

Frequency and predictors of a high clinical response in patients with psoriasis on biological therapy in daily practice: results from the prospective, multicenter BioCAPTURE cohort

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Linked Comment: Zheng. *Br J Dermatol* 2017; **176**:576.

Summary

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Accepted for publication

15 July 2016

Funding sources

This study was supported by the University Medical Centre St Radboud Foundation, which received funding from Pfizer, Janssen and AbbVie for the project. Pfizer, Janssen and AbbVie played no role in the design and execution of this study or in data collection, data management, data analysis, interpretation of the data, manuscript preparation, manuscript review or manuscript approval.

Conflicts of interest

See Appendix 1.

DOI 10.1111/bjd.14888

Background It is important to assess which patients with psoriasis are more likely to achieve high clinical responses on biologics.

Objectives To assess the number of treatment episodes (TEs) that achieve a 100% improvement in Psoriasis Area and Severity Index (PASI 100), PASI 90 or PASI ≤ 5 at week 24 of biological treatment, and which baseline patient characteristics predict treatment response.

Methods Data from patients with psoriasis treated with adalimumab, etanercept, infliximab or ustekinumab were extracted from a prospective cohort. TEs with high clinical responses were described. Uni- and multivariate regression analyses were performed with the generalized estimating equation method to elucidate which baseline patient characteristics were predictors for PASI 90 and PASI ≤ 5 at week 24. **Results** In total, 454 TEs were extracted (159 adalimumab; 193 etanercept; 19 infliximab; 83 ustekinumab) from 326 patients. At week 24, in 3%, 15% and 59% of TEs, respectively, PASI 100, PASI 90 and PASI ≤ 5 was reached. In TEs without a PASI 100 or PASI 90 response, PASI ≤ 5 was still achieved in 58% and 52%, respectively. Baseline PASI ≥ 10 was a strong predictor for achieving PASI 90; baseline PASI < 10 and a lower baseline body mass index (BMI) were significant predictors for PASI ≤ 5 at week 24.

Conclusions A limited number of patients achieved PASI 100 or PASI 90 at 24 weeks of biological treatment. Including an absolute PASI score in the assessment of psoriasis severity is important. Baseline BMI was an important, modifiable predictor for a high response.

What's already known about this topic?

- A high clinical response in patients with psoriasis is shifting towards a 90% improvement compared with baseline Psoriasis Area and Severity Index (PASI 90).

- To date, no studies have assessed which patients with psoriasis are more likely to achieve a high clinical response at week 24 of biological treatment.

What does this study add?

- We focused on high responders, defined as achieving PASI 100, PASI 90 or PASI ≤ 5 .
- Frequency of reaching high clinical responses at 24 weeks of biological treatment was assessed, as were predictors that could identify patients with the ability to respond well to biological treatment.
- In only a limited number of treatment episodes are PASI 90 (15%) or PASI 100 (3%) achieved.
- Lower baseline body mass index is a predictor for achieving PASI ≤ 5 .

A 90% improvement in Psoriasis Area and Severity Index (PASI 90) is observed more often with current therapies for psoriasis. PASI 90 corresponds better with a clear or almost clear psoriasis and with a good quality of life compared with PASI 75 (75% improvement in PASI).^{1–3} Therefore, treatment success in psoriasis is starting to shift from PASI 75 to PASI 90.¹ A high clinical response can be defined as reaching a relative PASI measure such as PASI 90 or PASI 100 (100% improvement in PASI) but can also be described by reaching a low absolute PASI score such as PASI ≤ 5 . Studies show that a good quality of life is also achieved more often in patients with an absolute PASI ≤ 5 compared with PASI > 5 .^{1,4,5} The difference between relative and absolute PASI might be important in the treatment of patients with psoriasis in daily practice, in which patients with high baseline PASI scores (PASI ≥ 10) and also those with lower baseline PASI scores (PASI < 10) are being treated with biologics. A lower baseline PASI score might occur in patients that switch from one biological treatment to another. It is more difficult to achieve PASI 90 in patients with a low PASI score at the start of treatment than in patients with high baseline PASI scores. In this study our first objective was to assess how many patients with psoriasis treated with biologics in daily practice for 24 weeks achieved a high clinical response (PASI 90, PASI 100, PASI ≤ 5) at week 24. The second objective was to assess how many patients that achieved PASI 90 at week 24 also reached PASI ≤ 5 at week 24. Finally, our third objective was to assess how many patients without a PASI 90 or PASI 100 response still achieved PASI ≤ 5 at week 24.

Baseline patient characteristics might predict whether a patient with psoriasis will achieve a high clinical response (PASI 90, PASI 100 or PASI ≤ 5) on biological treatment. To date, no studies have tried to assess which patients with psoriasis are more likely to achieve these high clinical responses. However, predicting a high clinical response is important for personalized treatment and can also increase the awareness of physicians for those patients at risk of not achieving a high clinical response. Moreover, knowledge of predictors might direct future research, for example randomized controlled trials (RCTs) that will try to improve the efficacy of biologics

for those patients who are not expected to achieve a high clinical response based on these predictors. Baseline patient characteristics associated with the effectiveness of biologics in previous studies were baseline body mass index (BMI), baseline severity score, duration of psoriasis and biological naivety.^{6–9} Our secondary objective was to assess which patients were more likely to achieve a high clinical response by analysing which baseline patient characteristics were predictors for high clinical response at 24 weeks of treatment with biologics. For our research objectives, we used prospective daily practice registry data from BioCAPTURE (Continuous Assessment of Psoriasis Treatment Use Registry with Biologics).¹⁰

Materials and methods

BioCAPTURE

BioCAPTURE is a registry containing prospective, multicenter data on biological treatment of patients with plaque psoriasis from daily practice.¹⁰ This registry contains prospective daily practice data on all consecutive patients with psoriasis treated with biologics from one academic and eight nonacademic centres. The use of BioCAPTURE was approved by the medical ethics committee. Informed consent was obtained from every patient. Treatment of patients with psoriasis is carried out according to European and Dutch guidelines.^{11,12} Treatment decisions, such as dose adjustments, were made by the treating physician.

Data extraction

Data from patients with psoriasis that were treated with biologics [adalimumab (ADA), etanercept (ETA), infliximab (IFX) and ustekinumab (USTE)] were extracted from BioCAPTURE (2005–May 2015). Extracted baseline variables were PASI score, age at start of biological treatment, sex, weight, length, BMI, psoriatic arthritis, positive family history of psoriasis, duration of psoriasis until start of biological treatment and biological naivety. A treatment episode (TE) was defined as a

period of time in which the patient received a biologic without interrupting treatment for > 90 days. Ninety days is a widely accepted interruption period.^{13–15} The baseline PASI score of a TE was defined as PASI score at start or if it was not recorded at that time point, the closest PASI between 90 days prior to and 7 days after the start of the biologic. For each patient, only the first TE per biologic was chosen if a patient had received the same biologic twice. One patient could have multiple TEs when the patient had switched from one biologic to a different one. The mean average biologic dose during the first 24 weeks was calculated. It was also calculated whether the total biologic dose during the first 24 weeks of treatment was low to normal or higher than European Medicines Agency (EMA) label dose. In addition, it was noted whether during a TE a concomitant conventional systemic agent [methotrexate (MTX); acitretin; fumaric acid esters; ciclosporin] was prescribed in the first 24 weeks of biological treatment. Bridging and combination therapy were both regarded as the prescription of a concomitant conventional agent.

Analyses

Patients that discontinued the biological treatment owing to ineffectiveness before week 24 were considered nonresponders (not achieving PASI 90, PASI 100 and PASI ≤ 5) at week 24. Data from patients who discontinued for other reasons, such as adverse events or pregnancy wish, were not included in the analyses. To optimize power, all biologics were grouped together. The time point used to evaluate whether treatment success is being achieved differs between biologics, but an evaluation at 24 weeks of treatment is considered appropriate.^{16,17} Firstly, percentages of TEs in which PASI 90, PASI 100 or PASI ≤ 5 were reached at week 24 were described. Secondly, the percentage of TEs in which PASI 90 and PASI ≤ 5 were reached at week 24, as well as the percentage of TEs in which PASI 90 or PASI 100 were not achieved but in which PASI ≤ 5 was still achieved at week 24, were calculated. Thereafter, the percentage of TEs with a baseline PASI ≥ 10 (≥ 10% improvement in PASI) in which PASI 90, PASI 100 and PASI ≤ 5 were reached at week 24 was described. Lastly, uni- and multivariate regression analyses were performed to elucidate which baseline patient characteristics were predictors for PASI 90 or PASI ≤ 5 at week 24 (Table S1; see Supporting Information). Baseline PASI score was divided into baseline PASI ≥ 10 and < 10. Owing to low numbers of TEs in which PASI 100 was achieved (15 TEs; 3.3%) at week 24, predictors for this outcome could not be assessed. As one patient could contribute to multiple TEs, the generalized estimating equation (GEE) analysis with patient as random effect was chosen in order to analyse which baseline patient variables predicted PASI 90 and PASI ≤ 5. A GEE analysis takes into account the patients that are included more than once in the analysis. With GEE analysis, parameters of a generalized linear model are estimated when the dependent variable is a dichotomous variable.¹⁸ After the univariate analyses with GEE, baseline patient variables with a P-value < 0.2 were

incorporated into the multivariate analyses. Backward selection was manually performed stepwise, excluding the baseline patient variable with the highest P-value above 0.05. The final predictor model included those baseline patient variables that had a P-value < 0.05. For the multivariate analyses, BMI was chosen over weight, as these variables are highly correlated. Sensitivity analyses with weight instead of BMI were performed. Additional sensitivity analyses were performed for (i) ADA/ETA as a group (excluding IFX and USTE); (ii) TEs with a low-to-normal label biologic dose; (iii) TEs without a treatment interruption; (iv) TEs without combination therapy; and (v) PASI ≤ 3 at week 24 because in all TEs with a PASI 90 at week 24 an absolute PASI score of ≤ 3 was present. Correction for missing baseline data was performed using multiple imputations in SPSS (IBM, Armonk, NY, U.S.A.). Predictors were described with 95% confidence intervals and P-value. Analyses were performed using Excel 2007 (Microsoft, Redmond, WA, U.S.A.) and SPSS 22.0 (IBM).

Results

Patients

Table 1 shows the characteristics of the 326 patients included from BioCAPTURE. Our cohort was comparable with other major daily practice psoriasis registries;^{19,20} most patients with psoriasis treated with biologics were male (62.0%), overweight (27.6 kg m⁻²) and had a positive family history of psoriasis (67.5%). Median baseline PASI score was 12.8.

Baseline characteristics of treatment episodes

In total, 483 TEs were extracted of which 454 TEs were included (159 ADA, 193 ETA, 19 IFX and 83 USTE). Baseline characteristics of TEs are shown per biologic in Table 2. Thirty-seven of 454 TEs did not complete 24 weeks owing to ineffectiveness, and were included in the analyses as

Table 1 Baseline patient characteristics of BioCAPTURE (n = 326)

Mean ± SD age at start of biologic (years)	47.2 ± 12.6
Sex (male)	202 (62.0)
Mean ± SD length (cm) ^a	175.6 ± 8.7
Median (IQR) weight (kg) ^b	86.4 (76.0–99.0)
Median (IQR) BMI (kg m ⁻²) ^a	27.6 (24.5–31.3)
Positive family history of psoriasis (yes) ^c	214 (67.5)
Psoriatic arthritis, diagnosis by a rheumatologist (yes) ^d	97 (31.1)
Median (IQR) duration of psoriasis until start of biologic (years) ^e	20.3 (12.9–30.1)
Median (IQR) baseline PASI score	12.8 (9.7–17.8)

Data are n (%) unless otherwise indicated. IQR, interquartile range; BMI, body mass index; PASI, Psoriasis Area and Severity Index. ^aSixty-two missing; ^b60 missing; ^cnine missing; ^d14 missing; ^etwo missing.

nonresponders. As no comparisons between biologics were made, no statistical comparisons between baseline characteristics were performed. Numerically, median baseline PASI score was highest for patients that were treated with IFX (14.5) and lowest for patients on ADA (12.0). Of 454 TEs, 67.4% ($n = 306$) had a baseline PASI ≥ 10 and 32.6% ($n = 148$) had a baseline PASI < 10 . Median baseline weight was highest for patients on IFX (92.0 kg), followed by USTE (91.3 kg), ADA (88.0 kg) and ETA (82.5 kg). In our cohort, IFX was the last resort treatment; all patients treated with IFX were biologic non-naïve.

Treatment characteristics of treatment episodes

The treatment characteristics of TEs are shown in Table S2 (see Supporting Information). The median biologic dose, including induction dose, was 46 mg every 2 weeks for ADA, 72 mg weekly for ETA, 7.6 mg kg⁻¹ every 8 weeks for IFX and 62 mg every 12 weeks for USTE (USTE 45-mg group: 62 mg every 12 weeks; USTE 90-mg group: 123 mg every 12 weeks). In 17.6%, 45.1% and 10.8% of ADA, ETA and USTE TEs, respectively, the biologic dose was higher than would be expected by EMA label dose after 24 weeks of treatment. Two of 16 (12.5%) TEs that started with 90-mg USTE received a starting dose higher than label (i.e. in these two TEs body weight was ≤ 100 kg) and nine of 67 (13.4%) TEs that started with 45-mg USTE received a starting dose lower than label (i.e. in these nine TEs body weight was > 100 kg). All doses of IFX were as per EMA labelling. Biologics were combined with conventional systemic agents in 114 TEs, varying from bridging therapy to continuous combination therapy. MTX was the agent most

often prescribed. Of 454 TEs, treatment was interrupted in 95 (20.9%) TEs, with a total of 114 treatment interruptions. Time of interruption was usually short (≤ 4 weeks in 97 interruptions; > 4 weeks in 17 interruptions). The median [interquartile range (IQR)] time of treatment interruption was 9.5 (7–21) days.

High clinical response

The number and percentages of TEs in which high clinical responses were achieved are shown in Table 3 and Figure 1.

A 100% improvement in the Psoriasis Area and Severity Index at week 24

At week 24, PASI 100 was only achieved in 3.3% (15 of 454) of TEs. In all TEs (100%) with a PASI 100 response at week 24, PASI ≤ 5 was also attained at week 24. Of the 439 TEs without PASI 100 response, PASI ≤ 5 was reached at week 24 in 57.6% (253 of 439). From 306 TEs with a baseline PASI ≥ 10 , PASI 100 was reached at week 24 in 3.9% ($n = 12$). In 2% (three of 148) of TEs with a baseline PASI < 10 , PASI 100 was achieved at week 24.

A 90% improvement in the Psoriasis Area and Severity Index at week 24

In 15% (67 of 454) of TEs PASI 90 was attained at week 24. In all TEs (100%) with PASI 90 response at week 24, PASI ≤ 5 was also attained at week 24. In all TEs (100%) with PASI 90 at week 24, PASI ≤ 3 was achieved at week 24. An absolute PASI score of 2.7 was the highest absolute PASI score

Table 2 Baseline characteristics of included treatment episodes (TEs)

Baseline TE characteristics	ADA TEs ($n = 159$)	ETA TEs ($n = 193$)	IFX TEs ($n = 19$)	USTE TEs ($n = 83$)
Mean \pm SD age at start of biologic (years)	48.9 \pm 12.5	47.0 \pm 12.5	49.3 \pm 12.9	50.4 \pm 12.6
Sex (male)	94 (59.1)	124 (64.2)	10 (52.6)	54 (65.1)
Mean \pm SD length (cm)	175.7 \pm 8.7 ^a	175.1 \pm 8.0 ^b	173.8 \pm 8.4	177.0 \pm 8.8 ^c
Median (IQR) weight (kg)	88.0 (78.5–101.5) ^a	82.5 (71.0–95.5) ^b	92.0 (83.2–105.0)	91.3 (79.9–101.1) ^d
Median (IQR) BMI (kg m ⁻²)	29.0 (25.5–32.0) ^e	26.7 (23.9–30.1) ^b	30.5 (27.4–34.6)	28.1 (25.6–31.9) ^c
Positive family history of psoriasis (yes)	107 (67.3) ^c	128 (66.3) ^f	11 (57.9) ^g	54 (65.1) ^d
Psoriatic arthritis (yes)	54 (34.0) ^h	57 (29.5) ⁱ	11 (57.9)	22 (26.5) ^h
Median (IQR) duration of psoriasis until start of biologic (years)	20.8 (13.6–32.1) ^d	21.0 (14.2–31.0)	16.4 (12.6–23.9) ^g	18.6 (13.9–28.4)
Median (IQR) baseline PASI score	11.1 (7.3–14.9)	12.6 (9.8–18.5)	14.5 (8.4–20.2)	13.6 (8.1–20.4)
Biologic naïve (yes)	53 (33.3)	126 (65.3)	0 (0)	15 (18.1)

Data are n (%) unless otherwise indicated. ADA, adalimumab; ETA, etanercept; IFX, infliximab; USTE, ustekinumab; BMI, body mass index.

^aFourteen missing; ^b52 missing; ^cfour missing; ^dtwo missing; ^e15 missing; ^ffive missing; ^gone missing; ^hsix missing; ⁱthree missing.

Table 3 Treatment episodes (TEs; $n = 454$) achieving 100% improvement in the Psoriasis Area and Severity Index (PASI) 100, 90% improvement in PASI (PASI 90) or Psoriasis Area and Severity Index less than or equal to five (PASI ≤ 5) at week 24

Outcome	Number of TEs that reached the outcome at week 24 ^a	Number of TEs that did not reach the outcome at week 24 ^a	Number of TEs that reached outcome and also reached PASI ≤ 5 at week 24 ^b	Number of TEs that did not reach outcome but still reached PASI ≤ 5 at week 24 ^c
PASI 100	15 (3.3)	439 (96.7)	15 (100)	253 (57.6)
PASI 90	67 (14.8)	387 (85.2)	67 (100)	201 (51.9)
PASI ≤ 5	268 (59.0)	186 (41.0)	268 (100)	0 (0)

^a n (%) of all TEs in study; ^b n (%) of TEs that reached outcome; ^c n (%) of TEs that did not reach outcome.

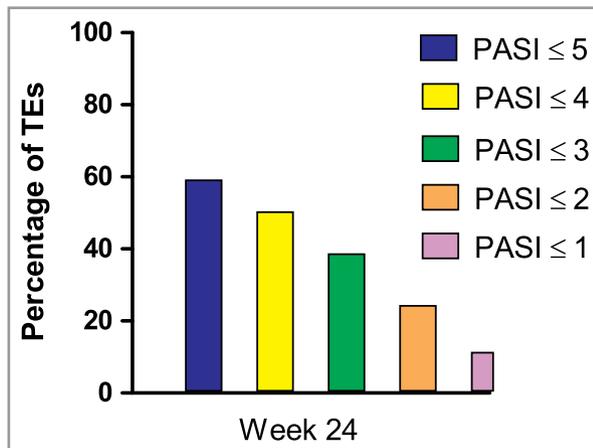


Fig 1. Percentage of treatment episodes (TEs) with high effectiveness based on absolute Psoriasis Area and Severity Index (PASI) scores at week 24.

in the PASI 90 group. Of the 387 TEs without PASI 90 response, PASI ≤ 5 was reached at week 24 in 51.9% (201 of 387). From 306 TEs with a baseline PASI ≥ 10 , in 19.0% (58 of 306) of TEs PASI 90 was reached at week 24. In only 6.1% (nine of 148) of TEs with a baseline PASI < 10 was PASI 90 achieved at week 24.

Psoriasis Area and Severity Index less than or equal to five at week 24

Of 454 TEs, in 268 (59.0%) TEs PASI ≤ 5 was reached at week 24. From 306 TEs with a baseline PASI ≥ 10 , in 54.6% (167 of 306) of TEs PASI ≤ 5 was achieved at week 24. This was 68.2% (101 of 148) of TEs with a baseline PASI < 10 . In 50.2%, 38.5%, 24.2% and 11.2% of 454 TEs, respectively,

PASI ≤ 4 , PASI ≤ 3 , PASI ≤ 2 and PASI ≤ 1 was reached at week 24 (Fig. 1).

Predictors for high clinical response

After correcting for multiple TEs from the same patients with multivariate GEE regression analysis, the most important predictor for achieving a PASI 90 response at week 24 was baseline PASI ≥ 10 [baseline PASI $\geq 10 = 1.284$ (95% CI 0.541–2.027); $P < 0.01$]. Predictors for PASI ≤ 5 at week 24 were baseline PASI < 10 and a lower baseline BMI [baseline PASI $< 10 = 0.555$ (95% CI 0.161–0.949) ($P = 0.01$); BMI -0.068 (IQR -0.108 to -0.028) ($P < 0.01$)].

Sensitivity analyses for PASI ≤ 3 at week 24 revealed the same predictors as the analyses for PASI ≤ 5 . Sensitivity analyses on ADA/ETA as one group (excluding IFX and USTE) also resulted in the same predictors for PASI 90, PASI ≤ 5 and PASI ≤ 3 . Sensitivity analyses with weight instead of BMI showed that baseline PASI remained the only predictor for PASI 90 at week 24 [baseline PASI $\geq 10 = 1.284$ (95% CI 0.541–2.027); $P < 0.01$]. For PASI ≤ 5 at week 24, the significant predictors were baseline PASI < 10 [PASI $< 10 = 0.540$ (95% CI 0.152–0.928); $P = 0.01$] and a lower baseline weight [-0.018 (95% CI -0.030 to -0.007); $P < 0.01$]. Sensitivity analyses for PASI ≤ 3 showed the same predictors.

Sensitivity analyses for the TEs with a low-to-normal label dose during the first 24 weeks of biologic treatment, as well as for the TEs without a treatment interruption, resulted in the same predictors for PASI 90 and for PASI ≤ 5 as described previously. Sensitivity analyses for PASI ≤ 3 in low-to-normal label dose, as well as in the TEs without a treatment interruption, yielded the same predictors as for PASI ≤ 5 .

Additional sensitivity analyses were performed excluding the TEs in which a conventional systemic agent was used in the first 24 weeks of biologic treatment. These analyses resulted in the same predictor for PASI 90, that is baseline PASI ≥ 10 . Predictors for PASI ≤ 5 were baseline PASI < 10 , lower baseline BMI (or lower baseline weight) and biologic naivety. However, biologic naivety was highly correlated with baseline PASI score. Biologic-naive patients were significantly more likely to have a baseline PASI ≥ 10 [0.599 (95% CI 0.214–0.983); $P < 0.01$] compared with patients that had previously used a biologic. Baseline BMI or baseline weight did not correlate with baseline PASI score.

As USTE is dosed by baseline weight (≤ 100 or > 100 kg), baseline weight was divided into these two categories for additional sensitivity analyses. These analyses showed that baseline PASI was the only predictor for PASI 90 and PASI ≤ 5 and that baseline weight was no longer a predictor for PASI ≤ 5 .

Discussion

At week 24 in our real-world prospective cohort of patients with psoriasis treated with biologics, in only a limited number of TEs was PASI 100 or PASI 90 reached. In all TEs with a

PASI 100 or PASI 90 response, PASI ≤ 5 was also achieved. However, in a substantial proportion of TEs without a PASI 100 or PASI 90 response, PASI ≤ 5 was still achieved (58% and 52%, respectively). Of note, from TEs with a baseline PASI ≥ 10 , a higher proportion achieved PASI ≤ 5 (55%) than PASI 90 (19%) at week 24. Baseline PASI ≥ 10 was a strong predictor for reaching PASI 90 at week 24. Baseline PASI < 10 and a lower baseline BMI were predictors for PASI ≤ 5 at week 24.

The prescription of concomitant conventional systemic agents and adjustment of dosages of biologics, as well as treatment interruptions, were allowed in this daily practice cohort in order to personalize treatment. When analysing the TEs that were characterized by a low-to-normal biologic dose compared with EMA label dose during the first 24 weeks of treatment, the same predictors for PASI 90 and PASI ≤ 5 were found. This was also the case when analysing TEs without treatment interruptions, as well as in the TEs in which no conventional systemic agents were used. Sensitivity analyses for weight instead of BMI showed the same predictors for PASI 90 and PASI ≤ 5 at week 24. As the number of TEs for USTE and IFX were small, sensitivity analyses were performed for ADA/ETA as one group. This also resulted in the same predictors for PASI 90 and PASI ≤ 5 . Therefore, our results on the predictors of PASI 90 and PASI ≤ 5 seem to be robust.

In our study, PASI ≤ 5 was chosen because PASI ≤ 5 is a goal that is widely accepted among physicians and is associated with a good quality of life.^{1,4,5} Sensitivity analyses were performed for PASI ≤ 3 , as in all TEs in which PASI 90 was achieved at week 24, PASI ≤ 3 was also achieved at week 24. These sensitivity analyses showed the same predictors as the analyses for PASI ≤ 5 at week 24, which underscores the robustness of our results.

The opinion about treatment success is changing, with PASI 90 becoming the new treatment goal.^{1,16} However, treatment success can also be defined by reaching PASI 100 or PASI ≤ 5 . With this study we have shown that in daily practice, patients with psoriasis treated with biologics (ADA, ETA, IFX, USTE) rarely achieved PASI 100 (3.3%) or PASI 90 (15%) and more frequently achieved PASI ≤ 5 (59%), and even lower absolute PASI scores, such as PASI ≤ 2 (24.2%) at week 24. However, in RCTs of these biologics PASI 90 is often achieved (20–58% of patients) at weeks 16–28.^{21–24} This might be owing to the higher PASI score at start of treatment in RCTs compared with daily practice. In our study, high baseline PASI score (PASI ≥ 10) was, indeed, a predictor for reaching PASI 90 at week 24. In addition, in daily practice, patients with psoriasis that switch from one biologic to another could have a lower baseline PASI score than biologic-naïve patients. Indeed, we showed that biologic-naïve patients significantly more often had a baseline PASI score ≥ 10 compared with biologic non-naïve patients. Also, the median baseline PASI score in our cohort was 12.8. However, the mean baseline PASI scores in RCTs were higher and ranged from 18 to 23.^{21–24} We also demonstrated that, in daily practice, PASI ≤ 5 was more often achieved than PASI 90 or PASI 100 at week 24, even in

patients with a baseline PASI ≥ 10 . Therefore, PASI 90 might not be the most suitable outcome with which to assess psoriasis severity in patients with psoriasis who are being treated with biologics in daily practice. Based on our results, we advise physicians to monitor both relative, as well as absolute, PASI scores in daily practice. We also advise including absolute PASI scores in publications about efficacy/effectiveness from RCTs and cohort studies.

So far, few studies have tried to assess which baseline patient characteristics are associated with the effectiveness of biologics. In the literature, baseline BMI, baseline severity score (PASI and physician global assessment), duration of psoriasis and biologic naivety are postulated.^{6–9} Our study showed that baseline PASI was the most important predictor for PASI 90 and one of the important predictors for PASI ≤ 5 at week 24. A lower baseline BMI was an important predictor of treatment response (PASI ≤ 5) at week 24. Both predictors were also found for the more stringent PASI ≤ 3 at week 24. Recently conducted RCTs have shown that weight loss during biologic treatment (ADA, ETA, IFX, USTE) increases the efficacy, even in biologics that are not dosed according to weight.^{25,26} Baseline BMI also predicted biologic discontinuation in drug survival studies.^{27–31} These findings are important because most biologics are not dosed based on weight and none of the biologics are currently being dosed based on BMI. Patients and physicians might benefit from the finding that baseline BMI is a factor that influences the response to biological therapy, also because BMI can be influenced by losing weight. More studies are needed to investigate whether weight loss has a positive influence on the short- and long-term efficacy, as well as on drug survival, of biological therapies before advising weight-reduction programmes to our patients.

Limitations of this study are the low patient numbers that achieve PASI 90 or PASI 100 in daily practice and, consequently, the inability to perform subanalyses for every biological agent separately. Another limitation is the lack of measurements of current alcohol and smoking status of patients at the start of biological treatment. Our findings warrant replication in larger daily practice studies. A strength of our study is the use of data from the daily practice and multi-centre BioCAPTURE registry, resulting in a high external validity. Other strengths include the registration of biologic doses and concomitant conventional systemic therapies, as well as the performed sensitivity analyses.

To conclude, in daily practice where baseline PASI is often lower than in RCTs, a limited number of patients achieved PASI 100 or PASI 90 at 24 weeks of biological treatment. Inclusion of an absolute PASI score is important in the assessment of psoriasis severity. Our results also underscore the importance of the modifiable predictor baseline BMI for achieving a high response on biological treatment. Future research into the influence of weight reduction in patients with psoriasis and the influence of BMI on treatment response with newly developed biologics is needed. Furthermore, pharmaceutical companies that perform future studies on biologics are advised to take into account the patients with high

baseline BMI when establishing the most appropriate biologic dose.

References

- Puig L. PASI90 response: the new standard in therapeutic efficacy for psoriasis. *J Eur Acad Dermatol Venereol* 2015; **29**:645–8.
- Torii H, Sato N, Yoshinari T *et al.* Dramatic impact of a Psoriasis Area and Severity Index 90 response on the quality of life in patients with psoriasis: an analysis of Japanese clinical trials of infliximab. *J Dermatol* 2012; **39**:253–9.
- Mattei PL, Corey KC, Kimball AB. Psoriasis Area Severity Index (PASI) and the Dermatology Life Quality Index (DLQI): the correlation between disease severity and psychological burden in patients treated with biological therapies. *J Eur Acad Dermatol Venereol* 2014; **28**:333–7.
- Reich K, Nestle FO, Papp K *et al.* Improvement in quality of life with infliximab induction and maintenance therapy in patients with moderate-to-severe psoriasis: a randomized controlled trial. *Br J Dermatol* 2006; **154**:1161–8.
- Reich K, Griffiths CE. The relationship between quality of life and skin clearance in moderate-to-severe psoriasis: lessons learnt from clinical trials with infliximab. *Arch Dermatol Res* 2008; **300**:537–44.
- Strober BE, Bissonnette R, Fiorentino D *et al.* Comparative effectiveness of biologic agents for the treatment of psoriasis in a real-world setting: results from a large, prospective, observational study (Psoriasis Longitudinal Assessment and Registry [PSOLAR]). *J Am Acad Dermatol* 2016; **74**:851–61.
- Menting SP, Sitaram AS, Bonnerjee-van der Stok HM *et al.* Drug survival is not significantly different between biologics in patients with psoriasis vulgaris: a single-centre database analysis. *Br J Dermatol* 2014; **171**:875–83.
- van Lumig PP, van de Kerkhof PC, Boezeman JB *et al.* Adalimumab therapy for psoriasis in real-world practice: efficacy, safety and results in biologic-naïve vs. non-naïve patients. *J Eur Acad Dermatol Venereol* 2013; **27**:593–600.
- Shear NH, Hartmann M, Toledo-Bahena M *et al.* Long-term efficacy and safety of infliximab maintenance therapy in patients with plaque-type psoriasis in real-world practice. *Br J Dermatol* 2014; **171**:631–41.
- Zweegers J, van den Reek JM, van de Kerkhof PC *et al.* Comparing treatment goals for psoriasis with treatment decisions in daily practice: results from a prospective cohort of patients with psoriasis treated with biologics: BioCAPTURE. *Br J Dermatol* 2014; **171**:1091–8.
- Zweegers J, de Jong EM, Nijsten TE *et al.* Summary of the Dutch S3-guidelines on the treatment of psoriasis 2011. Dutch Society of Dermatology and Venereology. *Dermatol Online J* 2014; **20**:pii:doj_21769.
- Pathirana D, Ormerod AD, Saiag P *et al.* European S3-guidelines on the systemic treatment of psoriasis vulgaris. *J Eur Acad Dermatol Venereol* 2009; **23** (Suppl. 2):1–70.
- Warren RB, Smith CH, Yiu ZZ *et al.* Differential drug survival of biologic therapies for the treatment of psoriasis: a prospective observational cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *J Invest Dermatol* 2015; **135**:2632–40.
- van den Reek JM, Zweegers J, Kievit W *et al.* 'Happy' drug survival of adalimumab, etanercept and ustekinumab in psoriasis in daily practice care: results from the BioCAPTURE network. *Br J Dermatol* 2014; **171**:1189–96.
- Esposito M, Gisondi P, Cassano N *et al.* Survival rate of antitumor necrosis factor-alpha treatments for psoriasis in routine dermatological practice: a multicentre observational study. *Br J Dermatol* 2013; **169**:666–72.
- Mrowietz U, Kragballe K, Reich K *et al.* Definition of treatment goals for moderate to severe psoriasis: a European consensus. *Arch Dermatol Res* 2011; **303**:1–10.
- Mrowietz U. Implementing treatment goals for successful long-term management of psoriasis. *J Eur Acad Dermatol Venereol* 2012; **26** (Suppl. 2):12–20.
- Zeger SL, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. *Biometrics* 1988; **44**:1049–60.
- Menter A, Thaci D, Papp KA *et al.* Five-year analysis from the ESPRIT 10-year postmarketing surveillance registry of adalimumab treatment for moderate to severe psoriasis. *J Am Acad Dermatol* 2015; **73**:410–19.
- Hagg D, Eriksson M, Sundstrom A *et al.* The higher proportion of men with psoriasis treated with biologics may be explained by more severe disease in men. *PLoS ONE* 2013; **8**:e63619.
- Leonardi CL, Powers JL, Matheson RT *et al.* Etanercept as monotherapy in patients with psoriasis. *N Engl J Med* 2003; **349**:2014–22.
- Menter A, Tyring SK, Gordon K *et al.* Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. *J Am Acad Dermatol* 2008; **58**:106–15.
- Reich K, Nestle FO, Papp K *et al.* Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet* 2005; **366**:1367–74.
- Leonardi CL, Kimball AB, Papp KA *et al.* Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* 2008; **371**:1665–74.
- Al-Mutairi N, Nour T. The effect of weight reduction on treatment outcomes in obese patients with psoriasis on biologic therapy: a randomized controlled prospective trial. *Expert Opin Biol Ther* 2014; **14**:749–56.
- Naldi L, Conti A, Cazzaniga S *et al.* Diet and physical exercise in psoriasis: a randomized controlled trial. *Br J Dermatol* 2014; **170**:634–42.
- Zweegers J, van den Reek JM, van de Kerkhof PC *et al.* Body mass index predicts discontinuation due to ineffectiveness and female sex predicts discontinuation due to side-effects in psoriasis patients treated with adalimumab, etanercept or ustekinumab in daily practice. A prospective, comparative, long-term drug survival study from the BioCAPTURE registry. *Br J Dermatol* 2016; **175**:340–7.
- Puig L, Ruiz-Salas V. Long-term efficacy, safety and drug survival of ustekinumab in a Spanish cohort of patients with moderate to severe plaque psoriasis. *Dermatology* 2015; **230**:46–54.
- Spertino J, Lopez-Ferrer A, Vilarrasa E *et al.* Long-term study of infliximab for psoriasis in daily practice: drug survival depends on combined treatment, obesity and infusion reactions. *J Eur Acad Dermatol Venereol* 2014; **28**:1514–21.
- van den Reek JM, van Lumig PP, Driessen RJ *et al.* Determinants of drug survival for etanercept in a long-term daily practice cohort of patients with psoriasis. *Br J Dermatol* 2014; **170**:415–24.
- Carrascosa JM, Vilavella M, Garcia-Doval I *et al.* Body mass index in patients with moderate-to-severe psoriasis in Spain and its impact as an independent risk factor for therapy withdrawal: results of the Biobadaderm Registry. *J Eur Acad Dermatol Venereol* 2014; **28**:907–14.

Appendix 1

Conflicts of interest

J.Z. carries out trials for AbbVie, Janssen and Sciderm, and has received research grants for the independent research fund of the Department of Dermatology, Radboud University Medical Center, Nijmegen, the Netherlands, from AbbVie. P.C.M.vK. serves as a consultant for Merck Sharp Dome, Celgene, Centocor, Almirall, UCB, Pfizer, Sofinnova, AbbVie, Actelion, Galderma, Novartis, Janssen-Cilag, Eli Lilly, Amgen, Mitsubishi and LEO Pharma; and receives research grants from Centocor, Pfizer, Merck Sharp Dome, Merck Serono, AbbVie and Philips Lighting. J.M.P.A.vR. carries out clinical trials for AbbVie and Janssen; has received speaking fees from Eli Lilly and AbbVie; and has received research grants for the independent research fund of the Department of Dermatology of Radboud University Medical Center, Nijmegen, the Netherlands, from AbbVie, and reimbursement for attending a symposium from Janssen, Pfizer and AbbVie. E.M.G.J.dJ. has received research grants for the independent research fund of the Department of

Dermatology of Radboud University Medical Center, Nijmegen, the Netherlands, from Merck-Serono, Wyeth, AbbVie, Pfizer and Janssen, and has acted as consultant and/or paid speaker for and/or participated in research sponsored by companies that manufacture drugs used for the treatment of psoriasis, including AbbVie, Janssen, MSD, Pfizer, Amgen and Lilly. M.D.N. serves as a consultant for Janssen. J.M.M. has served as a consultant for Novartis and Celgene. W.P.A. has served as a consultant for AbbVie and Janssen, and travelled with Pfizer, AbbVie and Janssen to medical congresses for 50% of the fees.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1. Variables selected as possible predictors from univariate generalized estimating equation regression analyses.

Table S2. Treatment characteristics of included treatment episodes.