistence compared with earlier anti-TNF agents (9) and, in contrast to earlier anti-TNF agents, GLM is available to patients by once-monthly subcutaneous self-administration, which may improve adherence and treatment response (10, 11).

While anti-TNF treatments have demonstrated efficacy and safety in clinical trial settings, observing treatment effects outside of a strict clinical trial setting is helpful to assess effectiveness and safety in real-world clinical practice. We conducted the QUality of Life as Outcomes and its VAriation with DIsease States (QUO-VADIS) prospective observational study to evaluate the effects of the anti-TNF treatments, GLM and IFX, on disease activity and quality of life over a 6-month treatment period in bionaive AS patients newly treated with these anti-TNF agents. We sought to better understand the relationship between baseline (pre-anti-TNF treatment) disease-specific parameters and HRQoL improvement during anti-TNF therapy

Methods

Ethics and study conduct

This was a multinational, prospective observational cohort study (Sponsor protocol number MK-2155-194) conducted in multiple centres across Europe and the Russian Federation. This study was conducted in accordance with principles of Good Clinical Practice. The study was approved by local Investigational Review Boards/Ethical Review Committees and patients provided informed consent prior to enrolment in the study.

Patients

Adult patients (>18 years of age) diagnosed with definite AS (as per modified New York criteria) (12) and naïve to anti-TNFs or other biologic agents (as indicated by medical records and patient interviews) were enrolled after the decision to treat with GLM or IFX according to routine clinical practice, but before initiation of treatment. Patients were excluded if they had any prior or current use of an anti-TNF or other biologic agents for any disease.

Study design

At baseline, socio-demographic data and disease characteristics were collected by investigators for each patient as per standard routine care. Comorbidities were collected by investigators or site staff based on a form that included the following conditions: inflammatory bowel disease, uveitis, psoriasis, hypertension, stroke, ischaemic heart disease, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, renal disease, liver disease, peptic ulcer disease, thyroid disease, depression, cerebrovascular accident, demyelinating disease, epilepsy, diabetes, tuberculosis, malignancy, mental illness (other than depression), gastrointestinal disease, anaemia or other blood disorder, fibromyalgia, or other. Patients received either IFX or GLM and were followed prospectively for 6 months with data collection at the following approxi-

mate time points: baseline (pre-treatment), three months and six months. A time window of approximately ± six weeks was allowed for the three- and six-month follow-up visits. C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR) were collected as part of the normal screening for patients prior to the initiation of a biologic agent in clinical practice and no additional blood specimens were collected as part of this study. CRP and ESR values were also collected at three months and six months if the measurements were available as part of routine clinical care. Human leukocyte antigen B27 (HLA-B27) status (*i.e.* positive or negative) was collected at baseline if available.

Clinical outcome assessments

Disease activity and functional data was collected at baseline, three months and six months, using the following instruments: Bath AS Disease Activiy Index (BASDAI) (13), Bath AS Functionality Index (BASFI) (14), Patient Global Assessment (PGA) of disease activity (0-10 Numeric Rating Scale (NRS) assessing average global well-being over previous 7 days), PGA of Pain (Total back pain; average 0-10 NRS over previous 7 days). Assessment of Spondyloarthritis (ASAS) (15) response was calculated from BASDAI, BASFI, PGA, and patient assessment of pain. AS Disease Activity Score (ASDAS) was calculated from the above instruments and CRP (16). Clinically important and major ASDAS improvements are defined as a decrease of ≥1.1 and ≥2.0 units, respectively. ASDAS less than 1.3 is the threshold for an inactive disease state. Data on IFX/GLM usage as well as reasons for discontinuation of treatment were collected at baseline, three months and six months.

HRQoL and evaluation of baseline factors associated with HRQoL improvement

At baseline, three months and six months, data on patient-reported HRQoL were collected using Short Form 36 (SF-36), which is a standardised instrument that assesses HRQoL and is measured using a 0–100 point scale (lower values indicate greater QoL impairment). Two summary scores of SF-36 were calculated: the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

Definition of responders and non-responders

Subjects with an improvement from baseline in SF-36 PCS score of ≥ five points at six months from baseline were considered to be PCS responders; those with no improvement or < five points were considered to be PCS non-responders.

Association of baseline parameters and HRQoL response

The Classification and Regression Trees (CART) modelling approach was used to develop an algorithm to evaluate baseline parameters (demographic, clinical, AS severity) associated with change in HRQoL, measured by PCS response, from baseline to six months (17). The dependent variable of the CART analysis was SF-36 PCS, which was classified into binary categories of 0 (improvement from baseline of < five points) and 1 (improvement from baseline of ≥ five points). The baseline predictor variables that were entered into the CART model included the following: 1) Demographic variables: age, gender; 2) Clinical variables: symptom duration, HLA-B27 genotyping, enthesitis score, CRP; 3) Disease activity variables: BASDAI score, BASFI score, ASDAS score, PGA of disease, PGA of pain; and 4) Other: number of comorbidities at baseline (<4r or ≥4). Details on the CART analysis are available in the Supplementary Material.

Safety and tolerability

Spontaneously reported adverse events (AEs) were collected throughout the study. Investigators evaluated AEs for severity, seriousness, and relation to study medication. AEs were tabulated and organised according to System Organ Class as defined by Medical Dictionary for Regulatory Activities (MedDRA), which uses a hierarchical structure of terms to categorise adverse events.

Statistical analysis

Sample size calculations were not made as this was an observational study. However, we used a generally accepted method to validate the required sample size for the CART analysis. This method involves estimating the proportion of patients in the total cohort who would be considered responders with a certain level of precision. A conservative total of 972 patients was estimated to be needed for this study. If the estimated proportion of responders at follow-up were observed to be 65%, with 972 patients, the 95%confidence interval for the point estimate would be (62%, 68%). If the observed proportion of responders were 40% to 60%, the chosen sample size would allow estimating those proportions with a slightly higher margin of error. The target sample size of 950 patients was chosen as it would allow a precise estimation of the proportion of patients who would have an improvement of 5 points on the PCS. It is also expected to be a large enough number to permit a CART analysis using several predictors with sufficient patients represented in the various nodes of the tree.

Statistical analyses were conducted using SAS v. 9.4 and CART (Salford Systems). For continuous variables, the number of patients, arithmetic mean, standard deviation (SD), median, and minimum and maximum were presented. For categorical variables, the number of patients and percentage in each category were presented. The number and percentage of patients with missing values in every continuous and categorical variable were summarised. Information bias from missing data is minimised in the CART analysis; missing data in CART were handled by substituting them with "surrogate splitters", which closely mimic the action of the primary splitting rules and contain information that is similar to what would be found in the primary splitter. The All Treated analysis set was defined as all patients enrolled in the study who received at least one dose of study treatment. This group includes patients who discontinued the study or switched therapy during follow-up. Those who switched therapy were considered to be discontinuers.

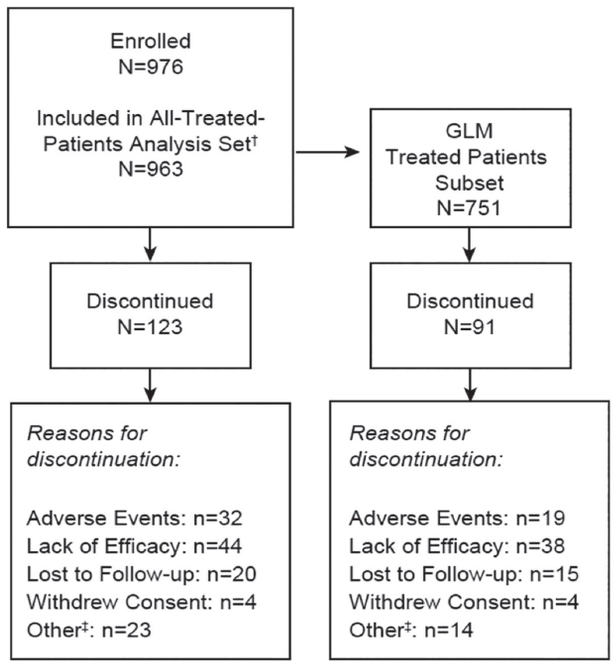
We also evaluated a subset of the All Treated analysis comprised only of pa-

tients who received GLM. The GLM-only subset was the largest patient cohort and was evaluated separately in order to verify and check the validity and applicability of the overall data and to screen for any deviations or differences from the overall cohort.

The tests of statistical significance were two-sided unless otherwise specified; any test resulting in $p<0.05$ was considered statistically significant. Two-sided 95% confidence intervals (CI) were used to assess the precision of endpoints, where relevant. Summaries and analyses were based on the All treated analysis set unless otherwise specified.

Supportive analyses for predictors of improvement in SF-36 PCS and MCS at 6 months were done using a logistic regression model with cross validation (75% of patients in training set and 25% of patients in the testing set) to study predictors associated with change in HRQoL from. All baseline parameters with a *p*-value ≤0.20 in a univariate logistic regression model were considered in a multivariate logistic regression model, requiring an entry criterion of *p*-value ≤0.05 and a retention *p*-value of ≤0.10. Variables deemed clinically important were forced into the final model regardless of *p*-values. Measures indicating model performance such ROC and Hosmer-Lemeshow test results were utilised; odds ratios (OR) and *p*-values were also generated.

Fig. 1.
Patient disposition
†All-Treated Patients Analysis Set includes all patients who received at least 1 dose of study medication
‡Other reasons include reasons linked to ineligibility for study, and inability to complete treatment or visits.



Results

Patients

There were 963 patients who received ≥1 dose of medication; 78% (n=751) received GLM and 22% (n=212) received IFX (Fig. 1). Mean age was 42.7 years, 61.4% were male, and 65.3% had ≥1 comorbidity. Mean symptom duration was 11.6 years, mean time since diagnosis was 5.3 years, and 63.8% of patients were human leukocyte antigen (HLA)-B27 positive (Table I). At baseline, mean (SD) BASDAI, ASDAS-CRP and BASFI scores were 6.21 (1.87), 3.59 (0.96) and 5.34 (2.44), respectively. High and very-high ASDAS disease activity was observed in 41.4% and 49.3% of patients, respectively. In the GLM-only group, mean (SD) BASDAI, ASDAS-CRP and BASFI scores were 6.18 (1.83), 3.55 (0.93) and 5.35 (2.43), respectively. High and very-high ASDAS disease activity was observed in 43.3% and 46.9% of patients, respectively. There was a low rate of discontinuation with 123 patients (12.8%) discontinuing for reasons including lack of efficacy (44/123 [35.8%]) and AEs (32/123 [26.0%]).

Clinical measures of disease activity

Over 6 months of treatment, treatment with GLM or IFX was associated with improvement from baseline in clinical outcome measurements of BASDAI, BASFI, Patient Global Assessment of Pain, and Patient Global Assessment of Disease Activity, ASAS outcomes, and ASDAS outcomes in both the All Treated Patients cohort as well as the GLM-only cohort (Table II; Fig. 2).

BASDAI 50 response was achieved by 34.6% of patients at Month 3 and 39.5% of patients at Month 6. ASAS20 response was achieved by 48.5% of patients at Month 3 and 50.6% of patients at Month 6 (Fig. 1). ASDAS major improvement was achieved by 24.0% of patients at Month 3 and 26.6% of patients at Month 6 (Table II). The proportion of patients with high or very high ASDAS disease activity decreased from 90.7% at baseline to 36.4% at six months (Fig. 2). Results for the GLM-only cohort were similar and super-imposable to those reported for the All Treated Patients cohort and are presented in Table II and Figure 2.

HRQoL measurements

The mean (SD) change in SF-36 PCS at six months from baseline was 8.2 (8.4), and the mean change in SF-36 MCS at six months from baseline was 6.5 (10.6) (Fig. 3A-B). At six months, 504 patients (52.3%) had an improvement in the SF-36 PCS of ≥ five points (PCS responders), and 444 patients (46.1%) had an improvement in the SF-36 MCS of ≥ five points (MCS responders) (Fig. 3C). The results for the GLM-only cohort were similar to the All Treated Patients cohort (Fig. 3).

Analysis of predictors of response

Using CART analysis, the baseline parameters, and their cut-off values, associated with HRQoL improvement as measured by SF-36 PCS response at 6 months were ASDAS (>3.48), C-reactive protein (CRP) (>8.55 mg/L), age (≤35.5 years), and BASFI (>1.15). Higher ASDAS and higher BASFI scores indicate higher disease activity and functional impairment, respectively. The first decision node was based upon ASDAS. Split into this node led to 62.2% PCS responders among patients with ASDAS > 3.48 (n=495), who were further split into two groups according

Table I. Patients' baseline characteristics.

Characteristic	Overall (n=963)	GLM Only (n=751)
Gender (male) [n (%)]	591 (61.4%)	455 (60.6%)
Age (years) [mean (SD)]	42.7 (12.85)	42.9 (12.87)
Caucasian race [n (%)]	742 (77.1%)	562 (74.8%)
Smoking status [n (%)]		
Never smoker	506 (52.5%)	394 (52.5%)
Former smoker	158 (16.4%)	119 (15.8%)
Current smoker	297 (30.8%)	236 (31.4%)
Symptom duration (years) [mean (SD)]	11.6 (10.45)	11.6 (10.46)
Time since diagnosis (years) [mean (SD)]	5.3 (7.71)	5.5 (7.98)
HLA-B27 positive [n (%)]	614 (63.8%)	484 (64.4%)
Enthesitis		
Berlin Enthesitis Score [mean (SD)]	1.8 (2.48)	1.8 (2.50)
Berlin Enthesitis Score > 0 [n (%)]	495 (51.4%)	388 (51.7%)
Enthesitis at Achilles tendon insertion (at least 1 at left or right heel) [n (%)]	266 (27.6%)	197 (26.2%)
Patients ≥1 comorbidity [n (%)]	629 (65.3%)	483 (64.3%)
Hypertension	210 (21.8%)	166 (22.1%)
Depression	86 (8.9%)	69 (9.2%)
Extra-articular manifestations		
Uveitis	125 (13.0%)	89 (11.9%)
Psoriasis	94 (9.8%)	75 (10.0%)
Gastrointestinal disease	82 (8.5%)	56 (7.5%)
Inflammatory bowel disease	38 (3.9%)	19 (2.5%)
Mean (SD) baseline disease activity measurements		
BASDAI Score	6.2 (1.9)	6.2 (1.8)
BASFI Score	5.3 (2.4)	5.4 (2.4)
PGA Disease Activity Score	6.6 (2.3)	6.7 (2.2)
PGA Pain Score	6.7 (2.3)	6.7 (2.3)
ASDAS-CRP Score	3.6 (1.0)	3.55 (0.9)
CRP (mg/L)	15.3 (23.0)	14.3 (22.1)
SF-36 PCS Score	34.7 (7.5)	34.7 (7.4)
SF-36 MCS Score	39.8 (11.1)	39.8 (10.9)

Table II. Summary of clinical and HRQoL outcomes

	All Treated Patients n=963		GLM-only n=751	
	3 Months	6 Months	3 Months	6 Months
Mean (SD) BASDAI change from BL	-2.4 (2.2)	-2.7 (2.3)	-2.3 (2.1)	-2.6 (2.3)
BASDAI50 response	34.6%	39.5%	35.2%	39.9%
Mean (SD) BASFI change from BL	-1.8 (2.1)	-2.1 (2.3)	-1.9 (2.1)	-2.2 (2.2)
ASAS20 response	48.5%	50.6%	50.1%	52.6%
ASAS40 response	29.7%	34.6%	30.5%	35.8%
ASAS partial remission	12.1%	14.3%	12.4%	13.3%
Mean (SD) PGA disease activity change from BL	-2.5 (2.8)	-2.8 (2.9)	-2.6 (2.8)	-2.9 (2.8)
Mean (SD) PGA pain change from BL	-2.5 (2.8)	-3.0 (2.8)	-2.6 (2.7)	-3.0 (2.8)
Mean (SD) CRP (mg/L)	5.6 (9.6)	4.9 (8.2)	5.5 (10.1)	4.3 (6.3)
ASDAS-CRP	2.2 (1.0)	2.1 (1.0)	2.2 (1.1)	2.0 (0.9)
ASDAS major improvement (≥2.0 unit decrease)	24.0%	26.6%	23.8%	26.0%
SF36 PCS responders (improvement of ≥5 points from BL)	--	52.3%	--	53.3%
SF36 MCS responders (improvement of ≥5 points from BL)	--	46.1%	--	

to CRP (cut-off of 8.55 mg/L). Terminal nodes produced from this split led to 67.3% PCS responders among patients with a higher CRP (>8.55 mg/L) and 47.7% PCS responders among patients with a lower CRP (≤8.55 mg/L). The population with ASDAS ≤3.48 was further split into two nodes based upon age (cut-off of 35.5 years). A higher proportion of PCS responders were identified in the age group ≤35.5 years *vs*. those >35.5 years (55.3% *vs*. 34.9%, respectively). The younger group of patients was further split into two terminal nodes by the BASFI variable at an optimal cut-off of 1.15. A higher BASFI score (>1.15) was associated with more PCS responders at the end of study follow-up at six months compared to a BASFI ≤1.15. No further split was observed among patients older than 35.5 years (Fig. 4).

Based on the ten-fold cross-validation test sample, the CART tree correctly classified 57.5% of PCS responders (sensitivity) and 61.0% of PCS non-responders (specificity). The ROC-AUC for the test sample was 0.61 with a misclassification rate of 40.8%.

The multivariate logistic regression analysis identified baseline ASDAS Scores of >3.5, Age <60 years), and the presence of comorbidities as being predictors of SF-36 PCS response.

Safety and tolerability

AEs occurred in 213 (22.1%) patients throughout the six months follow-up of the study. The most common AEs were infections or infestations, occurring in 7.7% (n=74) of the patients, followed by general disorders and administration site conditions, reported in 7.6% (n=73) of the patients. The most common individual AE under infections or infestations was influenza (7 patients [0.7%]). Among general disorders and administration site conditions, the most common AE was asthenia (15 patients [1.6%]). Serious AEs (SAEs) were reported in 17 patients (1.8%) and included the following events: acute myocardial infarction; general physical health deterioration; pyrexia; drug-induced liver injury; herpes zoster; lymph node tuberculosis; fall; ankylosing spondylitis; arthralgia; osteoarthritis; spinal column stenosis; spondylitis; coma; intracranial venous sinus thrombosis; pleural fibrosis; pulmonary embolism; and angioedema.

Discussion

The results of the QUO VADIS study demonstrated that treatment with GLM

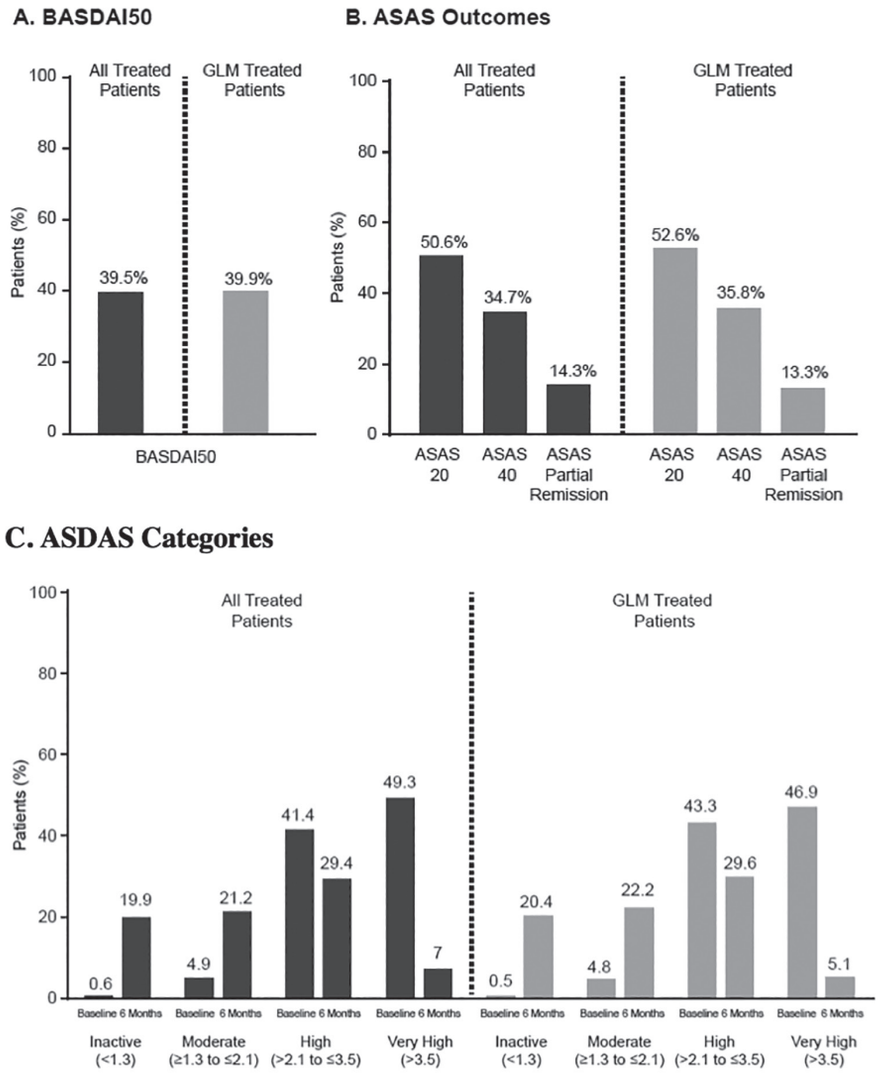


Fig. 2. Improvement in clinical outcomes over 6 months of treatment in the All-Treated Patients and the Golimumab-Treated cohorts. Panel A shows the % of patients who achieved BASDAI50 after 6 months and Panel B shows the % of patients who achieved ASAS20, ASAS40, or ASAS partial remission after 6 months. Panel C shows the % of patients in ASDAS categories at baseline and after 6 months.
*The Golimumab-Only group is depicted separately as it was the largest subgroup of the All-Treated-Patients group; these groups are not being compared.

or IFX led to improvement in disease activity measures in a real-world setting in patients with AS. Specifically, large improvements were observed with both medications in BASDAI50, ASAS20, ASAS40, ASAS partial remission, and in reduction of disease severity according to ASDAS. Results of SF-36 PCS and MCS also demonstrated improved quality of. Infections or infestations were observed as the most common AEs although SAEs were not common.

A recent Cochrane review of randomised controlled trials with anti-TNF agents including GLM (n=429) and IFX (n=355) demonstrated a 25% increased benefit for GLM *vs*. placebo and 40% increased benefit for IFX *versus* placebo in ASAS40; for BASFI, a 15% and 21% increased benefit were observed with GLM and IFX, respectively, *versus* placebo; for ASAS partial remission, a 13% and 44% increased benefit were observed with GLM and IFX, respectively, *versus* placebo (18). In the same review of clinical trials, increased harm with regard to SAEs was observed with a -0.5% increased risk (or 0.5% decrease) with GLM and 2.3% increased risk with IFX (18). The results from our observational study support this previous research from randomised controlled trials that have demonstrated efficacy with anti-TNF agents in AS (18). Although these data are observational, and each treatment was not compared to either placebo or each other for statistical comparison, these results provide results in the largest cohort of patients treated with GLM (n=751) in a clinical setting and add evidence that positive therapeutic results in randomised controlled trials are also observed in real-world settings.

This trial provided an opportunity to observe the implementation of anti-TNF treatment with GLM or IFX with regard to both treatment effects as well as patient characteristics for anti-TNF naïve patients in the course of routine clinical care for the treatment of AS. In this study, it should be noted that the study population consisted of a relatively low proportion of HLA B27 positive patients for a classic AS population. Of interest, despite recent advances in referral strategies and disease management, the delay between the first onset of symptoms and disease diagnosis observed in this real-world clinical care setting was still substantial, suggesting an important area with a potential for improving outcomes of patients with AS.

The identification of predictors of response with regard to HRQoL is an important goal for researchers in order to further improve the ability to individualise treatment to patients with AS. Observational studies better reflect real-world conditions compared with randomised controlled clinical trials; there are few observational trials that assess HRQoL or physical function in AS. One observational study identified factors such as female gender, higher Bath AS Functional Index (BASFI) score, and concurrent use of DMARDs as predictive of greater improvement in physical functioning after anti-TNF therapy (19). More data from trials that replicate real-world settings are needed to better articulate factors associated with optimal response with regard to HRQoL and physical function with anti-TNF therapy.

In this study, we used the CART analysis to examine factors associated with

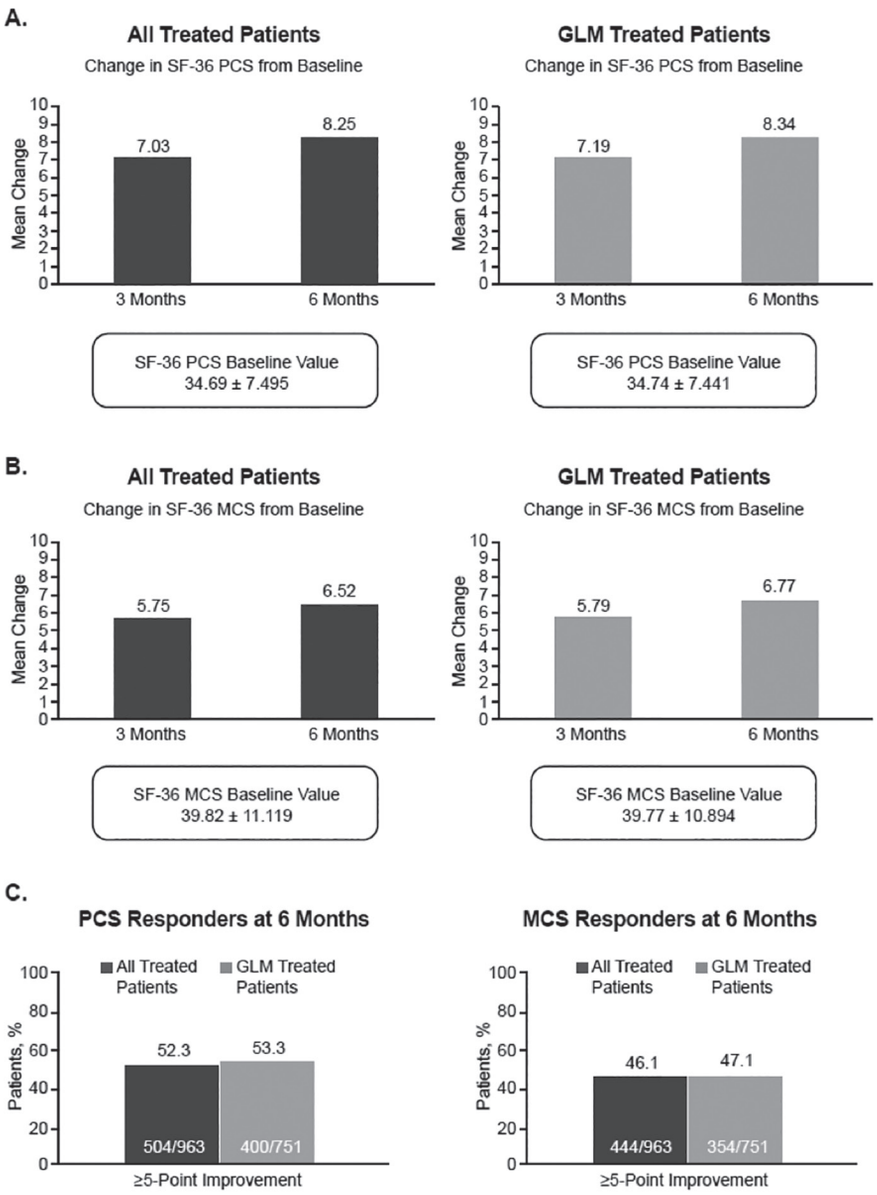


Fig. 3. SF 36 PCS and MCS Summary.

HRQoL response as measured by SF-36 PCS response at 6 months. CART was developed as a method of decision tree methodology (20); its application in public health was to allow researchers to segment populations into meaningful subsets and to identify population segments that have increased likelihood to engage or not engage in a health behaviour to maximise health resources (21). CART was subsequently used in clinical research settings to identify patient characteristics with increased likelihood for treatment response to help maximise treatment in a variety of conditions (21-25). We used CART as a binary recursive process to classify patients based on improvement of the SF-36 outcome; this method was used rather than multivariate logistic regression to better handle data that are highly skewed, non-parametric, and situations in which there are complex interactions among predictors. In our study, the following factors were shown to be associated with HRQoL response: ASDAS (>3.48), C-Reactive Protein (CRP) (>8.55 mg/L), age (≤35.5 years), and BASFI (>1.15). Higher ASDAS and higher BASFI scores indicate higher disease activity. These factors have previously been associated with clinical response and now indicate an association with HRQoL as well (26, 27). Importantly, the data-driven cut-off values for these endpoints that were identified in this study using the CART analysis are consistent with values identified clinically (28, 29). A supportive multivariate logistic regression was performed as well and also identified higher baseline ASDAS scores and younger age to be predictors of SF-36 PCS response.

There were several limitations to our CART analysis. Although developing an algorithm to identify factors associated with HRQoL response was one of our objectives, our results demonstrated moderate sensitivity and specificity as well as moderate ROC-AUC, all leading to moderate/low predictive ability and value of the model. Additionally, although a higher BASFI score was identified as a parameter associated with HRQoL improvement, the low cut-off value limits its utility in clinical practice. These results may be attributed to the SF-36 being a generic measure of HRQoL, and not specifically tailored to AS; additionally, the SF-36 questionnaire is a self-administered, generic measure of HRQoL and may be subject to recall error in this population of AS patients.

An additional limitation was that controlling variability in observational trials with practices across a large number of sites and countries can be challenging. There was also a large imbalance in the size of the GLM and IFX populations, so these treatments were not compared to one another. Nonetheless, this trial provides data on the use of anti-TNF treatment for AS in a large cohort of patients and represents the largest cohort of GLM patients studied. These data are an important component to the clinical evidence established with both randomised and observational trials.

In summary, this study demonstrated clinical and HRQoL improvements over 6 months in a large, real-world population of patients with AS newly treated with the anti-TNF treatments GLM (almost 80% of study population) or IFX. Although the overall predictive ability of the CART-derived algorithm linking baseline parameters with HRQoL response was moderate,

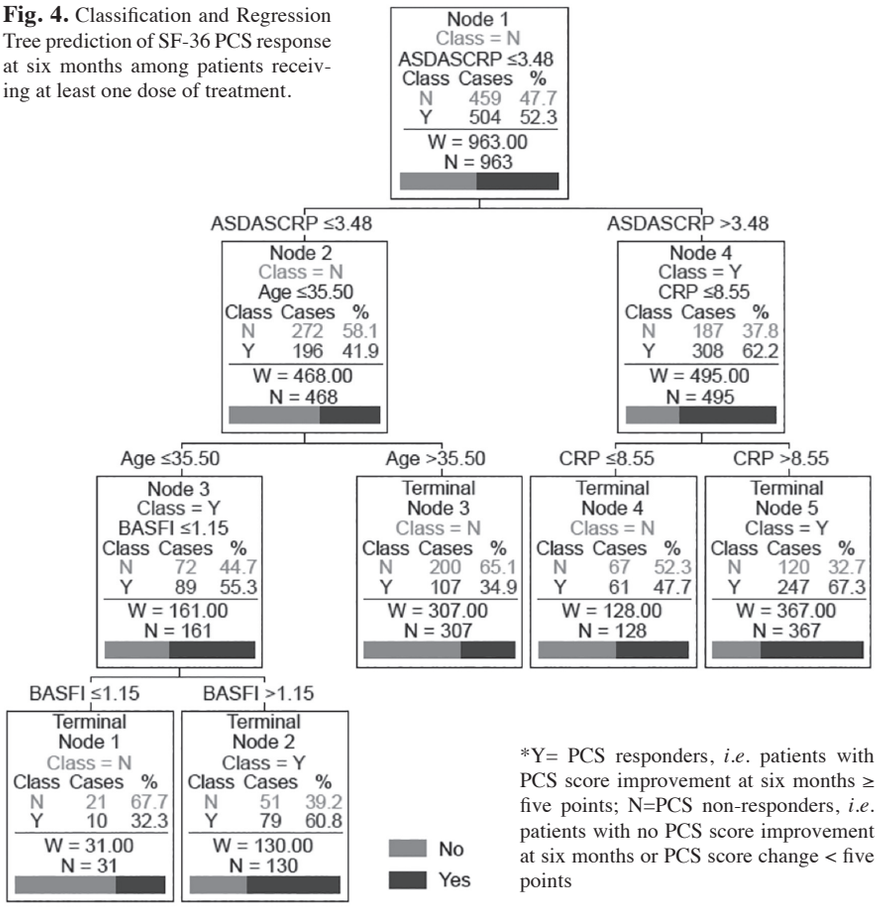


Fig. 4. Classification and Regression Tree prediction of SF-36 PCS response at six months among patients receiving at least one dose of treatment.

*Y= PCS responders, *i.e.* patients with PCS score improvement at six months ≥ five points; N=PCS non-responders, *i.e.* patients with no PCS score improvement at six months or PCS score change < five points

making it difficult to apply in daily clinical practice for patient selection, this study demonstrates for the first time the association of parameters such as higher ASDAS, elevated CRP, and younger age with improvements in HRQoL. These parameters have been described in literature as associated with improved clinical outcomes (26, 27). The QUO-VADIS study now confirms that parameters such as these are also associated with a robust HRQoL response. GLM and IFX were well tolerated in this study, with no unexpected AEs over 6 months of treatment.

Acknowledgements

The authors thank Anish Mehta for medical writing support, Jennifer Pawlowski for additional editorial and administrative support, and Kimberly Bonczynski for her pivotal role in the operational conduct in the study (all from Merck & Co., Inc. Kenilworth, NJ, USA). The authors also thank the patients and following investigators who participated in the study:

Belgium: Van den Bosch, Filip; Geusens, Piet; De Clerck, Luc; De Brabanter, Griet; Hoffman, Ilse; Malaise, Michel; Leon, Marc; Bentin, Jacques; Steinfeld, Serge; Van Bruwaene, Filip; Maertens, Martin; Poriau, Stefaan.

Bulgaria: Batalov, Anastas; Alimanska, Stanislava; Oparanov, Boycho; Vladeva, Stoianka; Marinchev, Lubomir; Goranov, Ivan.

Croatia: Anic, Branimir; Morovic-Vergles, Jadranka; Babic-Naglic, Durdica; Kehler, Tatjana.

Czech Republic: Nemec, Petr; Brabcova, Hana; Dokoupilova, Eva; Suchy, David; Kuba, Vit; Urbanova, Monika; Sirova, Klara.

Estonia: Kallikorm, Riina; Kiviväli, Aire; Pärsik, Eevi.

France: Claudepierre, Pascal; Hilliquin, Pascal; Berenbaum, Francis; Loeuille, Damien; Gilson, Melanie; Sibilia, Jean; Euller-Ziegler, Liana; Sarraux, Alain; Soubrier, Martin; Bertin, Philippe; Vittecoq, Olivier; Flipo, Rene-Marc; Fardellone, Patrice; Goupille, Philippe; Guillibert, Caroline; Heraud, Alain; Lassoued, Slim; Royant, Valerie; Liote, Frederic; Loiseau-Peres, Sylvie; Leblay, Pierre.

Germany: Aries, Peer-Malte; Berger, Sylvia; Braun, Juergen; Dockhorn, Rainer; Haentsch, Johannes; Kellner, Herbert; Klopsch, Thilo; Koerber, Helge; Krause, Andreas; Liebhaber, Anke; Max, Regina; Naumann, Jana; Pick, Dorothea; Remstedt, Sven; Rockwitz, Karin; Schuart, Thomas; Schwarze, Ilka; Sieburg, Maren; Thiele, Astrid; Vollmer, Markus; Wussow, Peter von; Wassenberg, Siegfried; Zinke, Silke; Scheibl, Ernst; Brandt-Juergens, Jan; Krueger, Klaus; Kupka, Thomas; Boche, Konrad; Bohl-Buehler, Martin; Wagener, Peter; Karberg, Kirsten; Fiene, Michael; Backhaus, Marina; Bruns, Anne; Fricke-Wagner, Henry; Schwenke, Holger; Haas, Florian; Kaestner, Peter; Meier, Lothar; Waehrisch, Juergen; Stille, Carsten; Scholz, Christine; Hein, Reinhard; Irmgard, Guertler.

Greece: Vassilopoulos, Dimitrios; Patrikos, Dimos; Stavropoulos, Efthymios; Vlachoyiannopoulos, Panagiotis; Sidiropoulos, Prodromos; Ioakeimidis, Dimitrios; Vosvotekas, Georgios; Triantafillidou, Eva.

Italy: Cantini, Fabrizio; Sabadini, Luciano; Gerli, Roberto; Biscarini, Luciano; Pellerito, Raffaele; Fusaro, Enrico; Epis, Oscar; Gorla, Roberto; Malavolta, Nazzarena; Ferri, Clodoveo; Vita, Salvatore de; Adami, Silvano; Perricone, Roberto; Afeltra, Antonella; Mathieu, Alessandro; Cantatore, Francesco; Foti, Rosario; Grembiale, Rosa; Scarpato, Salvatore; Muratore, Maurizio; Ostuni, Pierantonio; Corsaro, Santi; Pistone, Giovanni; Sarzi Puttini, Piercarlo; Giacomelli, Roberto; Longhi, Matteo; Versace, Francesco; Migliore, Alberto.

Portugal: Delgado Alves, Jose; Bernardo, Alexandra; Barcelos, Anabela; Vilar, Antonio; Sousa, Elsa; Monteiro, Paulo.

Romania: Opris, Daniela; Ionescu, Razvan Adrian; Rezus, Elena; Vlad, Violeta; Rosu, Anca; Bojinca, Mihai; Rednic, Simona; Ancuta, Ioan; Codreanu, Catalin.

Russian Federation: Myasoutova, Leisan; Evteeva, Natalia; Ilivanova, Elena; Mazurov, Vadim; Shmidt, Evgeniya; Bondareva, Irina; Antipova, Olga.

Slovenia: Sinozic, Dean; Pahor, Artur.
United Kingdom: Pickles, David; Goodson, Nicola; Isdale, Amanda; Coy, Aisling; Sengupta, Rajiv; Khan, Sophia; Patel, Yusuf; Saha, Amit; Gaffney, Karl; Al-Ansari, Atheer.
Hungary: Poor, Gyula; Bartha, Attila; Geher, Pal; Keszthelyi, Peter; Kiss, Csaba Gyorgy; Kovacs, Laszlo; Szanto, Sandor; Szanyo, Ferenc; Tamasi, Laszlo; Toth, Edit; Kerekes, Kata.

References

1. BRAUN J, SIEPER J: Ankylosing spondylitis. *Lancet* 2007; 369: 1379-90.
2. SINGH JA, STRAND V: Spondyloarthritis is associated with poor function and physical health-related quality of life. *J Rheumatol* 2009; 36: 1012-20.
3. WARD MM: Functional disability predicts total costs in patients with ankylosing spondylitis. *Arthritis Rheum* 2002; 46: 223-31.
4. BRAUN J, DEODHAR A, INMAN RD *et al*.: Golimumab administered subcutaneously every 4 weeks in ankylosing spondylitis: 104-week results of the GO-RAISE study. *Ann Rheum Dis* 2012; 71: 661-67.
5. DEODHAR A, BRAUN J, INMAN RD *et al*.: Golimumab administered subcutaneously every 4 weeks in ankylosing spondylitis: 5-year results of the GO-RAISE study. *Ann Rheum Dis* 2015; 74: 757-61.
6. INMAN RD, DAVIS JC, JR., HEIJDE D *et al*: Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. *Arthritis Rheum* 2008; 58: 3402-12.
7. THOMAS K, FLOURI I, REPA A *et al*.: High 3-year golimumab survival in patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis: real world data from 328 patients. *Clin Exp Rheumatol* 2017; 36: 254-62.
8. MANARA M, CAPORALI R, FAVALLI EG *et al*.:Two-year retention rate of golimumab in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis: data from the LORHEN registry. *Clin Exp Rheumatol* 2017; 35: 804-09.
9. DALEN J, SVEDBOM A, BLACK CM *et al*.: Treatment persistence among patients with immune-mediated rheumatic disease newly treated with subcutaneous TNF-alpha inhibitors and costs associated with non-persistence. *Rheumatol Int* 2016; 36: 987-95.
10. SCHULZE-KOOPS H, GIACOMELLI R, SAMBORSKI W *et al*.: Factors influencing the patient evaluation of injection experience with the SmartJect autoinjector in rheumatoid arthritis. *Clin Exp Rheumatol* 2015; 33: 201-8.
11. CALVO-ALÉN J, MONTEAGUDO I, SALVADOR ALARCÓN G *et al*.: Non-adherence to subcutaneous biological therapy in patients with rheumatoid arthritis. ARCO study. *Ann Rheum Dis* 2016; 75 (Suppl. 2): 1.
12. VAN DER LS, VALKENBURG HA, CATS A: Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984; 27: 361-68.
13. GARRETT S, JENKINSON T, KENNEDY LG, WHITELOCK H, GAISFORD P, CALIN A: A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994; 21: 2286-91.
14. CALIN A, GARRETT S, WHITELOCK H *et al*.: A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. *J Rheumatol* 1994; 21: 2281-85.
15. ANDERSON JJ, BARON G, VAN DER HD, FELSON DT, DOUGADOS M: Ankylosing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis. *Arthritis Rheum* 2001; 44: 1876-86.
16. LUKAS C, LANDEWÉ R, SIEPER J *et al*.: Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. *Ann Rheum Dis* 2009; 68: 18-24.
17. STROBL C, MALLEY J, TUTZ G: An introduction to recursive partitioning: rationale, application, and characteristics of classification and regression trees, bagging, and random forests. *Psychol Methods* 2009; 14: 323-48.
18. MAXWELL LJ, ZOCHLING J, BOONEN A *et al*.: TNF-alpha inhibitors for ankylosing spondylitis. *The Cochrane Database Syst Rev* 2015: Cd005468.
19. LORD PA, FARRAGHER TM, LUNT M, WATSON KD, SYMMONS DP, HYRICH KL: Predictors of response to anti-TNF therapy in ankylosing spondylitis: results from the British Society for Rheumatology Biologics Register. *Rheumatology* (Oxford) 2010; 49: 563-70.
20. BREIMAN L FJ, OLSHEN RA, STONE CJ: Classification and Regression Trees. Pacific Grove, CA: Wadsworth; 1984.
21. LEMON SC, ROY J, CLARK MA, FRIEDMANN PD, RAKOWSKI W: Classification and regression tree analysis in public health: methodological review and comparison with logistic regression. *Ann Behav Med* 2003; 26: 172-81.
22. GERMANSON T, LANZINO G, KASSELL NF: CART for prediction of function after head trauma. *J Neurosurg* 1995; 83: 941-42.
23. HENRARD S, SPEYBROECK N, HERMANS C: Classification and regression tree analysis vs. multivariable linear and logistic regression methods as statistical tools for studying haemophilia. *Haemophilia* 2015; 21: 715-22.
24. HESS KR, ABBRUZZESE MC, LENZI R, RABER MN, ABBRUZZESE JL: Classification and regression tree analysis of 1000 consecutive patients with unknown primary carcinoma. *Clin Cancer Res* 1999; 5: 3403-10.
25. MARSHALL RJ: The use of classification and regression trees in clinical epidemiology. *J Clin Epidemiol* 2001; 54: 603-9.
26. ARENDS S, BROUWER E, VAN DER VEER E *et al*.: Baseline predictors of response and discontinuation of tumor necrosis factor-alpha blocking therapy in ankylosing spondylitis: a prospective longitudinal observational cohort study. *Arthritis Res Ther* 2011; 13: R94.
27. MANEIRO JR, SOUTO A, SALGADO E, MERA A, GOMEZ-REINO JJ: Predictors of response to TNF antagonists in patients with ankylosing spondylitis and psoriatic arthritis: systematic review and meta-analysis. *RMD Open* 2015; 1: e000017.
28. MACHADO P, LANDEWÉ R, LIE E *et al*.: Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. *Ann Rheum Dis* 2011; 70: 47-53.
29. VASTESAEGER N, VAN DER HEIJDE D, INMAN RD *et al*.: Predicting the outcome of ankylosing spondylitis therapy. *Ann Rheum Dis* 2011; 70: 973-81.