

ORIGINAL ARTICLE

Long-term efficacy and predictors of remission following adalimumab treatment in peripheral spondyloarthritis: 3-year results from ABILITY-2

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ABSTRACT

Objectives Describe efficacy and safety of 3 years of adalimumab treatment in patients with peripheral spondyloarthritis (pSpA) and identify predictors of remission.

Methods Patients with pSpA were randomised to adalimumab 40 mg every other week or placebo for 12 weeks; a 144-week open-label extension followed (NCT01064856). Remission was assessed by the Peripheral SpA Response Criteria (PSpARC) and Ankylosing Spondylitis Disease Activity Score inactive disease (ASDAS ID). Logistic regression analyses were performed to determine predictors of remission at 1 and 3 years and sustained remission (≥ 24 consecutive weeks).

Results In 165 patients, ASDAS ID was achieved by 47% at 1 year and 39% at 3 years; 36% and 33% achieved PSpARC remission, respectively. Sustained ASDAS ID and PSpARC remission were achieved by 52% (86/165) and 42% (70/165) of patients, respectively. Achieving ASDAS ID at week 12 significantly predicted 1 year (OR, 8.64 (95% CI 2.97 to 25.14)), 3 year (OR, 36.12 (95% CI 2.29 to 569.08)) and sustained ASDAS ID (OR, 8.01 (95% CI 2.47 to 25.97)); achieving PSpARC remission at week 12 consistently predicted 1 year (OR, 6.47 (95% CI 1.91 to 21.95)), 3 years (OR, 15.66 (95% CI 4.19 to 58.56)) and sustained PSpARC remission (OR, 20.27 (95% CI 5.37 to 76.46)). No baseline variables consistently predicted 1-year or 3-year remission or sustained remission. The safety profile of adalimumab was consistent with observations in other SpA disease indications.

Conclusions In patients with pSpA, early response to adalimumab, but not baseline demographics or disease characteristics, was a better predictor of long-term remission.

INTRODUCTION

Peripheral spondyloarthritis (pSpA) typically presents with peripheral arthritis that is usually asymmetric and predominantly involves the lower limbs, enthesitis and/or dactylitis; this can be accompanied by

Key messages**What is already known about this subject?**

- To date, only a few other studies have evaluated the efficacy of tumour necrosis factor (TNF) inhibitors in patients with active peripheral spondyloarthritis (pSpA), and no long-term safety and efficacy data are available for pSpA.

What does this study add?

- In the ABILITY-2 study in patients with pSpA, the safety and efficacy of adalimumab were maintained through 3 years.
- Up to half of patients experienced sustained remission and remission at 1 and 3 years.
- Achievement of remission at week 12 was the strongest predictor of sustained and long-term remission.

How might this impact on clinical practice?

- Identification of factors that predict long-term and sustained remission in patients with pSpA after treatment with TNF inhibitors may facilitate clinical decisions regarding patient therapy.

additional extra-articular disease manifestations, such as uveitis, psoriasis and Crohn's disease.¹ In contrast to other rheumatic diseases, such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS)/axial SpA, long-term efficacy data in pSpA are very limited.

Recently, the ABILITY-2 study demonstrated the superior efficacy of adalimumab versus placebo over 12 weeks in patients with pSpA.² To date, only a few other studies have evaluated the efficacy of tumour necrosis factor (TNF) inhibitors in patients with active pSpA.^{3,4} In a small (n=40) investigator-initiated placebo-controlled trial, patients



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Table 1 Baseline demographics and disease characteristics

Characteristic, mean±SD*	Adalimumab N=165
Age, years	40.6±11.9
Women, n (%)	90 (55)
BMI (kg/m ²)	26.6±5.8
Smoker, yes, n (%)	39 (24)
Symptom duration, years	7.24±7.1
HLA-B27-positive, n (%)†	103 (63)
Prior DMARD use, n (%)	115 (70)
Concomitant DMARD use, n (%)	79 (48)
Elevated hs-CRP, n (%)	72 (44)
Swollen joint count (0–76)	6.7±6.9
Tender joint count (0–78)	13.3±14.5
Physician Global Assessment of disease activity (0–100)	58.7±15.3
Patient Global Assessment of pain (0–100)	64.9±14.9
Patient Global Assessment of disease activity (0–100)	65.8±15.5
Enthesitis count (0–29)	7.0±6.8
Dactylitis count (0–20)	0.5±1.1
BASDAI (0–10)	5.62±1.7
ASDAS	2.99±0.8

*Unless otherwise noted.

†n=164.

ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMI, body mass index; DMARD, disease-modifying antirheumatic drug; HLA, human leucocyte antigen; hs-CRP, high-sensitivity C-reactive protein.

received 12 weeks of adalimumab treatment followed by a 12-week open-label extension and a 16-week follow-up without active treatment.^{4 5} Another 12-week, double-blind, placebo-controlled trial evaluated infliximab in patients with active SpA, including patients with pSpA.³ These two studies classified patients using the European Spondyloarthropathy Study Group criteria,⁶ whereas ABILITY-2 used Assessment of SpondyloArthritis international Society (ASAS) classification criteria.¹

Currently, no long-term safety and efficacy data are available for pSpA. Furthermore, studies in other rheumatic diseases, including RA,^{7–13} PsA^{14 15} and AS,¹⁶ have evaluated predictors of short-term and long-term remission, but such data are lacking in pSpA. Here we report the long-term clinical efficacy and safety data from the ABILITY-2 study through the end of 3 years with a special focus on evaluation of potential predictors of long-term remission.

METHODS

The ABILITY-2 study, described previously (ClinicalTrials.gov, NCT01064856),² was a phase III, multicentre,

randomised, double-blind, placebo-controlled trial in patients with active non-psoriatic pSpA. Patients were randomised 1:1 to receive adalimumab (AbbVie, North Chicago, Illinois, USA) 40 mg every other week or placebo during a 12-week double-blind period,² followed by an open-label period of up to 3 years of adalimumab treatment. Eligible patients were aged ≥18 years, fulfilled the ASAS criteria for pSpA¹ and had pSpA symptoms for ≥3 months before the study baseline visit. Patients had active disease, a score ≥40 mm on a 0–100 mm visual analogue scale (VAS) for Patient Global Assessment of disease activity (PtGA) and Patient Global Assessment of pain (PtGA-pain) and an inadequate response to ≥2 non-steroidal anti-inflammatory drugs (NSAIDs) or intolerance to or contraindication for NSAIDs. The study was performed in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki.

Outcome measures

Patients were seen at baseline and weeks 2, 4, 8 and 12 of the double-blind study, then every 4 weeks until week 28, then every 8 weeks until week 68 and every 12 weeks thereafter. Disease activity outcome measures included PtGA, PtGA-pain, Physician Global Assessment (PGA), the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI),¹⁷ the Ankylosing Spondylitis Disease Activity Score (ASDAS),¹⁸ the Peripheral SpA Response Criteria (PSPARC; including PSPARC 20/40/50/70, defined as ≥20%, ≥40%, ≥50% or ≥70% improvement (≥10, ≥20, ≥20 or ≥30 mm absolute improvement on a VAS), respectively, from baseline in PtGA and PtGA-pain and ≥20%, ≥40%, ≥50% or ≥70% improvement from baseline in ≥1 of the following: tender joint count (TJC)/swollen joint count (SJC), total enthesitis count or dactylitis count)² and C-reactive protein (CRP). The ASDAS was calculated as described previously (0.12×back pain+0.06×duration of morning stiffness+0.11×PtGA+0.07×peripheral pain/swelling+0.58×(natural logarithm of CRP +1)).^{18 19} Two separate remission criteria were evaluated. PSPARC remission was defined as SJC≤1 plus ≥4 of the following five: PtGA≤20 mm VAS; PtGA-pain≤20 mm VAS; TJC≤1; enthesitis count≤1 and/or dactylitis count≤1.² Remission was also defined using ASDAS inactive disease (ASDAS ID; ASDAS score<1.3).¹⁹

Sustained remission was defined as achieving the specified remission criterion (PSPARC or ASDAS ID) for ≥24 consecutive weeks^{8 11 16 20} at any time during the 3-year study. The number of patients who achieved sustained remission in the first, second and third year of adalimumab exposure was calculated. In addition, we assessed how many patients experienced a disease flare after achieving sustained remission. For patients who achieved sustained ASDAS ID, flare was defined as ≥2 consecutive study visits with ASDAS≥2.1 and/or ≥1 visit with ASDAS>3.5.^{21 22} For patients who achieved sustained PSPARC remission, flare was defined as not

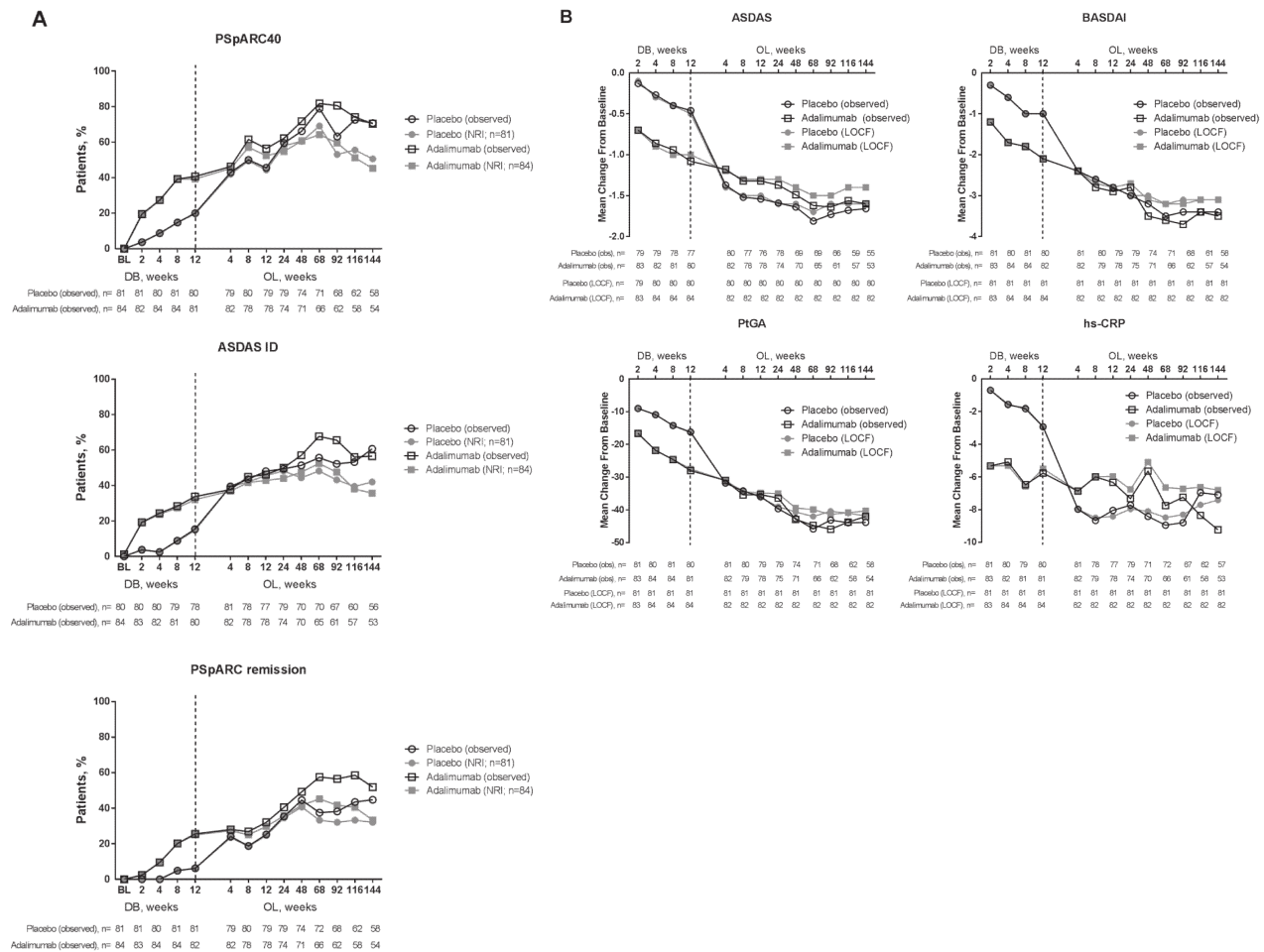


Figure 1 Percentage of patients achieving clinical outcomes (A) and mean changes from baseline (B). Clinical outcomes included (A) PSpARC40, ASDAS ID and PSpARC remission achievement and (B) ASDAS, BASDAI, PtGA and hs-CRP mean changes over 144 weeks in patients treated with adalimumab and placebo (up to week 12). Patients randomised to receive placebo during the DB period initiated OL adalimumab after week 12. ASDAS, Ankylosing Spondylitis Disease Activity Score; ASDAS ID, ASDAS inactive disease; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BL, baseline; DB, double blind; hs-CRP, high-sensitivity C-reactive protein; LOCF, last observation carried forward; obs, observed; OL, open label; PtGA, Patient Global Assessment; PSpARC, Peripheral SpondyloArthritis Response Criteria.

achieving PSpARC40 (PSpARC40-non-responder) at ≥ 2 consecutive visits.

Three different enthesitis tools were used in this study (the Maastricht Ankylosing Spondylitis Enthesitis Score, the Leeds Enthesitis Index and the Spondyloarthritis Research Consortium of Canada Enthesitis Index); to calculate the score using these three tools, a total of 29 different enthesal sites were examined per visit and patient.²

Statistical methods

Descriptive statistics were used to report mean change from baseline (as observed and last observation carried forward analyses) in ASDAS, BASDAI, PtGA and high-sensitivity CRP (hs-CRP) as well as the percentages of patients (as observed and using non-responder imputation (NRI)) achieving PSpARC remission, ASDAS ID

and PSpARC40 per visit over 144 weeks assessed by initial randomisation to adalimumab or placebo.

Univariate analysis

Univariate logistic regression was used to evaluate predictors of remission (PSpARC remission and ASDAS ID) at years 1 and 3. Possible predictors for remission after 1 and 3 years of adalimumab treatment were selected a priori; demographic and baseline disease characteristics included age, sex, body mass index (BMI), smoking status (current smoker vs current non-smoker), symptom duration, human leucocyte antigen B27-positive status, elevated baseline hs-CRP, prior use of disease-modifying antirheumatic drugs (DMARDs) and baseline values of the following: TJC, SJC, enthesitis count, BASDAI, ASDAS, PtGA and PGA. The response at week 12 of adalimumab

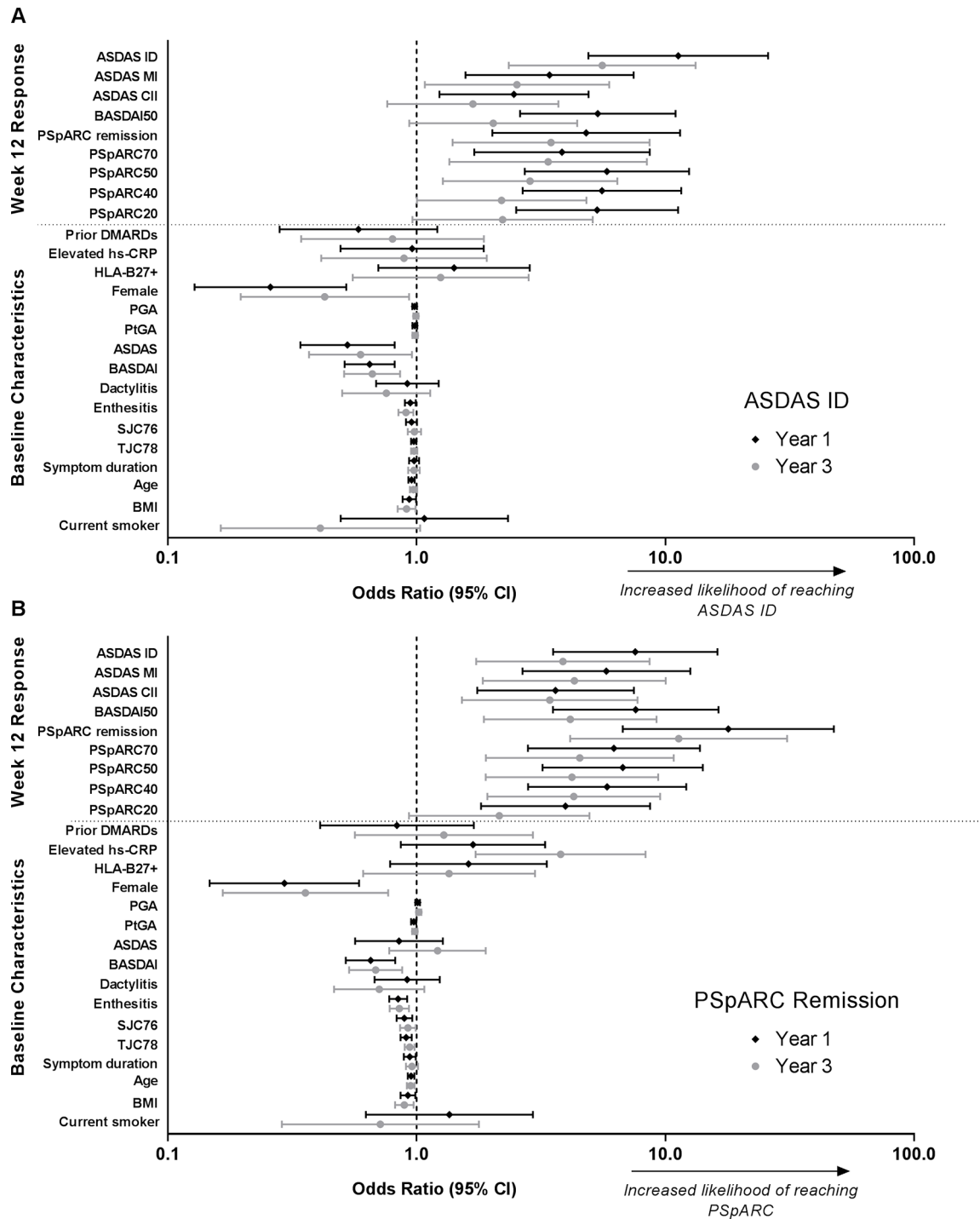


Figure 2 Univariate predictors of (A) ASDAS ID (<1.3) and (B) PSpARC remission. Predictors of remission shown after 1 and 3 years of adalimumab exposure. ASDAS, Ankylosing Spondylitis Disease Activity Score; ASDAS CII, ASDAS clinically important improvement; ASDAS ID, ASDAS inactive disease; ASDAS MI, ASDAS major improvement; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMI, body mass index; DMARD, disease-modifying antirheumatic drug; HLA, human leucocyte antigen; hs-CRP, high-sensitivity C-reactive protein; PGA, Physician Global Assessment; PtGA, Patient Global Assessment; PSpARC, Peripheral SpondyloArthritis Response Criteria; SJC, swollen joint count; TJC, tender joint count.

exposure was assessed using $\geq 50\%$ improvement in BASDAI (BASDAI50), ASDAS clinically important improvement (ASDAS CII; $\Delta \geq 1.1$), ASDAS major improvement (ASDAS MI; $\Delta \geq 2.0$), ASDAS ID, PSpARC20, PSpARC40, PSpARC50, PSpARC70 and PSpARC remission.

Multivariate analysis

Multivariate analysis was performed to determine predictors of achieving sustained ASDAS ID or PSpARC remission at any time during the study. All 25 variables with a critical significance level of 10% in the univariate analysis were included in the multivariate analysis (full model).

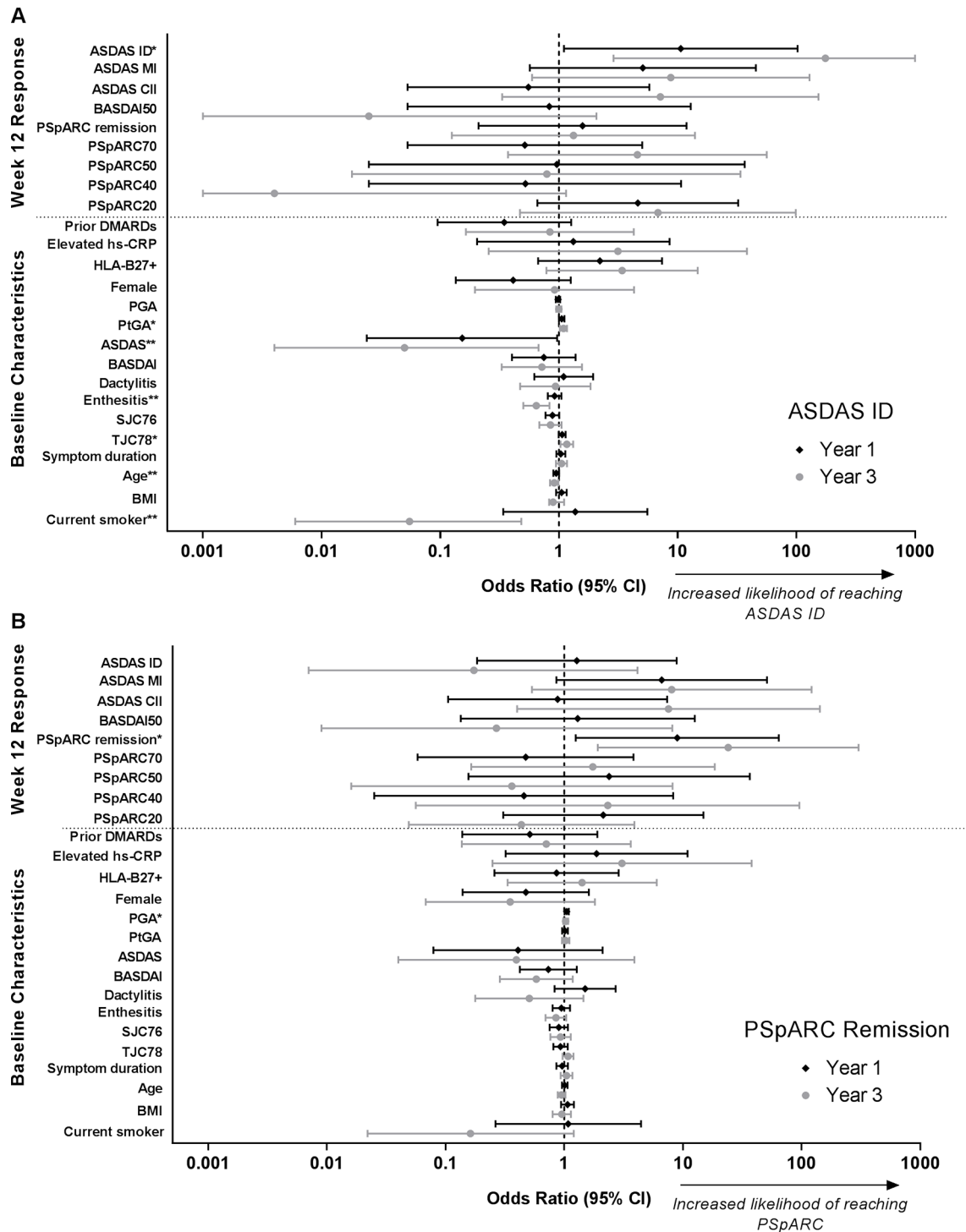


Figure 3 Multivariate predictors of (A) ASDAS ID (<1.3) and (B) PSpARC remission. Predictors of remission shown after 1 and 3 years of adalimumab exposure. *Statistically significant positive predictor of remission ($P < 0.05$; χ^2 test). For (A), includes ASDAS ID at week 12 (years 1 and 3) and PtGA and TJC (year 3); for (B), includes PSpARC remission (years 1 and 3) and PGA (year 1). **Statistically significant negative predictor of remission ($P < 0.05$; χ^2 test). For (A), includes baseline ASDAS (years 1 and 3) and age, current smoker and enthesitis (year 3). ASDAS, Ankylosing Spondylitis Disease Activity Score; ASDAS CII, ASDAS clinically important improvement; ASDAS ID, ASDAS inactive disease; ASDAS MI, ASDAS major improvement; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMI, body mass index; DMARD, disease-modifying antirheumatic drug; HLA, human leucocyte antigen; hs-CRP, high-sensitivity C-reactive protein; PGA, Physician Global Assessment; PtGA, Patient Global Assessment; PSpARC, Peripheral SpondyloArthritis Response Criteria; SJC, swollen joint count; TJC, tender joint count.

Table 2 Significant predictors of sustained remission over 3 years of adalimumab treatment

Predictor, OR (95% CI)	Sustained ASDAS ID		Sustained PSpARC remission	
	Full model	Reduced model	Full model	Reduced model
Baseline demographic and disease characteristics				
Normal hs-CRP (no vs yes)	NS	0.18 (0.06 to 0.52)	NS	NS
Enthesitis	NS	NS	0.79 (0.68 to 0.93)	0.85 (0.77 to 0.95)
Prior DMARDs (yes vs no)	NS	NS	0.20 (0.05 to 0.74)	0.22 (0.07 to 0.66)
BASDAI	NS	0.57 (0.41 to 0.78)	NS	0.70 (0.50 to 0.97)
BMI	NS	NS	NS	0.88 (0.77 to 0.99)
Treatment response (yes vs no)				
ASDAS MI at week 12	8.19 (1.08 to 61.91)	NS	NS	NS
ASDAS ID at week 12	NS	8.01 (2.47 to 25.97)	NS	NS
PSpARC remission at week 12	NS	NS	13.05 (1.75 to 97.52)	20.27 (5.37 to 76.46)

ASDAS, Ankylosing Spondylitis Disease Activity Score; ASDAS ID, ASDAS inactive disease; ASDAS MI, ASDAS major improvement ($\Delta \geq 2.0$); BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMI, body mass index; DMARD, disease-modifying antirheumatic drug; hs-CRP, high-sensitivity C-reactive protein; NS, not significant; PSpARC, Peripheral SpondyloArthritis Response Criteria.

To reduce the number of explanatory variables entering the analysis while maximising the variation explained by them, a backward variable selection in logistic regression analysis was conducted to obtain the best model (elimination model), which isolates the most influential contributing factors.²³

All statistical analyses were conducted using SAS V.9.3 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Patient disposition

A total of 165 patients were initially randomised to adalimumab (n=84) or placebo (n=81); in the open-label phase, all patients received ≥ 1 dose of adalimumab. Approximately half of the patients were women and 44% had an elevated CRP at baseline. The mean (SD) age was 41 (12) years and symptom duration was 7 (7) years (table 1).

Of the 165 patients, 163 (99%) completed the week 12 visit and 114 (69%) completed the week 156 visit. The primary reasons for premature discontinuation were adverse events (n=19), withdrawal of consent (n=12), loss to follow-up (n=3) or other reasons (n=14; including lack of efficacy, pregnancy, investigator decision and patient relocation).

Adalimumab efficacy over 3 years

The percentages of patients who achieved PSpARC40 (the primary endpoint of ABILITY-2),² ASDAS ID and PSpARC remission increased over time, generally reaching a plateau around week 48 of the open-label period, in observed as well as NRI analyses (figure 1A). In the observed analysis, ASDAS ID was achieved by 55% (78/143) of patients at 1 year and 59% (64/109) of patients at 3 years; 41% (60/145) and 48% (54/112) achieved PSpARC remission, respectively. Using NRI analysis, 47% and 39% of patients achieved ASDAS ID

and 36% and 33% achieved PSpARC remission at years 1 and 3, respectively. During the 3-year study, more patients achieved sustained ASDAS ID (52% (86/165)) than sustained PSpARC remission (42% (70/165)).

Improvements in the signs and symptoms of pSpA after 1 year of adalimumab treatment were sustained through 3 years. Continuous efficacy outcomes showed improvement as early as 2 weeks after initiation of adalimumab treatment, and improvements were sustained throughout the study in patients originally randomised to receive adalimumab in observed as well as last observation carried forward analyses (figure 1B). In patients originally randomised to receive placebo, similar findings were observed after initiation of open-label adalimumab at week 12.

Of the 86 patients who achieved sustained ASDAS ID, 64% (55/86) did so in the first year of adalimumab exposure, whereas only 7% (6/86) had delayed achievement in the third year of exposure. Only two patients (2%) had a subsequent disease flare after achieving sustained ASDAS ID. Notably, of the 31 patients who did not achieve sustained ASDAS ID in the first year, most (87%) achieved ASDAS ID on ≥ 1 visit in the first year of adalimumab exposure.

Similarly, of the 70 patients who achieved sustained PSpARC remission, 60% (42/70) did so in the first year of adalimumab exposure, whereas only 7% (5/70) had a delayed onset of sustained PSpARC remission in the third year of exposure. Among patients who achieved sustained PSpARC remission, only seven patients (10%) had a subsequent disease flare. Of the 28 patients who did not achieve sustained PSpARC remission in the first year, most (82%) achieved PSpARC remission on ≥ 1 visit in the first year of adalimumab exposure.

Additionally, there was a large overlap between patients who achieved sustained remission definitions: of 70 patients achieving sustained PSpARC remission, 63 (90%) also achieved sustained ASDAS ID.

Table 3 Treatment-emergent AEs

Event (Event/100 PY)	Any adalimumab n=165 PYS=390.7
Any AE	1194 (305.6)
Severe AE	36 (9.2)
Serious AE	29 (7.4)
AE leading to study discontinuation	31 (7.9)
Infectious AE	376 (96.2)
Serious infectious AE	4 (1.0)
Opportunistic infections (excluding oral candidiasis and tuberculosis)	1 (0.3)
Tuberculosis*	2 (0.5)
Lymphoma	0
NMSC	1 (0.3)
Malignancies (excluding lymphoma, HSTCL, leukaemia, NMSC or melanoma)	2 (0.5)
Demyelinating disorder	0
Deaths	2 (0.5)

*Category captured active and latent tuberculosis; however, only latent cases were reported.

AE, adverse event; HSTCL, hepatosplenic T-cell lymphoma; NMSC, non-melanoma skin cancer; PY, patient-year.

Predictors of remission at years 1 and 3

Univariate analysis showed that week 12 treatment response rates were more consistent predictors of remission at both years 1 and 3 compared with baseline disease characteristics. Significant positive predictors of ASDAS ID and PSpARC remission at years 1 and 3 were PSpARC remission as well as other PSpARC response categories at week 12 and ASDAS ID and other ASDAS response categories (figure 2A and 2B) at week 12. Of note, elevated baseline hs-CRP was a predictor of PSpARC remission at year 3 only and was not predictive of ASDAS ID at either year 1 or year 3.

In multivariate analyses (full model), only ASDAS ID at week 12 remained as a consistent and strong predictor for ASDAS ID at years 1 (OR, 10.61 (95% CI 1.10 to 102.25)) and 3 (OR, 175.79 (95% CI 2.88 to >999); figure 3A). Higher baseline disease activity, measured by ASDAS, was associated with a lower chance of achieving ASDAS ID at years 1 and 3, while the baseline enthesal count was a negative predictor of ASDAS ID at year 3. Baseline TJC and PtGA were only marginally predictive of ASDAS ID response at year 3 (OR, 1.16 and 1.09, respectively).

In backward elimination modelling, ASDAS ID at week 12 was a consistent predictor of ASDAS ID at year 1 (OR, 8.64 (95% CI 2.97 to 25.14)) and year 3 (OR, 36.12 (95% CI 2.29 to 569.08)), as was baseline ASDAS at year 1 (OR, 0.31 (95% CI 0.16 to 0.62)) and at year 3 (OR, 0.10 (95% CI 0.02 to 0.45)).

In multivariate analyses (full model), only PSpARC remission at week 12 remained as a consistent and strong

predictor of PSpARC remission at both years 1 (OR, 8.96 (95% CI 1.25 to 64.17)) and 3 (OR, 24.08 (95% CI 1.92 to 302.21); figure 3B). Baseline PGA was marginally associated with PSpARC remission at year 1 (OR, 1.05 (95% CI 1.00 to 1.09)). Notably, ASDAS ID at week 12 was not predictive of long-term PSpARC remission at years 1 and 3, and PSpARC remission at week 12 was not predictive of ASDAS ID at years 1 and 3.

In backward elimination modelling, PSpARC remission at week 12 was a consistent predictor of PSpARC remission at 1 year (OR, 6.47 (95% CI 1.91 to 21.95)) and at 3 years (OR, 15.66 (95% CI 4.19 to 58.56)).

Predictors of sustained remission over 3 years of adalimumab treatment

In backward elimination modelling, ASDAS ID at week 12 was a predictor of sustained ASDAS ID (table 2). PSpARC remission at week 12 was a consistent predictor of sustained PSpARC remission in all multivariate analyses, including the full model and the backward elimination model.

Only marginal associations with sustained remission were found for other factors (table 2). Baseline enthesitis count (full and elimination models), BASDAI (elimination model), BMI (elimination model) and prior use of DMARDs (full and elimination models) were negatively associated with achievement of sustained PSpARC remission. Baseline BASDAI and elevated hs-CRP were negative predictors of sustained ASDAS ID (elimination model).

Long-term safety

Patients had 390.7 patient-years of adalimumab exposure in this 3-year study. Rates of serious adverse events and serious infections were low (7.4 and 1.0 events per 100 patient-years, respectively; table 3). There were no cases of lymphoma, demyelinating disorders or active tuberculosis. Two patients died: a 20-year-old man died of injuries resulting from a car accident and a 58-year-old woman of pulmonary embolism. One event of opportunistic infection (bronchopulmonary aspergillosis) in a 47-year-old woman resolved with appropriate treatment. One case of parasitic infection (acarodermatitis) in a 43-year-old woman led to discontinuation from the study but resolved post-treatment. Two malignancies were reported: one patient had non-melanoma skin cancer and one patient had bilateral pheochromocytoma. The incident of pheochromocytoma was subsequently treated by laparoscopic bilateral adrenalectomy and resolved.

DISCUSSION

This is the first study in patients with pSpA evaluating the long-term efficacy and safety of a TNF inhibitor over 3 years and evaluating predictors of long-term remission. Most patients showed early and sustained improvements with adalimumab treatment. Among patients who continued study drug, approximately 50% achieved sustained remission defined by ASDAS ID and approximately 40% when defined by PSpARC remission criteria,

most within the first year of adalimumab exposure without subsequent flare. Consistent and strong predictors for long-term (1 and 3 years) ASDAS ID and PSpARC remission as well as sustained ASDAS ID and PSpARC remission were early (week 12) responses for ASDAS ID and PSpARC remission.

The long-term and sustained remission rates from our study are consistent with other studies in patients with RA,^{8 11 24} AS¹⁶ and PsA¹⁵ treated with various therapies, including TNF inhibitors and DMARDs. Additionally, within our study, sustained remission rates were similar to point remission rates at 1 and 3 years, emphasising the durability of response to adalimumab in this population.

In some studies of patients with RA⁹ and AS,^{25–28} baseline demographic characteristics, such as younger age or elevated CRP, predicted short-term response and remission. In our study, no baseline variables, including BMI, smoking status, hs-CRP and sex, consistently predicted long-term or sustained response. However, we examined predictors of long-term rather than short-term remission. Similar to our study, multiple studies have found that good early clinical response after treatment initiation predicts good long-term outcomes for up to 1 year or longer.^{7 10 11 16 29 30} For example, in a similarly designed randomised, double-blind, placebo-controlled phase III study in patients with AS receiving adalimumab, achievement of early (12-week) remission was a stronger predictor of favourable long-term (up to 5 years) treatment outcomes than baseline characteristics, including elevated CRP.¹⁶ In axial SpA and PsA, the lack of a robust early (12-week) clinical response to another anti-TNF treatment, certolizumab, identified a subset of patients who were unlikely to achieve a good response at 48 weeks.³¹ Defining early clinical response as 12 weeks after initiation of new treatment aligns with studies and treatment recommendations in RA and axial SpA.^{32 33}

The presence or absence of early response to treatment can also impact long-term outcomes in other non-SpA rheumatic diseases. For example, in a study of patients with very early RA, worse outcomes (greater radiographic progression, Health Assessment Questionnaire disability and number of workdays missed) were observed for patients who had persistent moderate disease activity versus those who achieved early sustained clinical remission during the first year.²⁴ Also, associations between early response and long-term remission have been reported in multiple other studies in RA,^{7 13 29} and earlier time to remission was a consistent and strong predictor of sustained remission in patients with RA.^{8 11}

As mentioned above, baseline patient factors were less robustly predictive for long-term response in our study. Other studies have reported an association of female sex with a decreased likelihood of achieving remission.^{11 34} In our study, female sex was a negative predictor for achieving ASDAS ID and PSpARC remission at 1 and 3 years in univariate analyses only (figure 2A and B), but this finding was not confirmed in the more stringent multivariate analysis (figure 3A and B). Similarly, tobacco

use was a negative predictor of ASDAS ID at year 3 only, and BMI only marginally predicted sustained PSpARC remission but not PSpARC remission at 1 year or 3 years or ASDAS ID at 1 year, 3 years or sustained ASDAS ID. Both smoking and obesity have been described as negative predictors of clinical response in some RA, axial SpA and PsA studies^{10 34–37} but not in others^{9 13 34 38 39}; future studies are needed to confirm these results, especially in patients with pSpA. Baseline PGA was also marginally predictive of PSpARC remission at 1 year in our full model. Although the ORs for some measurements from our full models had large CIs, the direction of the treatment effects was confirmed by findings in the reduced models. Intuitively, patients with lower baseline values for disease activity measures would seem better positioned to achieve a low disease activity state in RA, and studies support this expectation.^{12 34 40} In our multivariate and backward elimination analyses, baseline ASDAS predicted ASDAS ID at years 1 and 3, and baseline BASDAI predicted sustained ASDAS ID and PSpARC in the reduced models.

In this study, two different definitions of remission were used. PSpARC remission, which differs from ASDAS ID in that it includes aspects of the disease such as TJC and SJC and enthesitis, appears to be more suitable for this patient population given its better face validity. The different domains captured by ASDAS and PSpARC response might explain why ASDAS ID at week 12 was not predictive of long-term PSpARC remission and vice versa. Although ASDAS was established in patients with AS, a recent analysis showed that AS-specific outcome measures (including ASDAS) perform reasonably well in pSpA in terms of discrimination.⁴¹ Despite conceptual differences, the overlap between patients achieving sustained ASDAS ID and PSpARC remission was considerable. Also, minimal disease activity, which has been used in PsA and captures very similar disease aspects as PSpARC,⁴² has recently been evaluated in this patient population.⁴³

There is no consensus on the length of time required for remission to be considered sustained in pSpA; however, this is also true in other rheumatic diseases, including RA, for which the 2016 European League Against Rheumatism treatment recommendations specify a treatment goal of sustained remission or low disease activity.^{13 44 45} The defined timing for achieving sustained remission in pSpA used in our analysis (≥ 6 months out of 3 years) was based on other published studies in RA and axial SpA.^{8 16 20} Although some studies in patients with RA used up to 5 or 8 years to define sustained remission,^{12 44} and other RA or PsA studies used 1 year,^{10 15} those were mostly cohort studies and not randomised controlled trials, with widely spaced visit intervals (every 6–12 months or longer), unlike the prescribed shorter intervals in our study. Nonetheless, defining sustained remission as ≥ 6 months may not adequately reflect patients' clinical condition over the course of 3 years of follow-up and may be considered a study limitation. Still, our chosen

definition of sustained remission appears to have clinical utility because patients who achieved sustained remission, whether defined by ASDAS ID or PSpARC, rarely experienced subsequent disease flare (rate $\leq 10\%$).

Identification of factors that predict long-term and sustained remission in patients with pSpA after treatment with anti-TNF agents may facilitate clinical decisions regarding patient therapy. Because our study did not include imaging assessments, future research can help to establish whether a state of sustained remission might prohibit structural damage progression, as has been shown in RA and PsA.^{12 15 24 46 47} Additional investigation might also address whether patients who achieve consistent sustained remission would benefit from drug withdrawal; so far, drug-free remission appears feasible in only a limited subset of patients with early RA and axial SpA.^{48–50}

Most patients in our study achieved sustained remission within the first year of treatment with adalimumab. In patients with RA, shorter time to remission has been associated with sustainability of remission.^{8 11} Among patients with pSpA who achieved sustained remission in the second or third year of adalimumab treatment, a substantial proportion met remission criteria at individual but not consecutive visits in the first year. Sustained remission is a more stringent endpoint; patients who achieve sustained remission after a delay show good response at earlier time points. Clinically, this also suggests continuing therapy may be warranted in patients who do not achieve (sustained) remission during the first year owing to some fluctuations in disease activity.

The safety findings, including the type and frequency of adverse events observed through 3 years of adalimumab treatment, are in line with the known overall safety profile of adalimumab in other immune-mediated inflammatory diseases.^{51 52} The serious infection rate observed in our study (1.0 event per 100 patient-years) was numerically lower than for RA and PsA but similar to AS.⁵³ These findings need further confirmation.

Overall, among participants in the ABILITY-2 study receiving adalimumab, most achieved and maintained long-term efficacy, a significant number achieved sustained remission without subsequent flare and a rapid response after initiation of adalimumab treatment was the best predictor of sustained remission over time.

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