

Comparison of the 1- and 5-year effectiveness of adalimumab, etanercept and ustekinumab in patients with psoriasis in daily clinical practice: results from the prospective BioCAPTURE registry

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Summary

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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 of University Medical Centre St Radboud Nijmegen, the Netherlands from AbbVie. J.M.P.A.vdR. carries out clinical trials for AbbVie and Janssen and received speaking fees from Eli Lilly and AbbVie, and has received research grants for the independent research fund of the Department of Dermatology of University Medical Centre St Radboud Nijmegen, the Netherlands from AbbVie and reimbursement for attending a symposium from Janssen, Pfizer and AbbVie. P.C.M.vdK. serves as a consultant for Merck Sharp Dohme, Celgene, Centocor, Almirall, UCB, Pfizer,

Background The efficacy of etanercept and ustekinumab in psoriasis has been compared in one randomized controlled trial. Comparison of the long-term effectiveness of biologics in daily-practice psoriasis treatment is currently lacking.

Objectives To compare the effectiveness between the three widely used outpatient biologics adalimumab, etanercept and ustekinumab in daily-practice psoriasis treatment and to correct for confounders.

Methods Data were extracted from the prospective, multicentre BioCAPTURE registry. Multilevel linear regression analyses (MLRAs) and generalized estimating equation (GEE) analyses were performed on the course of mean Psoriasis Area and Severity Index (PASI) and PASI 75 ($\geq 75\%$ reduction vs. baseline). Both models were corrected for confounders. Subgroup analyses for biological dose were performed.

Results We included 356 patients with 513 treatment episodes: 178 adalimumab, 245 etanercept and 90 ustekinumab. MLRA showed a similar effectiveness between adalimumab, etanercept and ustekinumab after 1 year, but the highest effectiveness for ustekinumab during 5 years of treatment ($P = 0.047$; ustekinumab vs. etanercept, $P = 0.019$). GEE analysis revealed a higher chance of attaining PASI 75 with adalimumab and ustekinumab than with etanercept at 1 year of treatment. A higher than label dose was more often used in patients treated with etanercept (adalimumab, etanercept and ustekinumab: respectively 31.5%, 55.1% and 17% after 1 year, $P < 0.001$; 39.3%, 71.4% and 24% after 5 years, $P < 0.001$).

Conclusions Compared with etanercept, ustekinumab had the highest effectiveness during 5 years of treatment. Patients receiving adalimumab and ustekinumab more often reached PASI 75 than those on etanercept at 1 year of treatment. Dose escalation was more frequent in etanercept and adalimumab than in ustekinumab.

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What's already known about this topic?

- Randomized controlled clinical trials (RCTs) have shown that biologics are effective in treating selected patients with psoriasis.
- RCTs comparing ustekinumab with adalimumab or etanercept with adalimumab have not been performed.
- Patients from RCTs differ from patients in daily practice, and this might influence the effectiveness of biologics in the clinic.

What does this study add?

- This prospective daily-practice study compared the 1- and 5-year effectiveness of adalimumab, etanercept and ustekinumab in psoriasis, corrected for confounders.
- We showed a significantly higher confounder-corrected Psoriasis Area and Severity Index (PASI) decrease for ustekinumab vs. etanercept over 5 years.
- At 1 year of treatment, patients treated with adalimumab and ustekinumab had a higher chance of attaining PASI 75 than patients on etanercept after correction for confounders.
- Etanercept was the agent most often prescribed in high doses in daily practice.

Biologics have revolutionized the treatments of psoriasis.¹ Randomized controlled clinical trials (RCTs) have shown that biologics are effective in treating selected patients with psoriasis.^{2–10} In RCTs, a higher efficacy has been found for ustekinumab than for etanercept.² However, RCTs comparing ustekinumab with adalimumab or etanercept with adalimumab have not been performed. Moreover, patients from RCTs differ from patients in daily practice, and this might influence the effectiveness of biologics in the real world.¹¹

The effectiveness of biologics has been assessed in real-world cohorts (BADBIR, PSOCARE, PSOLAR, BioCAPTURE, AMC database). However, direct comparison of biological treatments in real-life settings is sparse. A recently performed systematic review¹² showed that two retrospective studies^{13,14} and two prospective studies^{15,16} were described that as a secondary objective compared the effectiveness of biologics in daily practice. However, these studies had short treatment periods (3–7 months), with few data on ustekinumab and were uncorrected for baseline variables or other confounding factors. Long-term comparative real-world effectiveness data on biological treatment for psoriasis are currently lacking, using the Psoriasis Area and Severity Index (PASI) and appropriately correcting for confounders and accounting for biological dose.

This prospective daily-practice study was performed in order to compare the effectiveness of the three widely used outpatient biological treatments adalimumab, etanercept and ustekinumab by comparing the mean PASI decrease during the first 5 years of biological treatment.^{17,18} Our secondary objective was to compare the mean PASI decrease and the PASI 75 response ($\geq 75\%$ reduction of PASI vs. baseline) between these agents, during the first year and at 1 year of

treatment. All effectiveness analyses were corrected for confounders.

Patients and methods

BioCAPTURE

Data were extracted from the Continuous Assessment of Psoriasis Treatment Use Registry with Biologics (BioCAPTURE)^{19,20} for all patients from inception of the registry in 2005. This registry contains prospective daily-practice data on all consecutive patients with psoriasis treated with biologics from one academic and eight nonacademic centres. Patients were treated according to the guidelines,^{21,22} and recommendations were at the discretion of the attending dermatologist. When switching between biologics the newly introduced biologic was usually administered at the time point of the next scheduled drug dose of the previous biologic (for adalimumab after 2 weeks, for etanercept after 1 week and for ustekinumab after 12 weeks).²³ Dose adjustments, adjustments of treatment intervals and/or the addition of combination therapies with conventional systemic therapies were recorded. The registry was approved by our medical ethics committee. Informed consent was obtained from every patient.

Data collection and extraction

Outcomes

Data from patients were collected at baseline, week 6 and week 12, then every 3 months until the first year of biological treatment and thereafter every 3–6 months. PASI data were

extracted for all treatment episodes (TEs): the periods in which a patient was treated with a certain biologic. In cases where the patient interrupted the biological treatment for > 90 days or if the patient switched to another biological treatment, a new TE commenced. Ninety days is a widely accepted maximum interruption period.^{20,24,25} Thus, one patient might have multiple TEs. TEs with at least a baseline PASI and one follow-up PASI at week 6 were included for analysis. Baseline PASI was defined as PASI at the start, or if PASI was not recorded at that time point, the closest PASI between 90 days before and 7 days after the start of the biologic. The last PASI was the PASI at the stop date, or if it was not recorded at that time point, the closest PASI until a maximum of 90 days after the stop date. Baseline patient characteristics, biological treatment duration, the biological dose and the use of concomitant systemic conventional therapy were extracted. Body mass index was calculated from height and weight and expressed as kg m^{-2} .

Treatments

The cumulative biological dose was calculated for each TE, and subsequently this dose was divided by the expected cumulative dose if the patient had been treated according to the European Medicines Agency label. Then, this ratio was expressed as a categorical variable (low to normal or high biological dose compared with the label dose, in which high dose represented a ratio > 1). The mean biological dose including the induction dose was used to present the dose per biological group (adalimumab, etanercept, ustekinumab). The use of concomitant conventional therapies, such as acitretin, ciclosporin, fumarates and methotrexate was categorized into combination therapy or bridging therapy. Bridging therapy was defined as the use of a conventional systemic agent before the start of a biological treatment until at least 28 days and for a maximum of 90 days after start of the biological treatment. Combination therapy was defined as the start of a conventional systemic agent during biological treatment with the conventional systemic agent being prescribed for at least 28 consecutive days. Exposure to a conventional systemic during biological treatment was defined as bridging and/or combination therapy with a conventional systemic during the TE.

Statistical analysis

Analyses were performed using Microsoft Office Excel 2007, SPSS 22.0 (IBM, Armonk, NY, U.S.A.) and SAS 9.2 software (SAS Institute Inc., Cary, NC, U.S.A.). Variables with a normal distribution were presented as the mean \pm SD, non-normally distributed variables as the median and interquartile range, and categorical data as n (%). Baseline variables were compared between treatment groups using one-way ANOVA in case of parametric distribution and the Kruskal–Wallis test in case of nonparametric distribution. Categorical variables were compared using the χ^2 -test. Analysis on baseline characteristics was executed including multiple TEs from the same patient. A

sensitivity analysis was performed on baseline variables in which only one TE per patient per treatment group was included. A P-value of 0.05 was considered significant.

For the primary analysis, multilevel linear regression analysis (MLRA) was performed to investigate differences between biological treatments in mean PASI decrease over time during the first year and first 5 years of biological treatment. With MLRA it is possible to have repeated, correlated measurements, such as multiple TEs from the same patient.²⁶ In addition, a moment in time with very few observations will contribute little to the estimate of the treatment effect. Independent variables in this model were treatment and time. Firstly, a model was created including the interaction between time and biological treatment to investigate whether a different pattern existed between the biological agents over time. The pattern over time was irregular for all biological agents and therefore a parallel-line model was created without the interaction term. In this model, residuals were tolerably normally distributed and the requirement of homoscedasticity (similar variances of residuals at each level of the predictor variables) was reasonably met.

For the secondary analysis, PASI 75 scores were calculated with the per protocol method²⁷ for generalized estimating equation (GEE) analyses. GEE analysis allows estimation of parameters of a generalized linear model when the dependent variable is a dichotomous variable.²⁸ A GEE analysis can handle multiple TEs of the same patient. For GEE analysis it was possible to include only the first TE of the same biologic if there were two TEs of the same biologic within the same patient. In addition, a sensitivity analysis was performed calculating PASI 75 using the last-observation-carried-forward (LOCF) method,²⁷ in which the last available absolute PASI value was carried forward until 1 year of treatment.

The outcomes of all of the above-mentioned analyses were corrected for confounders. Baseline variables that were considered as possible confounders were age, sex, height, body weight, smoking status, alcohol use, family history of psoriasis, psoriatic arthritis, duration of psoriasis, baseline PASI, prior biologics and prior tumour necrosis factor (TNF)- α use differing between biologics. Those that were significantly different between the treatment groups were included in the MLRA and GEE as confounders and set as fixed variables.

The biological dose was expressed as low to normal or high compared with the label dose, and exposure to a concomitant systemic conventional therapy during a TE, as well as the use of combination therapy, were also compared between the adalimumab, etanercept and ustekinumab treatment groups. When these were significantly different, subgroup analyses were performed.

Results

Patients

In total 513 TEs from 356 patients were included: adalimumab 178 TEs, etanercept 245 TEs and ustekinumab 90 TEs.

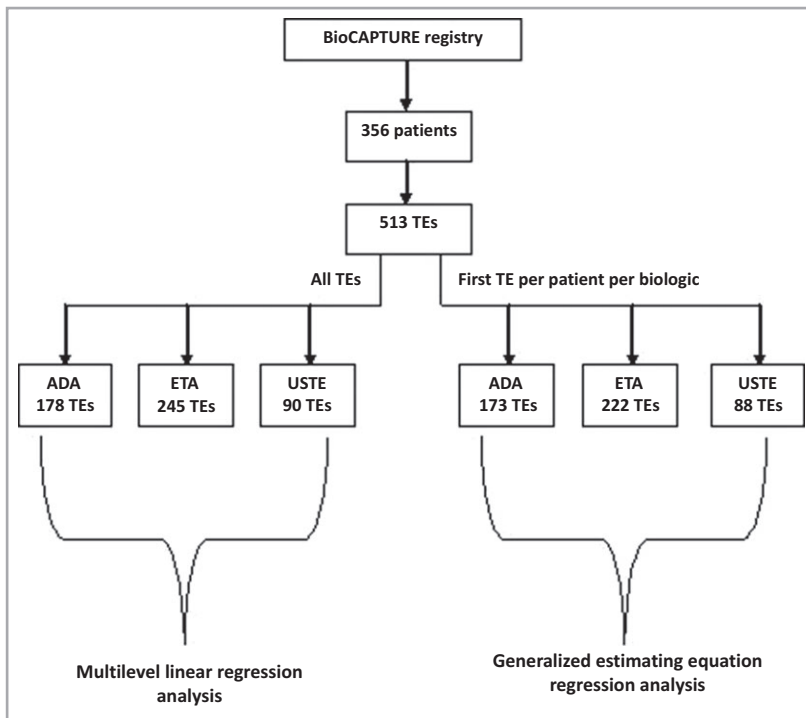


Fig 1. Flowchart of included patients in the multilevel linear regression analyses and generalized estimating equation analyses. TE, treatment episode; ADA, adalimumab; ETA, etanercept; USTE, ustekinumab.

For the MLRA all 513 TEs, and for GEE analysis 483 TEs were included (Fig. 1). The baseline patient characteristics (at inclusion in BioCAPTURE) are shown in Table 1. The majority of patients were male (62.1%), overweight (median body mass index 27.4 kg m⁻²) and smokers (74.2%) and had a positive family history of psoriasis (65.7%). The median baseline PASI

was 13.1. This is comparable with other major psoriasis patient registries.^{29–31}

Baseline treatment episode characteristics

The baseline characteristics of the TEs are presented in Table 2; all TEs are included and therefore patients can appear more than once. Sensitivity analysis on baseline variables with one TE per patient per treatment group resulted in similar P-values to those from analyses comparing baseline TE variables with multiple TEs (Table 2 and Table S1; see Supporting Information). The median baseline PASI was significantly higher for ustekinumab (14.6) and etanercept (13.0) than for adalimumab (11.1; P = 0.001 and P < 0.001, respectively). The median baseline weight was significantly higher for ustekinumab (92.0 kg) and adalimumab (88.0 kg) than for etanercept (82.8 kg; P = 0.001 and 0.003, respectively). Other significantly different baseline TE characteristics were biological naivety (P < 0.001) and anti-TNF-α naivety (P < 0.001; Table 2). Patients were significantly less often biologic naive and anti-TNF-α naive in TEs of ustekinumab compared with adalimumab (P = 0.003 and P = 0.009, respectively) and etanercept (P < 0.001 in both analyses). All significantly different baseline characteristics were incorporated into the MLRA and GEE analysis to correct for their possible confounding effects.

Treatment characteristics

Treatment characteristics during the first year and first 5 years of biological treatment are shown in Table 3. Only the biological dose, expressed as low to normal or high, was statistically

Table 1 Baseline patient characteristics

Baseline patient characteristics	First treatment episode in BioCAPTURE (n = 356)
Age at start of biologic (years), mean ± SD	47.6 ± 12.7 (0 missing)
Sex male, n (%)	221 (62.1) (0 missing)
Height (cm), mean ± SD	175.5 ± 8.8 (82 missing)
Weight (kg), median (IQR)	84.6 (75.9–98.0) (78 missing)
Body mass index (kg m ⁻²), median (IQR)	27.4 (24.5–31.1) (82 missing)
Smoking status, present or past (yes), n (%)	264 (74.2) (6 missing)
Alcohol use, present or past (yes), n (%)	255 (71.6) (9 missing)
Positive family history of psoriasis (yes), n (%)	234 (65.7) (12 missing)
Psoriatic arthritis, diagnosis by a rheumatologist (yes), n (%)	104 (29.2) (18 missing)
Duration of psoriasis until start of biologic (years), median (IQR)	19.6 (12.8–29.9) (2 missing)
Baseline PASI, median (IQR)	13.1 (9.8–17.8) (0 missing)

IQR, interquartile range; PASI, Psoriasis Area and Severity Index.

Table 2 Baseline characteristics of included treatment episodes (TEs)

Baseline TE characteristics	Adalimumab (178 TEs)	Etanercept (245 TEs)	Ustekinumab (90 TEs)	P-value
Age at start of biologic (years), mean ± SD	49.0 ± 12.4	47.1 ± 12.8	49.3 ± 12.5	0.21 ^a
Sex (male), n (%)	103 (57.9)	152 (62.0)	58 (64)	0.52 ^b
Height (cm), mean ± SD	175.6 ± 8.6	175.2 ± 8.0	176.6 ± 8.6	0.48 ^a
Weight (kg), median (IQR)	88.0 (78.8–103.5)	82.8 (71.8–96.1)	92.0 (80.0–101.1)	0.001 ^c
Body mass index (kg m ⁻²), median (IQR)	29.2 (25.5–32.0)	27.1 (24.0–30.5)	28.6 (25.8–32.2)	0.002 ^c
Smoking status, present or past (yes), n (%)	135 (75.8)	185 (75.5)	67 (74)	0.96 ^b
Alcohol use, present or past (yes), n (%)	126 (70.8)	172 (70.2)	63 (70)	0.97 ^b
Positive family history of psoriasis (yes), n (%)	121 (68)	159 (65.0)	59 (66)	0.80 ^b
Psoriatic arthritis (yes), n (%)	55 (30.9)	72 (29.4)	23 (26)	0.33 ^b
Duration of psoriasis until start of biologic (years), median (IQR)	20.4 (13.3–31.0)	20.4 (13.3–31.0)	18.4 (13.5–27.3)	0.67 ^c
Baseline PASI, median (IQR)	11.1 (7.3–14.8)	13.0 (10.0–17.9)	14.6 (8.3–20.5)	< 0.001 ^c
Biologic naïve (yes), n (%)	63 (35.4)	147 (60.0)	16 (18)	< 0.001 ^b
Anti-TNF-α naïve (yes), n (%)	70 (39.3)	170 (69.4)	21 (23)	< 0.001 ^b

IQR, interquartile range; PASI, Psoriasis Area and Severity Index; TNF, tumour necrosis factor. Missing data for adalimumab, etanercept and ustekinumab, respectively are height: 16, 76, 8; weight: 16, 75, 4; body mass index: 17, 76, 8; smoking: 2, 4, 1; alcohol: 4, 4, 2; family history: 5, 7, 3; psoriatic arthritis: 7, 4, 9; duration: 2, 0, 0; otherwise no missing data. ^aOne-way ANOVA, ^bχ²-test, ^cKruskal–Wallis test.

Table 3 Treatment characteristics of included treatment episodes (TEs) at 1 year and 5 years of biological treatment

Treatment characteristics	Adalimumab (178 TEs)	Etanercept (245 TEs)	Ustekinumab (90 TEs)	P-value (χ ² -test)
First year of treatment				
Cumulative dose of biologic (mg), mean ± SD	991 ± 376	3001 ± 1070	268 ± 108	NA
Dose of biologic (mg per day), mean ± SD	3.5 ± 0.8	10.4 ± 2.5	0.9 ± 0.3	NA
Dose higher than EMA label during TE (yes), n (%)	56 (31.5)	135 (55.1)	15 (17)	< 0.001
Exposure to a conventional systemic agent during TE (yes), n (%)	47 (26.4)	58 (23.7)	16 (18)	0.29
Combination therapy without bridging during TE (yes)	37 (20.8)	44 (18.0)	14 (16)	0.55
First 5 years of treatment				
Cumulative dose of biologic (mg), mean ± SD	2627 ± 2199	9611 ± 8407	604 ± 555	NA
Dose of biologic (mg per day), mean ± SD	3.4 ± 0.9	9.9 ± 2.6	0.9 ± 0.3	NA
Dose higher than EMA label during TE (yes), n (%)	70 (39.3)	175 (71.4)	22 (24)	< 0.001
Exposure to a conventional systemic agent during TE (yes), n (%)	50 (28.1)	64 (26.1)	18 (20)	0.35
Combination therapy without bridging during TE (yes), n (%)	40 (22.5)	50 (20.4)	16 (18)	0.66
Combination or bridging with conventional agent	Total 52 CS. Combination 42 (81%), bridging 10 (19%)	Total 72 CS. Combination 57 (79%), bridging 15 (21%)	Total 20 CS. Combination 18 (90%), bridging 2 (10%)	NA
Concomitant CS drugs (combination or bridging; number of agents)	Methotrexate 40, ciclosporin 7, acitretin 4, fumarates 1	Methotrexate 42, ciclosporin 11, acitretin 14, fumarates 3, tacrolimus 1, MMF 1	Methotrexate 14, ciclosporin 1, acitretin 5, fumarates 0	NA

No missing data. EMA, European Medicines Agency; NA, not applicable; CS, conventional systemic; MMF, mycophenolate mofetil.

significantly different between biologics after 1 and 5 years. Ever being exposed to a conventional systemic or combination therapy was not significantly different between the biologics.

A description of biological dose and bridging and combination therapy in our cohort can be found in Appendix S1 and Table S2 (see Supporting Information).

Overall effectiveness

Course of mean Psoriasis Area and Severity Index

The mean PASI decreases of adalimumab, etanercept and ustekinumab during 5 years, uncorrected for confounders, are shown in Figure 2(a). The mean baseline PASI differed between the agents (adalimumab 11.6 ± 5.8 , etanercept

14.7 ± 8.2 , ustekinumab 15.1 ± 8.0). It is shown that adalimumab, etanercept and ustekinumab treatment resulted in a rapid decrease in mean PASI during the first 3 months. After 1 year of treatment the mean PASI decrease seemed to stabilize for all three biologics (Fig. 2a). Uncorrected for confounders, Figure 2(a) gives the impression that adalimumab and ustekinumab show better responses than etanercept at 1 year and 5 years of treatment. This impression remains

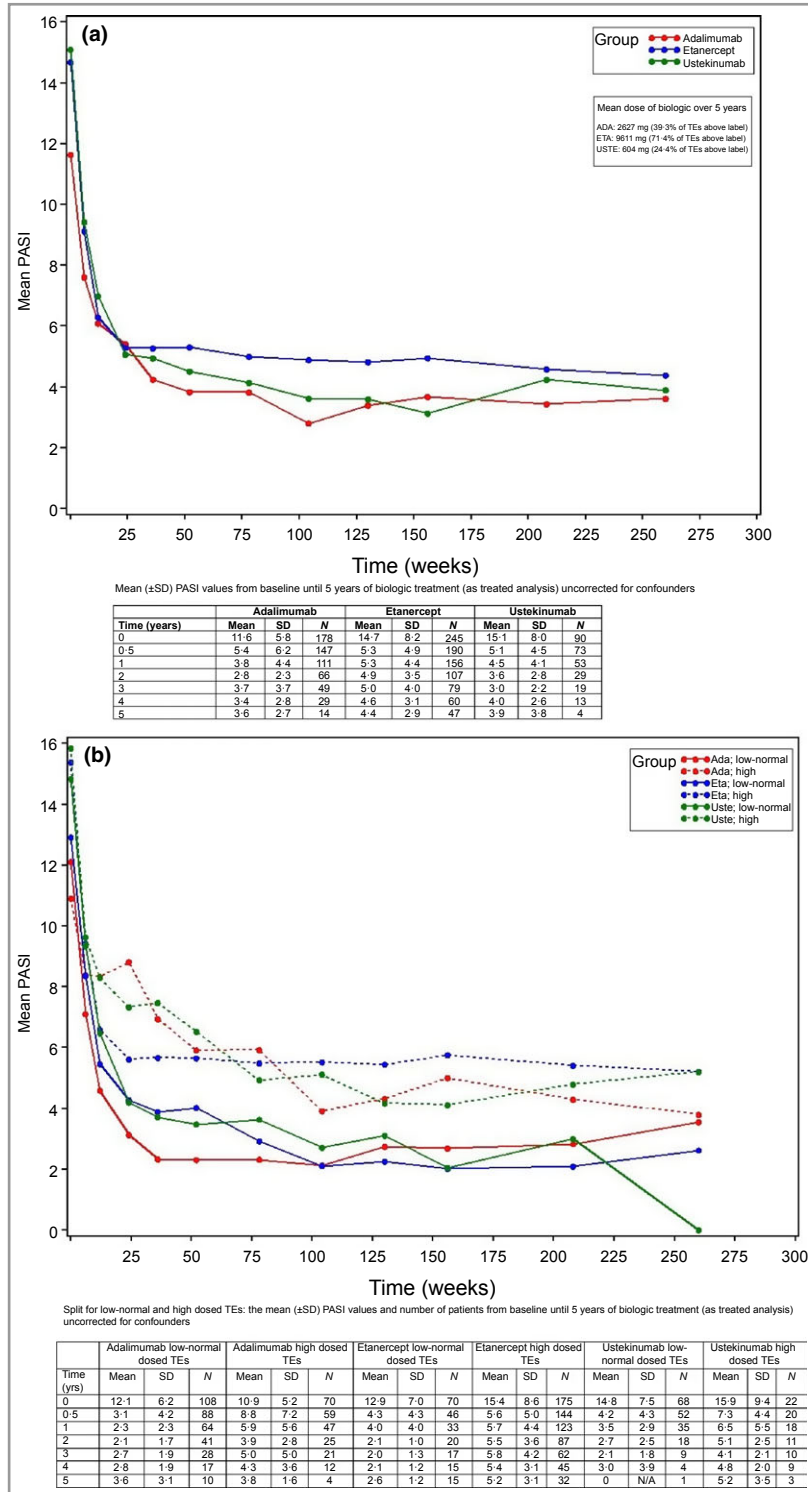


Fig 2. Mean Psoriasis Area and Severity Index (PASI) from baseline until 5 years of biological treatment (as-treated analysis): (a) uncorrected for confounders and (b) split for low-to-normal and high-dosed treatment episodes (TEs). ADA, adalimumab; ETA, etanercept; USTE, ustekinumab. Low-normal, actual dose was low to normal compared with the calculated expected dose during the treatment episode. High, actual dose was higher than the calculated expected dose during the TE. Notice the difference in mean baseline PASI between the different dosing groups.

when correcting only for baseline PASI (Fig. S1; see Supporting Information).

As a high biological dose was more often prescribed in etanercept-treated patients, followed by adalimumab and ustekinumab, effectiveness was split for low-to-normal-dosed TEs and high-dosed TEs (Fig. 2b; uncorrected for confounders). From this figure, it can be seen that all patients with high-dosed TEs remained at a higher PASI than those with low-dosed TEs.

Five-year effectiveness

Course of mean Psoriasis Area and Severity Index

Over 5 years of treatment, MLRA showed a significant difference between medication ($P = 0.047$), with overall the most favourable effectiveness results for ustekinumab vs. etanercept ($P = 0.019$). There were no significant differences between the other biological groups (Table S3; see Supporting Information).

Split for biological dose, the levels of effectiveness of the low-to-normal-dosed TEs of adalimumab, etanercept and ustekinumab were comparable, as were those for the high-dosed TEs (Table S3).

One-year effectiveness

Course of mean Psoriasis Area and Severity Index

Overall, MLRA showed no significant differences between adalimumab, etanercept and ustekinumab during the first year of treatment (Table S3). Also, no significant differences were encountered in the low-to-normal-dosed TEs between biologics. However, numerically, adalimumab and ustekinumab performed better than etanercept in both overall effectiveness and the effectiveness of low-to-normal doses.

Psoriasis Area and Severity Index $\geq 75\%$ improvement

Per protocol PASI 75 data uncorrected for confounders for the first year of treatment are shown in Figure S2 (see Supporting Information). The uncorrected PASI 75 percentages were etanercept 39.1%, adalimumab 45.9% and ustekinumab 45.3% after 1 year of treatment. Uncorrected PASI 75 data for low-to-normal-dosed TEs during the first year of treatment are shown in Figure S3 (see Supporting Information). This figure represents the percentage of low-to-normal-dosed TEs in which PASI 75 was reached, from the total group of low-to-normal-dosed TEs.

GEE analysis on per protocol data showed that, overall, adalimumab and ustekinumab had a higher chance of achieving PASI 75 than etanercept at 1 year of treatment (Table S3, overall $P = 0.028$; adalimumab vs. etanercept $P = 0.010$; ustekinumab vs. etanercept $P = 0.048$). Sensitivity analysis on PASI 75 LOCF data showed that ustekinumab was more effective than adalimumab and etanercept (Appendix S1 and Figs S4, S5; see Supporting Information).

GEE subanalysis of low-to-normal-dosed TEs showed that adalimumab had a higher chance than etanercept, but not ustekinumab, in providing PASI 75 response (adalimumab vs. etanercept $P = 0.011$, adalimumab vs. ustekinumab $P = 0.55$, ustekinumab vs. etanercept $P = 0.11$; Table S3). Sensitivity analysis on the LOCF data showed that ustekinumab was more efficacious than etanercept, but not compared with adalimumab (Appendix S1 and Figs S4, S5).

Discussion

This prospective, multicentre study provides data for the comparative effectiveness of adalimumab, etanercept and ustekinumab in real-life treatment of patients with psoriasis. Ustekinumab had a higher overall effectiveness during the first 5 years of treatment than etanercept. Dose escalation was more frequent with etanercept and adalimumab than with ustekinumab. During the first year of treatment ustekinumab and adalimumab had a higher chance of attaining PASI 75 than etanercept.

No major differences existed between adalimumab, etanercept and ustekinumab in the course of mean PASI in low-to-normal doses during 1 and 5 years of treatment. Thus, when low-to-normal doses of biologics were maintained during the study, all biologics had a similar effectiveness. However, physicians were less often able to maintain a low-to-normal dose in etanercept-treated patients, followed by adalimumab and ustekinumab. Also, all high-dosed TEs remained at a higher PASI than low-dosed TEs. High doses of biologics were thus prescribed to a subpopulation of patients with psoriasis with a suboptimal response to biological therapy. Hence, a suboptimal response was more often the case in etanercept-treated patients, followed by adalimumab and ustekinumab. Therefore, ustekinumab was the drug with the highest overall effectiveness compared with etanercept in daily clinical practice during 5 years of treatment. Data from other prospective patient registries are needed to verify these observations.

High doses of adalimumab, etanercept and ustekinumab were equally effective over 5 years of treatment. However, high-dosed patients remained at a higher mean PASI than low-dosed patients. Currently, knowledge about the effect of dose adjustments in daily practice is scarce.¹² Studies on the effect of dose adjustments of the different biologics are needed to aid the physician in deciding whether to adjust the biological dose or switch to another biological agent.

Dose adjustments were most frequently made in etanercept, followed by adalimumab and ustekinumab. The observation that the treatment doses of etanercept and adalimumab are more frequently adjusted than with ustekinumab corresponds to data from a recent systematic review.¹² Although more TEs of etanercept had a higher dosing regimen than with adalimumab and ustekinumab, it did not result in a more successful mean PASI course in the long term during the 5-year treatment.

That ustekinumab is an effective agent has been shown in RCTs,^{2,6,7,32} with ustekinumab being more effective than etanercept.² The real-world effectiveness of biologics has been

reported with data from other registries, but usually concerned noncomparative effectiveness data.¹² Studies with the secondary objective to compare the PASI of biologics had short treatment periods, few data on ustekinumab, or did not correct for baseline variables or other confounding factors such as biological dose.¹² Recent real-world data show that ustekinumab has the highest first-course drug survival, which is a comprehensive measure of effectiveness, safety and patients' and doctors' preferences.^{24,33} In addition, the results from our study indicate that ustekinumab might be the preferred agent for long-term psoriasis treatment.

Differences in effectiveness results between biologics might be explained by the difference in the mode of action between the anti-TNF- α receptor blocker etanercept, the anti-TNF- α antibody adalimumab and the anti-interleukin (IL)12/IL23 antibody ustekinumab. Ustekinumab, by blocking IL-12 and IL-23, reduces the survival and proliferation of T helper (Th)1 and Th17 cells, respectively. In particular, Th17 cells play a key role in the development of psoriasis.³⁴ It can be hypothesized that ustekinumab exhibits a higher effectiveness than TNF- α inhibitors because the IL-12 and IL-23 cytokines function further downstream in the cascade of cytokines involved in the immunopathogenesis of psoriasis compared with the TNF- α cytokine.^{1,35} However, it is also known that not every patient reaches the same effectiveness results, which in theory could be explained by the activation of different sets of genes between patients.³⁶ More research is needed to explain why differences in effectiveness are seen between biological agents and between patients.

A limitation of our study is that patient adherence to biologics was not measured, for example with patient questionnaires. The exact dose with which patients are treated might therefore vary from the calculated dose. However, dose adjustments were recorded in our registry, and the data showed that dose adjustments were indeed given to a patient group with suboptimal responses to therapy. Another limitation might be that we used PASI 75 as an outcome measure for our secondary objective instead of PASI 90 or 100. However, the numbers of patients reaching PASI 90 or 100 were insufficient for sound analysis in our study. Research with cohorts including larger numbers of patients could answer this question.

Strengths of our study include the similarity of our patients to those in other major registries, the prospective nature and multicentre character of the study, the inclusion of long-term PASI data and biological doses, and correcting all analyses for confounders. Another strength is the use of MLRA, which provides us with an estimate of the effect of ustekinumab that is only slightly influenced by the low number of TEs of ustekinumab at the end of 5 years of treatment.

This is the first prospective, real-world study in which effectiveness data (the course of mean PASI and PASI 75) from the first 5 years of biological treatment have been compared between the three most commonly prescribed outpatient biologics: adalimumab, etanercept and ustekinumab. The data were corrected for confounders and accounted for biological doses in patients with psoriasis who were comparable with

those in other major psoriasis patient registries. Our data show that, among outpatient biologics, ustekinumab is the most effective agent in daily practice during 5 years of psoriasis treatment. Of note, ustekinumab was superior to adalimumab only on dose escalation above the licensed dose. When the physician was able to keep the patient on a low-to-normal biological dose, the effectiveness between the outpatient biologics was similar. Patients on low-to-normal doses had lower mean PASIs than high-dosed patients. Keeping a low-to-normal dose was most often the case in ustekinumab-treated patients, which resulted in ustekinumab being the most effective agent in psoriasis treatment in daily practice. When high doses were needed, a similar effectiveness was seen between biologics during long-term treatment. These findings warrant replication from other prospective daily-practice cohorts and further research into dose adjustments of biologics in the clinic.

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Supporting Information

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

Appendix S1. Biological dose, combination and bridging therapy, and generalized estimating equation regression analysis, last-observation-carried-forward analysis.

Fig S1. Mean Psoriasis Area and Severity Index (PASI) over time according to multilevel linear regression analysis corrected only for baseline PASI.

Fig S2. Uncorrected 1-year $\geq 75\%$ improvement in Psoriasis Area and Severity Index percentages of adalimumab, etanercept and ustekinumab (per protocol analysis).

Fig S3. Uncorrected 1-year $\geq 75\%$ improvement in Psoriasis Area and Severity Index percentages of adalimumab, etanercept and ustekinumab for low-to-normal-dosed treatment episodes (per protocol analysis).

Fig S4. Uncorrected 1-year $\geq 75\%$ improvement in Psoriasis Area and Severity Index percentages of adalimumab, etanercept and ustekinumab (last-observation-carried-forward analysis).

Fig S5. Uncorrected 1-year $\geq 75\%$ improvement in Psoriasis Area and Severity Index percentages of adalimumab, etanercept and ustekinumab for low-to-normal-dosed treatment episodes (last-observation-carried-forward analysis).

Table S1. Baseline and treatment characteristics of included treatment episodes (TEs; one TE per patient per treatment group).

Table S2. Mean doses and mean expected label doses of the biologics.

Table S3. Results from the multilevel linear regression analysis and generalized estimating equation analysis for adalimumab, etanercept and ustekinumab over 1 years and 5 years of treatment.