Predictors of Clinical Remission With Etanercept in Paediatric Patients With Extended Oligoarticular, Enthesitis-Related Arthritis and Psoriatic Arthritis: Findings From the CLIPPER Study

A. Consolaro[1], G. Horneff[1], R. Burgos-Vargas[1], T. Constantin[1], I. Foeldvari[1], J. Vojinovic[1], J. Dehoorne[1], V. Panaviene[1], G. Susic[1], V. Stanevica[1], K. Kobusinska[1], Z. Zuber[1], R. Mouy[1], I. Rumba-Rozenfelde[1], P. Dolezalova[1], C.I. Job-Deslandre[1], N. Wulffraat[1], R. Pederson[2], J. Bukowski[2], T. Hinnershitz[2], B. Vlahos[2], A. Martini[1], N. Ruperto[1] for the Paediatric Rheumatology International Trials Organisation (PRINTO)

[1]Paediatric Rheumatology International Trials Organisation (PRINTO), Genoa, Italy; [2]Pfizer, Collegeville, PA, USA

INTRODUCTION

- Juvenile idiopathic arthritis (JIA) is the most common type of chronic rheumatic disease of childhood,[1-3] which encompasses 7 mutually exclusive disease categories according to the International League of Associations for Rheumatology classification criteria.[4]
- Several biologics have been shown to be effective in reducing the signs and symptoms of moderately to severely active JIA in children who have not responded to or are intolerant of first-line therapy.[5-9]
- The biologic etanercept (ETN) is approved in the European Union for the treatment of JIA categories of polyarticular, extended oligoarticular (eoJIA), enthesitis-related arthritis (ERA), and psoriatic arthritis (PsA), and in the United States for polyarticular JIA.
- Although data from clinical treatment trials in JIA populations are accumulating, relatively little evidence is currently available regarding predictors of clinical remission in patients with these JIA categories.

OBJECTIVE

- To evaluate whether patients' demographic and disease characteristics at baseline or early clinical response or disease activity predicted their achievement of clinical remission after 24 weeks of ETN treatment in the CLIPPER study.

METHODS

Study Design

- CLIPPER is an ongoing, Phase 3b, open-label study conducted at 38 centres in 19 European and Latin American countries.[10,11]
- Paediatric patients with JIA received ETN 0.8 mg/kg once weekly (maximum 50 mg) for up to 96 weeks.

Major Eligibility Criteria

- eoJIA (aged 2–17 y), ERA (aged 12–17 y), or PsA (aged 12–17 y).
- ≥2 active joints (swollen or limitation of motion [LOM] with pain or tenderness).
- Intolerance of or unsatisfactory response to ≥1 disease-modifying antirheumatic drug (DMARD) administered for ≥3 months or unsatisfactory response to ≥1 non-steroidal anti-inflammatory drug (NSAID) administered for ≥1 month (only for ERA).
- Concomitant treatment with only 1 DMARD (methotrexate, hydroxychloroquine, chloroquine, or sulfasalazine), 1 oral corticosteroid, and 1 NSAID permitted, with no dose changes, during the study.

Definitions of Clinical Remission

- Juvenile Arthritis Disease Activity Score 71-joint reduced count (JADAS71) clinical remission criteria (≤1) for ≥24 weeks.
- JIA American College of Rheumatology (ACR) Wallace 2011 remission criteria[12] for ≥24 weeks.

Categorical Predictors

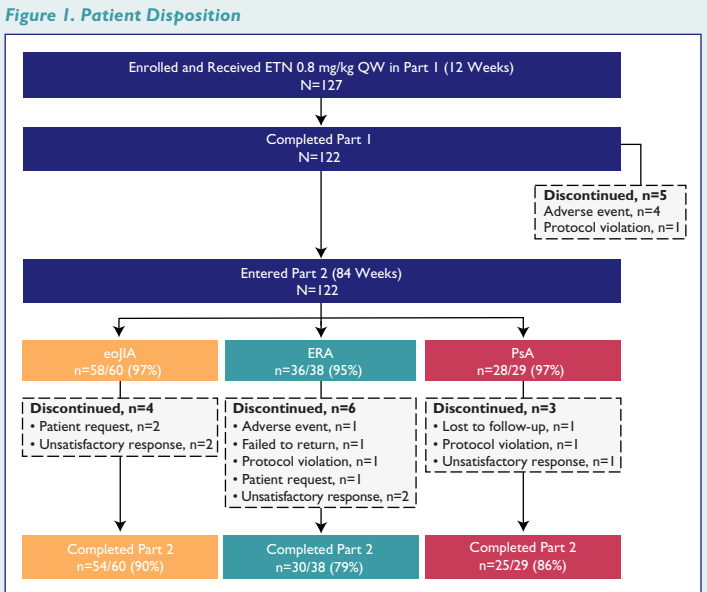
- Dichotomised continuous characteristics predictive of clinical remission were analysed post hoc using univariate logistic regression models and stepwise regression models based on receiver operating characteristic (ROC)-derived cut-off points.
  - Demographic and disease characteristics at baseline.
  - Clinical response and disease activity status after 12 weeks of ETN treatment, ie, JADAS low disease activity (LDA; ≤3.8 [polyarthritis], ≤2 [oligoarthritis]), JADAS inactive disease (≤1), and ACR Wallace remission.[12]

RESULTS

Patients

- 127 patients enrolled in the study and received ETN treatment (eoJIA, n=60; ERA, n=38; PsA, n=29; **Figure 1**).
- Baseline demographic and disease characteristics are summarised in **Table 1**. Of 127 patients enrolled in the trial, 54 (43%) and 42 (33%) achieved JADAS71 or JIA ACR clinical remission over 24 weeks, respectively.

Figure 1. Patient Disposition



QW, once weekly

Table 1. Baseline Demographics and Disease Characteristics at Baseline[10]

Patient Characteristics	eoJIA (n=60)	ERA (n=38)	PsA (n=29)	Overall (n=127)
Age, y	8.6 (4.6)	14.5 (1.6)	14.5 (2.0)	11.7 (4.5)
Female, n (%)	41 (68)	8 (21)	23 (79)	72 (57)
Height, cm	132.4 (27.8)	167.0 (9.8)	162.5 (10.5)	149.9 (26.1)
Weight, kg	34.8 (18.9)	54.4 (8.8)	60.0 (14.2)	46.4 (19.0)
Body mass index, kg/m^2	17.9 (3.6)	19.5 (2.4)	22.7 (4.5)	19.5 (4.0)
Age at disease onset, y	6.1 (4.5)	12.5 (2.1)	12.6 (2.7)	9.5 (4.8)
Disease Characteristics				
Disease duration, mo	31.6 (31.7)	23.0 (19.8)	21.8 (20.2)	26.8 (26.4)
JIA core set				
Physician global assessment of disease activity, VAS	5.0 (1.8)	5.4 (1.9)	4.7 (1.4)	5.0 (1.8)
Parent/patient global assessment (PPGA) of overall well-being, VAS	4.8 (2.4)	5.4 (2.3)	4.6 (2.2)	5.0 (2.3)
Childhood Health Assessment Questionnaire (CHAQ) score	0.9 (0.7)	0.7 (0.5)	0.7 (0.6)	0.8 (0.6)
Joints with active arthritis, no.	7.6 (5.1)	5.2 (3.6)	7.0 (4.3)	6.7 (4.6)
Joints with LOM, no.	6.3 (4.4)	4.8 (4.0)	5.6 (4.1)	5.7 (4.2)
C-reactive protein, mg/L	6.3 (10.6)	15.3 (21.5)	3.2 (4.7)	8.2 (14.7)
Morning stiffness, min	72.8 (97.2)	89.3 (128.9)	54.3 (54.2)	73.5 (100.6)
JADAS71	17.9 (7.5)	17.2 (7.1)	15.9 (5.4)	17.2 (7.0)
Concomitant Medications				
Any DMARD, n (%)	54 (90)	32 (84)	23 (79)	109 (86)
Oral corticosteroid, n (%)	7 (12)	8 (21)	1 (4)	16 (13)
Oral NSAID, n (%)	32 (53)	26 (68)	16 (55)	74 (58)

All values are mean (standard deviation) unless otherwise specified.
VAS, visual analogue scale

RESULTS (CONT'D)

Baseline and 12-Week Predictors of Sustained Clinical Remission

Univariate analyses

- Children who were shorter height and had lower scores on the PPGA at baseline and those who were younger at the time of disease onset were significantly more likely to achieve sustained JADAS71 and JIA ACR Wallace remission (**Figure 2A**, **B**).
  - A greater number of joints with LOM at baseline was a predictor of sustained JADAS71 remission.
  - Younger age and higher C-reactive protein (CRP) levels at baseline were significant predictors of sustained ACR Wallace remission.
- Induction of JADAS71 and ACR Wallace responses at 12 weeks was also predictive of sustained JADAS71 and ACR Wallace remission (**Figure 2C**, **D**).
- The strongest baseline predictor of sustained JADAS remission was a greater number of joints with LOM (**Figure 3A**); the strongest predictor of sustained ACR Wallace remission was younger age at onset (**Figure 3B**).
- The strongest early response predictor of sustained JADAS remission was ACR Wallace remission at 12 weeks (**Figure 3A**); the strongest predictor of sustained ACR Wallace remission was JADAS remission at 12 weeks (**Figure 3B**).

Multivariate analyses

- Children who achieved JADAS LDA at week 12 were significantly more likely to achieve sustained JADAS71 and JIA ACR Wallace remission (**Figure 3C, D**).
  - Shorter height, greater number of joints with LOM, lower score on CHAQ, and greater morning stiffness at baseline, and achievement of ACR Wallace remission at week 12, were significant predictors of sustained JADAS71 remission.
  - Lower scores on the PPGA, younger age at disease onset, and greater number of joints with active arthritis at baseline were significant predictors of sustained ACR Wallace remission.
- Greater morning stiffness at baseline was the strongest predictor of sustained JADAS remission, whereas greater number of joints with active arthritis at baseline was the strongest predictor of sustained ACR Wallace remission (**Figure 3C, D**).
- ACR Wallace remission at 12 weeks and JADAS LDA at 12 weeks were identified as comparably powerful early response predictors of sustained JADAS and ACR Wallace remission (**Figure 3C, 3D**).

Figure 2. Prevalence of Clinical Remission at 24 Weeks by Predictor Subgroup

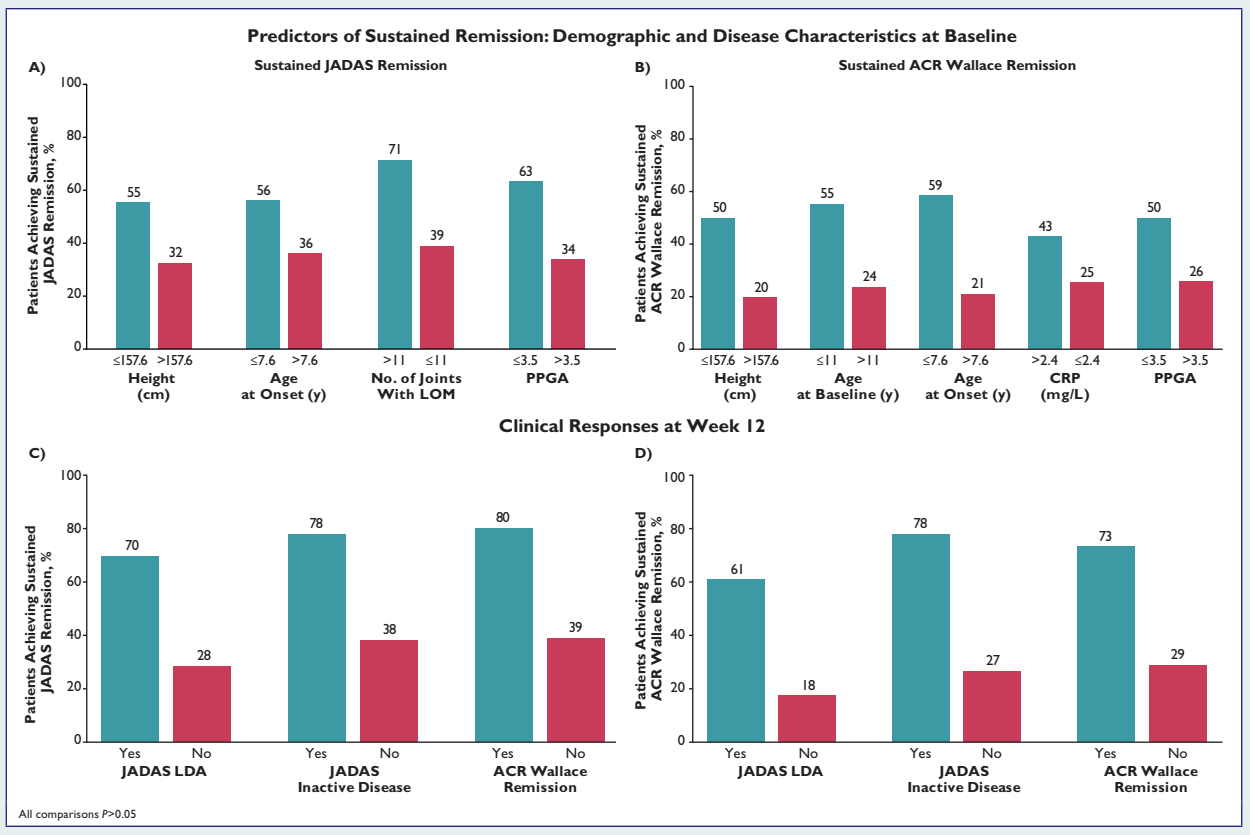
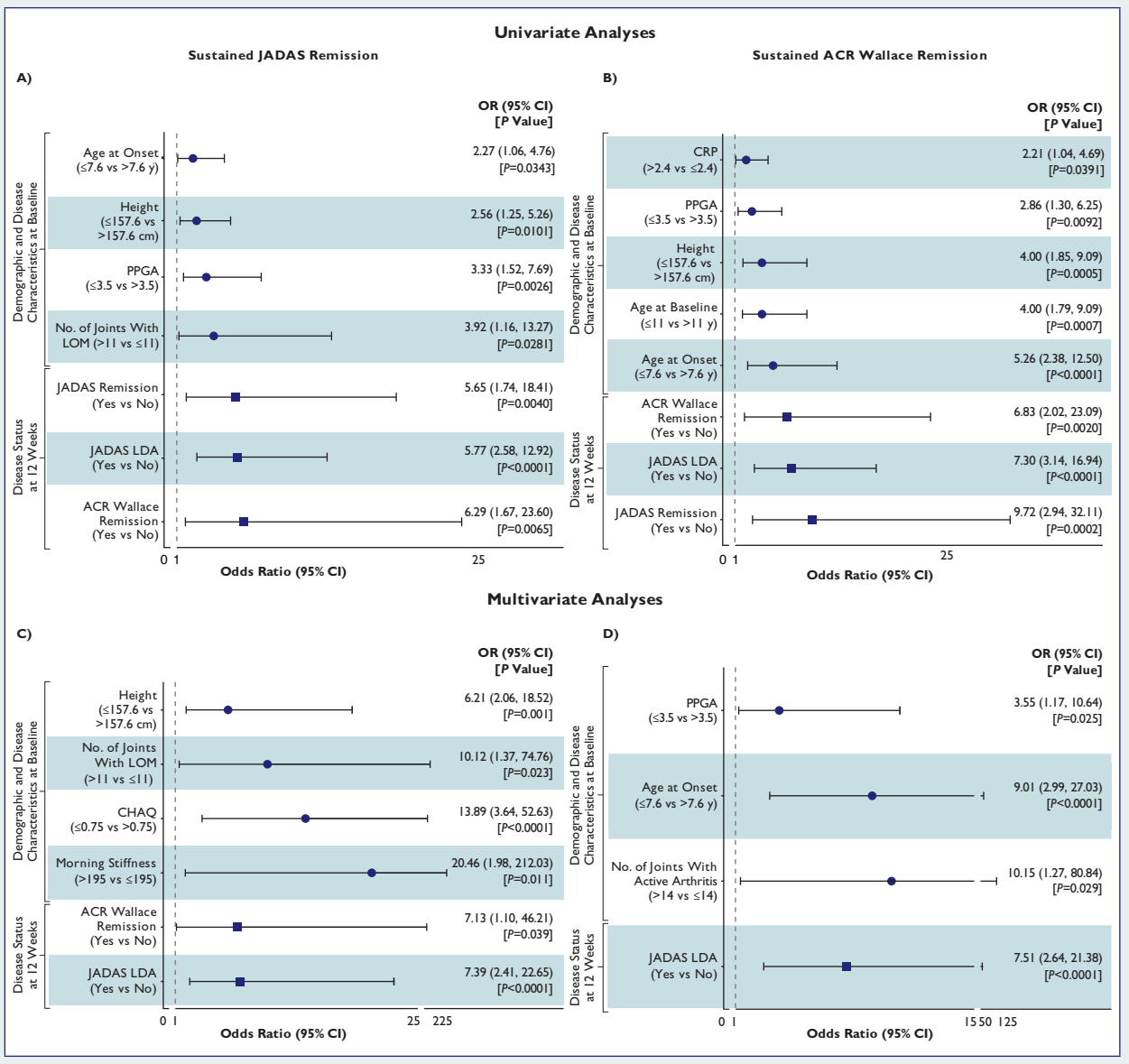


Figure 3. Factors Associated With Clinical Remission at 24 Weeks



CONCLUSIONS

- Greater morning stiffness and numbers of joints with LOM and active arthritis, shorter height, lower scores on PPGA and CHAQ, and younger age at onset were the strongest pre-treatment predictors of sustained clinical remission in response to biologic therapy with etanercept in this population of paediatric patients with eoJIA, ERA, or PsA JIA subtypes.
- Induction of remission or LDA after 12 weeks of etanercept treatment was an important predictor of sustained clinical remission over 24 weeks.

REFERENCES

1. Oen KG, et al. *Semin Arthritis Rheum.* 1996;26:575-91. 2. Gare BA. *Baillière's Clin Rheumatol.* 1998;12:191-208. 3. Sacks JJ, et al. *Arthritis Rheum.* 2007;57:1439-45. 4. Petty RE, et al. *J Rheumatol.* 2004;31:390-2. 5. Lovell DJ, et al. *N Engl J Med.* 2000;342:763-9. 6. Lovell DJ, et al. *N Engl J Med.* 2008;359:810-20. 7. Ruperto N, et al. *Lancet.* 2008;372:383-91. 8. De Benedetti F, et al. *N Engl J Med.* 2012;367:2385-95. 9. Ruperto N, et al. *N Engl J Med.* 2012;367:2396-406. 10. Horneff G, et al. *Ann Rheum Dis.* 2014;73:1114-22. 11. Constantin T, et al. *J Rheumatol.* 2016;43:816-24. 12. Wallace CA, et al. *Arthritis Care Res.* 2011;63:929-36.

We wish to thank all patients who participated in the trial and investigators and medical staff of all participating centres.

The study (ClinicalTrials.gov, NCT00962741/NCT01421069) was sponsored by Pfizer. Medical writing support was provided by Donna McGuire of Engage Scientific Solutions and was funded by Pfizer.

Presented at the 23rd European Pediatric Rheumatology Congress; 28 September–1 October, 2016; Genoa, Italy