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Predictors of response to etanercept-methotrexate treatment: a post hoc logistic regression analysis of a randomized, open-label study in Latin American patients with rheumatoid arthritis

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Abstract

Background: Determining potential predictors of clinical response would allow a more personalized rheumatoid arthritis (RA) treatment approach in heterogeneous populations such as Latin American (LA) patients.

Methods: Post hoc analysis to identify baseline characteristics predictive of clinical remission in response to treatment with etanercept (ETN) plus methotrexate (MTX) in LA patients with moderate to severe MTX-resistant RA. We report data from the group of patients who received ETN 50 mg/week plus MTX (ETN + MTX, $n = 281$) in a clinical trial consisting of an initial 24-week open-label phase, followed by a 104-week extension. Remission was defined as 28-joint Disease Activity Score with erythrocyte sedimentation rate (DAS28-ESR) score < 2.6 . Cutoff values to dichotomize baseline variables maximizing the detection of remission were obtained from Receiver Operator Curve analyses. Baseline dichotomized and categorical variables were analyzed altogether in a stepwise logistic regression model. Odds of attaining response at Weeks 24 and 128 were estimated for each significant predictor.

Results: At Week 24 and Week 128, 27% (66/241) and 42% (91/219) of patients in the ETN + MTX group achieved remission. On average, patients achieving remission were younger and had lower baseline ESR, lower Physician Global Assessment (PGA) scores, lower total Health Assessment Questionnaire (HAQ) scores, and lower visual analog scale (VAS) Pain scores compared with patients who did not achieve remission. The best subset of baseline variables predicting Week 24 remission in the stepwise regression model were age ≤ 49 years (odds ratio [OR] 2.93), body mass index (BMI) > 28.5 kg/m² (OR 3.24), disease duration > 3.7 years (OR 2.22), ESR ≤ 42 mm/h (OR 2.72), PGA ≤ 6 (OR 3.21), tender joint count ≤ 14 (OR 2.25), and total HAQ score ≤ 1.6 (OR 2.86). At Week 128, age ≤ 42 years (OR 2.21), SF-36 Mental Health Scale score > 39.6 (OR 2.16), White race (OR 4.07), > 18 swollen joints (OR 2.11), and VAS Pain ≤ 41 (OR 6.05) at baseline were the best subset of significant predictors of remission.

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Conclusions: In LA patients with RA, younger age, higher BMI, longer disease duration, higher SF-36 Mental Health Scale score, higher swollen joint count, and overall lower disease activity predicted clinical response to ETN + MTX therapy.

Trial registration: ClinicalTrials.gov Identifier: NCT00848354.

Background

Rheumatoid arthritis (RA) is characterized by chronic inflammation and joint erosion, often leading to inability to work and poor quality of life [1]. The prevalence of RA in Latin America is estimated to be around 0.4% [2], compared with 0.24–1.0% worldwide [3, 4]. A majority of clinical trials investigating treatments for RA, including those of the tumor necrosis factor (TNF) inhibitor etanercept (ETN), have been conducted in patients from North America and Europe. However, the population of Latin America is highly diverse and differs from Western populations in its racial, ethnic, and socio-economic make-up [5], factors that have been associated with the treatment outcomes of RA [6, 7].

In a 24-week, randomized open-label study of methotrexate (MTX)-resistant patients with moderate or severe RA, conducted in Latin America (NCT00848354), ETN plus MTX was shown to be superior to MTX plus another conventional disease-modifying antirheumatic drug (DMARD) [8]. During the open-label, 104-week extension phase, benefits of ETN plus MTX treatment were maintained for up to 2 years [9], and a post hoc analysis demonstrated that clinical outcomes at Week 12 could be used as predictors of patient-reported outcomes at Week 24 [10].

However, as in most RA trials, treatment benefits were not distributed uniformly among the participants [8, 9]. Determining potential baseline predictors of clinical remission would allow a more personalized approach to the treatment of RA in this heterogeneous patient population. The aim of this post hoc analysis of the trial was to identify potential baseline characteristics that predict which participants were more likely to respond to treatment with ETN plus MTX at Weeks 24 and 128.

Methods

Study design and patient selection

The study design and primary outcomes have been described in detail previously [8]. Briefly, patients from Argentina, Chile, Colombia, Mexico, and Panama with moderate to severe active RA and inadequate response to MTX were included in the study. In the initial phase, participants were randomized 2:1 to receive open-label treatment with ETN 50 mg weekly plus MTX (ETN+MTX, $n=281$) or an additional conventional DMARD (hydroxychloroquine or sulfasalazine)

plus MTX ($n=142$) for 24 weeks. The second phase (104 weeks) was an optional extension period allowing investigators to select a treatment regimen (ETN, MTX, hydroxychloroquine, or sulfasalazine, in any combination at the desired dosage) based on the participants' previous response to randomized treatment, their preference, and local product labeling [9]. Clinical efficacy endpoints at Weeks 24 and 128 included the proportion of participants who achieved response based on the 28-joint Disease Activity Score with erythrocyte sedimentation rate (DAS28-ESR) consistent with disease remission (<2.6). We report data from a post hoc analysis of predictors of response to treatment in only the group of participants randomized to receive ETN+MTX.

Statistical analysis

This observed-cases analysis included participants who were initially randomized to receive ETN+MTX (Week 24 assessment) and their subset who enrolled in the extension phase (Week 128 assessment). Clinical response at both Weeks 24 and 128 was defined as DAS28-ESR remission. Differences between Week 24 (and Week 128) remitters for demographic and baseline disease characteristics were analyzed in one-way analysis of variance (ANOVA) models (for continuous characteristics) and in chi-square tests (for categorical characteristics). Each continuous baseline variable was dichotomized twice using the Receiver Operator Curve approach from logistic regression model of Week 24 remission (or Week 128 remission). Variables were dichotomized by determining the cutoff values that maximized the sensitivity (true positive rate) plus specificity (true negative rate) of detecting Week 24 (and Week 128) remission. These dichotomized variables along with other categorical baseline variables were then analyzed altogether in a stepwise logistic regression model, and the odds of attaining response in the ETN+MTX group at Weeks 24 and 128 (observed cases) were estimated for each significant predictor, with the cutoff p -value to enter of 0.15 and stay in the model set at 0.05. Baseline characteristics used in the stepwise model as dichotomized/categorical variables included: age; body mass index (BMI); C-reactive protein (CRP); cyclic citrullinated peptide antibody positive; DAS28; disease duration; ESR; modified total Sharp score; morning stiffness; prior use of MTX, non-steroidal anti-inflammatory drugs

and corticosteroids; Physician Global Assessment (PGA); race; rheumatoid factor (RF); sex; Short Form 36 (SF-36) physical component summary; SF-36 mental component summary; SF-36 vitality domain score; subject global assessment; swollen joint count; tender joint count; total Health Assessment Questionnaire (HAQ) score; visual analog scale (VAS) General Health; VAS Fatigue; and VAS Pain.

Results

Baseline characteristics

Most of the 281 patients assigned to ETN+MTX treatment were women (248; 88%); the average disease duration was 7.9 years (Table 1). A total of 269 participants from the ETN+MTX group completed the initial phase. Of those, 260 participants enrolled in the ETN+MTX group in the extension phase [9]. DAS28 remission data were available for 241 and 219 patients at Weeks 24 and 128, respectively.

At Week 24, 27% (66/241) of participants in the ETN+MTX group achieved DAS28-ESR remission. This increased to 42% (91/219) of participants at Week 128 (Table 2). On average, responders were significantly younger than non-responders ($p < 0.05$ at Weeks 24 and 128). Responders also had, on average, a lower baseline ESR, lower PGA scores, lower total HAQ scores, lower

VAS Pain scores (all $p < 0.05$ at Week 24), and a lower rate of RF positivity ($p < 0.05$ at Week 128) compared with non-responders. There were no significant differences in terms of baseline CRP (Table 2).

Predictors of response at weeks 24 and 128

Baseline factors found to be associated with response to ETN+MTX at Weeks 24 and 128 in the one-way ANOVA models and in chi-square tests are shown in Fig. 1. The subsets of baseline factors that predicted response to ETN+MTX therapy at Weeks 24 and 128 in the stepwise regression analysis are shown in Fig. 2. Significantly higher odds of attaining remission at Week 24 were associated with a younger age (≤ 49 years vs > 49 years; odds ratio [OR] 2.93 [95% CI 5.91–1.45]), higher BMI (> 28.5 kg/m² vs ≤ 28.5 kg/m²; OR 3.24 [95% CI 1.54–6.83]), longer disease duration (> 3.7 years vs ≤ 3.7 years; OR 2.22 [95% CI 1.09–4.52]), lower ESR (≤ 42.0 mm/h vs > 42.0 mm/h; OR 2.72 [95% CI 1.28–5.80]), lower PGA score (≤ 6.0 vs > 6.0 ; OR 3.21 [95% CI 1.62–6.35]), lower prorated number of tender joints (≤ 14 vs > 14 ; OR 2.25 [95% CI 1.01–5.01]), and lower total HAQ score (≤ 1.6 vs > 1.6 ; OR 2.86 [95% CI 1.40–5.88]) (all $p < 0.05$). Significantly higher odds of attaining remission at Week 128 were associated with a younger age (≤ 42 years vs > 42 years; OR 2.21 [95% CI 1.16–4.21]), higher SF-36 Mental Health Scale score (> 39.6 vs ≤ 39.6 ; OR 2.16 [95% CI 1.15–4.05]), White versus other race (OR 4.07 [95% CI 1.48–11.11]), higher number of swollen joints (> 18 vs ≤ 18 ; OR 2.11 [95% CI 1.12–3.97]), and a lower VAS Pain score (≤ 41 mm vs > 41 mm; OR 6.05 [95% CI 2.37–15.48]) (all $p < 0.05$).

Table 1 Select Baseline Demographic and Clinical Characteristics of the ETN+MTX Group*. Adapted From [8]

	ETN+MTX (n=281)
Age, years	48.4 ± 12.0
Women, n (%)	248 (88.3)
Race, n (%)	
White	134 (47.7)
Mestizo	60 (21.4)
African-Latin American	39 (13.9)
Other	48 (17.1)
BMI, kg/m ²	26.4 ± 5.1
CRP, mg/L	20.7 ± 25.4
ESR, mm/h	43.2 ± 16.6
Disease duration, years	7.9 ± 7.0
RF positive, n (%)	242 (86.1)
DAS28-ESR	6.6 ± 0.7
HAQ total score	1.6 ± 0.7
PGA	6.7 ± 1.6
VAS Pain, mm (0–100 scale)	65.6 ± 21.3

* Data are mean ± SD unless stated otherwise

BMI body mass index, CRP C-reactive protein, DAS28-ESR 28-joint Disease Activity Score with erythrocyte sedimentation rate, ETN etanercept, HAQ Health Assessment Questionnaire, MTX methotrexate, PGA Physician Global Assessment, RF rheumatoid factor, SD standard deviation, VAS visual analog scale

Discussion and conclusions

To the best of our knowledge, this is the first analysis of baseline predictors of clinical response to treatment with ETN in Latin American patients with RA. The best subset of factors that predicted clinical response to ETN+MTX therapy for 24 weeks were younger age, higher BMI, longer disease duration, and an overall lower disease activity (lower ESR, PGA, and total HAQ scores). At 128 weeks, the best subset of factors that predicted clinical response to ETN+MTX therapy were younger age, higher SF-36 score, White race, higher number of swollen joints, and lower pain.

In line with our findings, younger age of patients with RA predicted a stronger clinical response in a study of the TNF inhibitor adalimumab [11, 12] and in a study of the IL6 inhibitor tocilizumab [13]. However, age did not predict clinical response in a British registry study of the TNF inhibitor infliximab [14].

Although it could be argued that younger age may be a surrogate marker for shorter disease duration—which has

Table 2 Select Baseline Demographic and Baseline Disease Characteristics of Responders and Non-Responders (Observed Cases)

Baseline Characteristic*	Week 24			Week 128		
	Responders (n = 66)	Non-responders (n = 175)	p value**	Responders (n = 91)	Non-responders (n = 128)	p value**
Age, years	45.4 ± 11.8	49.2 ± 11.7	0.024	45.7 ± 11.8	50.1 ± 11.8	0.008
Men, n (%)	13 (20)	16 (9)		15 (17)	13 (10)	
Women, n (%)	53 (80)	159 (91)	0.025	76 (84)	115 (90)	0.167
Race, n (%)						
White	34 (52)	77 (44)	0.622	46 (51)	57 (45)	0.015
Mestizo	15 (23)	38 (22)		25 (28)	23 (18)	
African-Latin American	7 (11)	27 (15)		13 (14)	18 (14)	
Other	10 (15)	33 (19)		7 (8)	30 (23)	
BMI, kg/m ²	26.6 ± 5.3	26.3 ± 4.8	0.669	26.3 ± 4.4	26.4 ± 5.2	0.860
CRP, mg/L	19.5 ± 25.9	21.8 ± 25.4	0.521	22.5 ± 26.8	21.1 ± 26.1	0.707
ESR, mm/h	37.3 ± 11.2	44.3 ± 17.4	0.003	39.6 ± 13.8	43.1 ± 16.5	0.104
Disease duration, years	8.2 ± 7.1	7.4 ± 6.5	0.428	7.4 ± 6.4	8.0 ± 7.0	0.534
RF positive, n (%)	55 (83)	155 (89)	0.279	73 (80)	117 (91)	0.016
HAQ total score	1.3 ± 0.7	1.7 ± 0.7	0.001	1.5 ± 0.7	1.6 ± 0.7	0.376
VAS Pain, mm	60.0 ± 23.6	66.1 ± 20.3	0.047	61.6 ± 25.7	66.0 ± 18.2	0.141
PGA	6.5 ± 1.9	7.2 ± 1.9	0.013	6.7 ± 2.2	7.1 ± 1.8	0.122
SF-36 Mental Health Scale	41.0 ± 11.3	40.3 ± 11.0	0.665	41.5 ± 10.8	39.6 ± 11.3	0.223
Prorated number of tender joints	22.2 ± 10.9	26.0 ± 11.9	0.024	24.6 ± 11.1	25.5 ± 12.4	0.600
Prorated number of swollen joints	17.6 ± 7.9	18.4 ± 8.6	0.504	19.9 ± 8.9	17.3 ± 8.2	0.029

*Data are mean ± SD unless stated otherwise

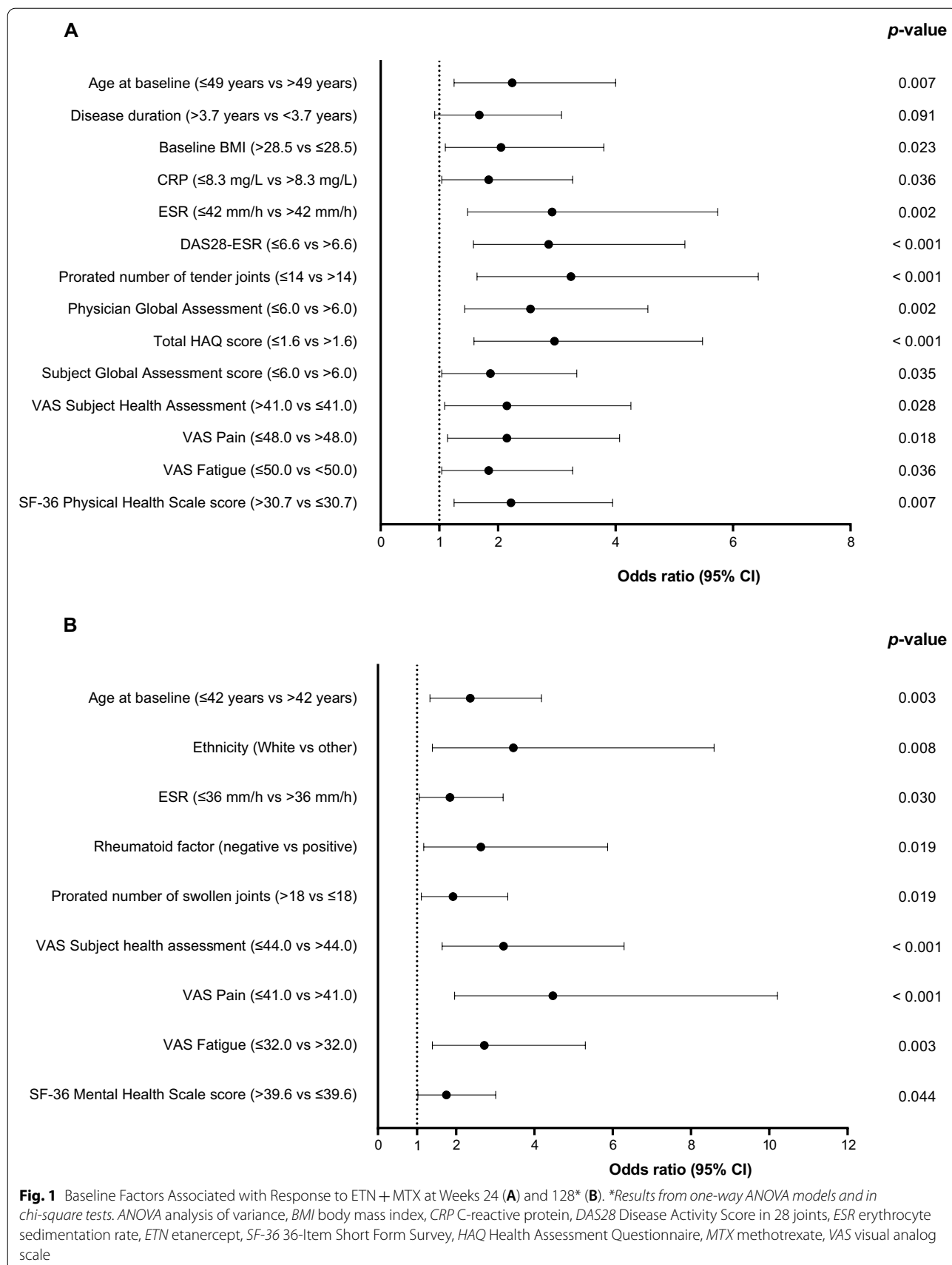
**p value from either a one-way ANOVA model to analyze continuous characteristics or a chi-square test to analyze categorical characteristics; baseline characteristics with p values < 0.05 are highlighted in bold

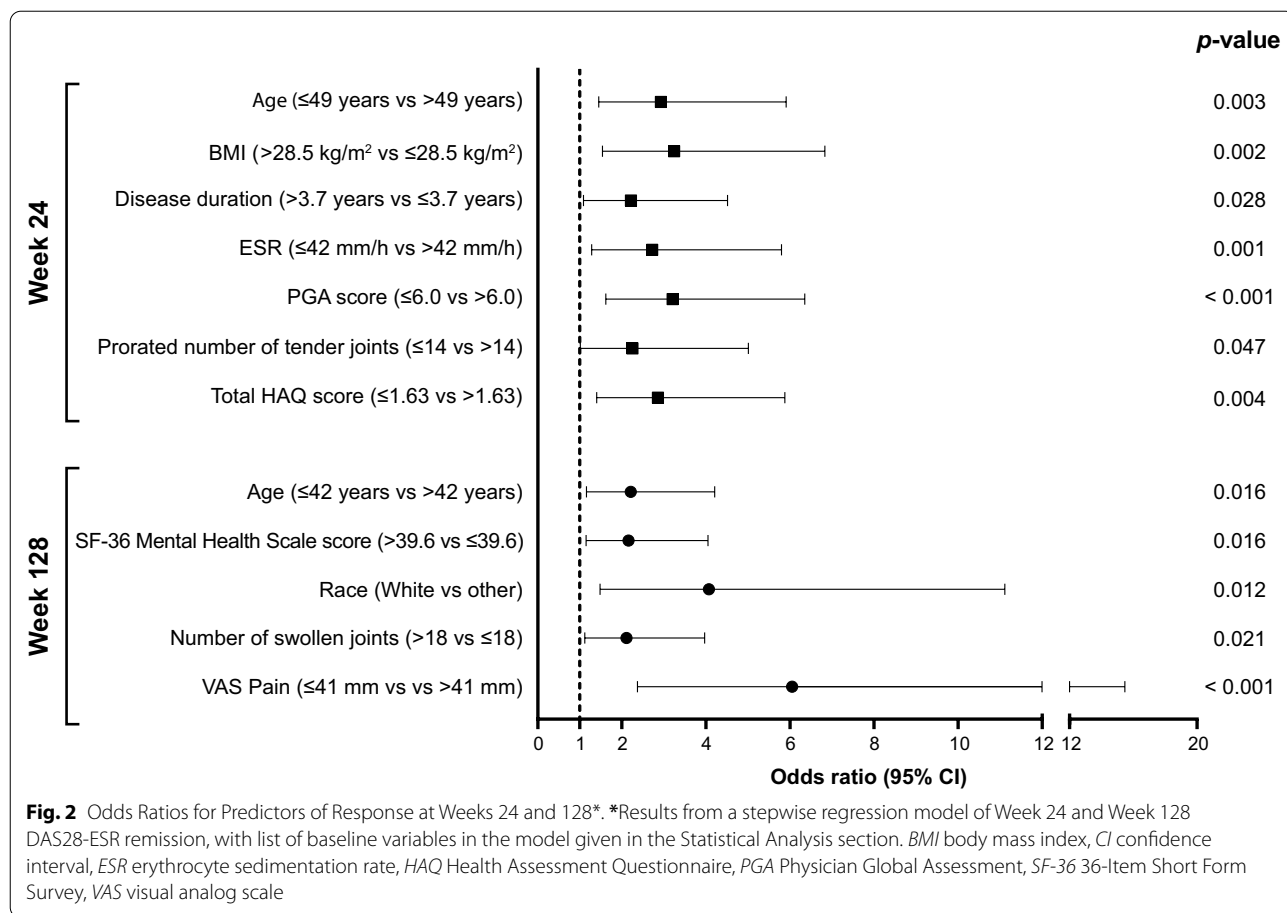
BMI body mass index, CRP C-reactive protein, ESR erythrocyte sedimentation rate, HAQ Health Assessment Questionnaire, PGA Physician Global Assessment, RF rheumatoid factor, SD standard deviation, SF-36 36-Item Short Form Survey, VAS visual analog scale

been shown to predict higher responses to ETN + MTX [15] and other biologics [16–18]—our analysis, surprisingly, found a marginally significant association of longer disease duration (>3.7 years) with clinical response at Week 24 when analyzed in combination with other significant predictors in a stepwise analyses, but it was not significant on its own. However, other confounding factors may influence the relationship between disease duration and DAS28 remission. Overall, the role of disease duration as a predictor of clinical response to treatment of RA with biologic agents appears to be unclear, with the data from the British Society for Rheumatology Biologics registry [14] and a study in Japanese patients treated with infliximab, ETN, adalimumab, or tocilizumab [19] failing to establish a link between disease duration and response to treatment.

In our analysis, parameters indicating lower disease activity at baseline (ESR ≤ 42 mm/h, PGA score ≤ 6.0, tender joint count ≤ 14, and total HAQ score ≤ 1.6) were also associated with a stronger response to ETN + MTX treatment at Week 24 on their own and in combination with other significant predictors from a stepwise

model. These observations are in line with a number of studies. For example, in a cohort of Chinese patients treated with a TNF inhibitor, ESR ≤ 60 mm/h and total HAQ score ≤ 1.31 were identified as predictors of clinical response [20]. Data from the British Society for Rheumatology Biologics registry [14], as well as a study in Swedish patients [21], showed that lower baseline HAQ scores were correlated with higher response rates. Similarly, Japanese patients with higher baseline PGA scores were less likely to achieve response to biologic agents [19]. The same study identified low levels of CRP as a predictor of response, which was not the case in our analysis. In the GO-MORE study, lower tender joint count score was associated with a greater likelihood of achieving DAS28-ESR ≤ 3.2 and DAS28-ESR < 2.6 at 1 and 6 months after treatment with the anti-TNF golimumab in biologic-naïve patients with active RA despite treatment with DMARD [22]. However, in a systematic review that included 4 studies of patients with RA treated with anti-TNF therapy + MTX, tender joint count at baseline was not associated with sustained remission [23].





Conversely, a higher number of swollen joints (>18) on its own (from univariate analysis) and in combination with other significant predictors from a stepwise model, indicating higher disease activity at baseline, was associated with a stronger response at Week 128. Although synovitis can be a predictor for radiographic progression [24], an increased number of swollen joints was associated with a higher likelihood of achieving sustained remission in a UK observational study [25].

Lower pain (VAS ≤41 mm) and SF-36 Mental Health Scale score >39.6 at baseline were identified as predictors of clinical response at Week 128 only in combination with other significant predictors from a stepwise model, with lower pain being only marginally significant on its own for Week 24 response. Although we could not identify any studies investigating either of these potential predictors, they may be associated with lower disease activity at baseline.

In our study, White patients (on its own and in combination with other significant predictors) were more likely to achieve clinical remission at Week 128 compared with patients of other races. This is in line with a study

from the United States in which African-American and Hispanic patients with RA showed higher disease activity and worse clinical outcomes compared with White patients [26]. The role of race as a predictor is likely to be complex and include both genetic as well as socio-cultural and socio-economic factors.

Interestingly, we also identified higher BMI (>28.5 kg/m²) as a predictor of clinical response at Week 24 when analyzed in combination with other significant predictors in a stepwise model but not on its own in a univariate model. This is in contrast with a study showing higher BMI (>30 kg/m²) to be associated with lower response rates to infliximab [27]. In an Italian study, patients with higher BMI (>30 kg/m²) were less likely to achieve response to infliximab, but no correlation was found for ETN and adalimumab [28]. In another study of adalimumab, BMI (>30 kg/m²) had no impact on response rates [29]; this was also apparent in studies of rituximab [30] and tocilizumab [31]. Overall, the role of BMI as predictor of response seems to be unclear. Although higher BMI is generally associated with lower socio-economic status, 1 Brazilian study found a positive correlation between BMI and higher socio-economic status

[32], which may facilitate access to health care and could therefore explain the favorable outcomes observed here.

In this stepwise regression analysis, RF positivity had no impact on clinical response. This is in line with observations from studies of ETN and infliximab [14] and of tocilizumab [13]. Based on the currently available evidence, no clear conclusion can be drawn on the role of RF positivity as predictor of response, with some studies finding a positive association although others have identified it as a negative predictor [12].

Although Week 24 and Week 128 responders to ETN + MTX were more likely to be male, sex was not a significant predictor of clinical response in our study. An earlier study in a Swedish cohort also found no significant predictive value of sex on clinical response after 3 or 6 months of therapy with ETN, infliximab, or adalimumab [21]; although males had lower DAS28 scores. This is somewhat in contrast to the findings of other studies where males were more likely to achieve clinical remission following treatment with ETN or infliximab [14], and adalimumab [11]. Within the patient population with RA, differences in severity of disease between sexes and differences in other factors, such as biological, physical, or social, may underlie any observed differences by sex.

Limitations of this study included the post hoc nature of this analysis and the absence of an adequate control group. The lack of a control group limits the ability to make conclusions about the specificity of the identified subset of predictive characteristics to the ETN + MTX treatment regimen. The low proportion of male participants makes it difficult to ascertain the impact of sex. It is not possible to generalize the results from this study, which was conducted in selected clinical trial participants, to other populations that were not sufficiently represented in the clinical trial population (e.g., men and individuals of different ages and with different disease durations).

In conclusion, this post hoc logistic regression analysis of a trial of Latin American patients with RA yielded several baseline predictors of clinical response to treatment with ETN + MTX, which may be useful for future clinical decision-making. These baseline predictors of clinical response included younger age, higher BMI, longer disease duration, higher SF-36 Mental Health Scale score, higher swollen joint count, and overall lower disease activity. Discrepancies between our findings and those from studies conducted in other geographic areas of the world, however, underline the need for further prospective studies, adequately powered to detect predictors of response.

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Authors' contributions

MdIV, GGB, RMX, CP-T, AES, GS, RDP, CB, KS, BV, Conceptualization, Data curation, Writing – review and editing. All authors read and approved the final manuscript.

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Availability of data and materials

Upon request, and subject to certain criteria, conditions, and exceptions (see <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices: (1) for indications that have been approved in the USA and/or EU; or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

Declarations

Ethics approval

The final protocol, any amendments, and informed consent documentation were reviewed and approved by the Institutional Review Board(s) (IRB) and/or Independent Ethics Committee(s) (IEC) at each of the investigational centers participating in the study. Investigators were required to inform their IRBs or IECs of the study's progress and occurrence of any serious and/or unexpected adverse events. This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonisation Good Clinical Practice Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial participants.

Consent to participate

A signed and dated informed consent was required before any screen procedures were done. The investigators explained the nature, purpose, and risks of the study to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. Subjects who chose to participate signed an informed consent document.

Consent for publication

Not applicable.

Competing interests

MdIV, AbbVie, Genzyme, Lilly, Pfizer, and TRB Pharma (consulting fees); BMS, Gilead, Glaxo, Pfizer, and Roche (trial investigator); AbbVie, Genzyme, Janssen Lilly, and Pfizer (speaker); GGB, no disclosures to report; RMX, AbbVie, BMS, Janssen, Lilly, Novartis, Pfizer, Roche, and UCB (consulting fees, speaker); CP-T, Pfizer, Sanofi, Roche, Eli Lilly, AbbVie, UCB, and BMS (consulting fees and speaker); AES, AES is an employee of Syneos Health and was contracted by Pfizer to provide statistical support for the development of this paper; RDP, RDP was an employee of Pfizer at the time of data generation and manuscript development and own stock in Pfizer; GS, CB, KS, BV, Pfizer (stock options, employment).

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