ORIGINAL ARTICLE

A Randomized, blinded assessor study to Evaluate the efFIcacy and safety of etanercept 50 mg once weekly plus as Needed topical agent vs. Etanercept 50 mg twice weekly in patients with moderate to severe plaque psoriasis (REFINE)

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Abstract

Background Topical corticosteroids are used with systemic therapies for treatment of plaque psoriasis, but data from randomized clinical trials to document efficacy of combination therapy are lacking.

Objective To evaluate efficacy and safety of adding topical corticosteroid therapy from the time that etanercept dosage is reduced from initial label dose [50 mg twice weekly (BIW)] to maintenance dose [50 mg once weekly (QW)].

Methods In this phase 3b, multicentre, randomized, open-label study, patients with moderate-to-severe plaque psoriasis received etanercept 50 mg BIW for 12 weeks, and then were randomized to etanercept 50 mg BIW or 50 mg QW plus topical agent as needed to achieve static physician global assessment (sPGA) status of clear for 12 weeks. Endpoints included percentage change in Psoriasis Area and Severity Index (PASI) score from week 12 to week 24 (primary endpoint); proportion of patients achieving 50% improvement in (PASI 50), PASI 75 and PASI 90; patients achieving sPGA of clear/almost clear; and change in affected body surface area (BSA).

Results Mean difference [95% confidence interval (CI)] between etanercept arm (n = 140) and etanercept plus topical arm (n = 142) in change in PASI score from week 12 to week 24 was 16.2% (−3.5%, 35.8%). PASI response rates were similar between groups. Percentage (95% CI) of patients achieving sPGA status of clear/almost clear was 40.6% (32.5%, 48.6%) and 45.8% (37.6%, 54.0%) at week 12 for patients in etanercept and etanercept plus topical arms, respectively, and 53.5% (45.3%, 61.7%) and 45.4% (37.2%, 53.6%) at week 24. Difference (95% CI) between groups in change in affected BSA from week 12 to week 24 was 4.9% (−23.4%, 33.2%).

Conclusion Patients who received etanercept 50 mg QW at week 12 plus as-needed topical therapy and those who stayed on etanercept 50 mg BIW maintained clinical response through week 24 with no notable differences in PASI responses.

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Conflict of interest

K.A.P. is a consultant, speaker, or investigator for AbbVie, Amgen Inc., Astellas, Celgene, Eli Lilly, Galderma, Incyte, Janssen, Merck (MSD), LEO Pharma, Novartis, and Pfizer. R.B. has been an investigator, advisory board member, consultant and/or speaker and has received grants and/or honoraria from Abbvie, Amgen, Novartis, Janssen, Pfizer, Tribute, Eli Lilly, Merck, Astellas and Incyte. M.B. has received grants/honoraria and has been a clinical trialist for AbbVie, Abbott, Amgen, Leo Pharma, Novartis, Eli Lilly, and Celgene. C.W.L. is a consultant, speaker and investigator for AbbVie, Amgen Inc., Janssen, Celgene, Eli Lilly, Novartis, and LEO Pharma. Y.P. is a consultant, speaker and investigator for AbbVie, Amgen Inc., and Janssen, and an investigator for LEO Pharma, Celgene, Eli Lilly, Novartis, Merck, and Pfizer. J.S., A.V.,

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Introduction

Etanercept is a tumour necrosis factor (TNF) blocker that binds to TNF and blocks its interaction with TNF receptors. The recommended starting dose for adults with plaque psoriasis is 50 mg twice weekly (BIW) for 3 months followed by maintenance dose of 50 mg once weekly (QW). Some patients are unable to maintain response after transitioning to maintenance dose and require treatment supplementation. Topical corticosteroid therapies have been used with etanercept for psoriasis,[1–3] and addition of clobetasol propionate to etanercept has been shown to increase efficacy compared with etanercept alone.[3] Further clinical studies are needed to identify effective treatment regimens and provide information on when to initiate treatment with topical medications.

REFINE, the Randomized, blinded assessor study to Evaluate the efFIcacy and safety of etanercept 50 mg QW plus as Needed topical agent vs. Etanercept 50 mg BIW in patients with moderate-to-severe plaque psoriasis study, was designed to evaluate efficacy and safety of adding topical corticosteroid therapy when etanercept dosage is reduced from initial dose to maintenance dose.

Patients and methods

Study design

This phase 3b, multicentre, randomized, open-label study was conducted in accordance with the Declaration of Helsinki. The study protocol and consent was approved by the institutional review board at each study site. All patients provided written informed consent before initiation of study-related procedures. This study was registered under ClinicalTrials.gov identifier NCT01313221.

All patients received etanercept 50 mg BIW for the first 12 weeks of the study. Patients were then randomized (1:1) to receive etanercept 50 mg BIW for 12 weeks or etanercept 50 mg QW plus topical agent for 12 weeks. Randomization was stratified by body mass index (BMI; $\leq$30 kg/m^2 or >30 kg/m^2) and previous TNF-blocker exposure. Patients receiving topical agents were treated as needed to achieve a target static physician global assessment (sPGA) score of 0 (clear). Topical agent was selected by the investigator from hydrocortisone 2.5%, betamethasone valerate 0.1%, betamethasone dipropionate 0.05%, clobetasol 0.05%, calcitriol, or calcipotriol plus betamethasone dipropionate 0.05%. Change in topical agent was allowed.

Patients

Eligible patients had stable moderate-to-severe plaque psoriasis for $\geq$6 months, psoriasis-affected body surface area (BSA) $\geq$10%, Psoriasis Area and Severity Index (PASI) score $\geq$10, and qualified as a candidate for systemic therapy or phototherapy. Exclusions included guttate, erythrodermic or pustular psoriasis or significant concurrent medical conditions.

Endpoints

The primary efficacy endpoint was percentage change in PASI score from week 12 to week 24. Secondary efficacy endpoints included percentage change in PASI score from baseline to weeks 12, 16, 20 and 24 and from week 12 to weeks 16 and 20; proportion of patients achieving 50% improvement in PASI score (PASI 50), PASI 75 and PASI 90 from baseline to weeks 12, 16, 20 and 24; achievement of sPGA status of clear/almost clear (score of 0/1) at weeks 12, 16, 20 and 24; and change in percentage BSA involvement from baseline to weeks 12, 16, 20 and 24 and from week 12 to weeks 16, 20 and 24. Safety endpoints included nature, frequency, severity and relationship to treatment of all adverse events (AEs).

Statistical considerations

Three hundred patients (150 per arm) were estimated to provide a 95% confidence interval (CI) for difference between treatment arms of mean percentage change in PASI with a half-width of 7.2% and to accommodate a 10% attrition rate.

Efficacy analyses were conducted on all randomized patients with $\geq$1 postrandomization efficacy evaluation. Some efficacy analyses were also done on the full analysis set of all enrolled patients with $\geq$1 postbaseline efficacy evaluation. Least squares means and 95% CIs for treatment difference in percentage change in PASI and affected BSA from week 12 were calculated using repeated measures models across weeks 16, 20 and 24 with no imputation for missing data. Secondary endpoints were summarized by mean, standard deviation (SD), 95% CI, or percentage for categorical variables. Last observation carried forward imputation was used for missing data for some secondary endpoints. Multiple imputation was used for sensitivity analyses on summary statistics for primary and some secondary endpoints.[4] AEs were summarized and coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 15.1. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Patients

Of 310 patients enrolled, 144 were randomized to etanercept, 143 to etanercept+topical, and 23 discontinued prior to week 12 and were not randomized. Forty-three (13.9%) patients discontinued because of withdrawn consent (n = 10), loss to follow-up (n = 10), AE (n = 7), non-compliance (n = 5), protocol violation (n = 2), disease progression (n = 2), requirement for alternative therapy (n = 2), administrative decision (n = 2), pregnancy (n = 2) and other reasons (n = 1) (Fig. 1).

The population was predominantly white (87.7%); most patients were men (64.8%), and mean (SD) age was 45.3 (13.9) years (Table 1). Demographic and clinical characteristics were similar across treatment arms; non-randomized patients were mostly women (60.9%), were younger, appeared to have milder disease (lower mean PASI score, smaller percentage affected BSA), and were less likely to have psoriatic arthritis than randomized patients (Table 1).

The full analysis set comprised all patients in the two treatment arms. Of randomized patients, 140 (97.2%) receiving etanercept and 142 (99.3%) receiving etanercept+topical were included in the efficacy evaluable set (Fig. 1). All patients were included in the safety analysis set.

Of patients randomized to etanercept+topical, 11 (7.7%) decided not to use a topical agent. One patient in the etanercept monotherapy arm used a topical agent. Of patients who used topical therapies, 65 (48.9%) used calcipotriol plus betamethasone dipropionate 0.05%, 33 (24.8%) used betamethasone valerate 0.1%, 23 (17.3%) used betamethasone dipropionate 0.05%, 19 (14.3%) used clobetasol 0.05%, 12 (9.0%) used hydrocortisone 2.5% and 3 (2.3%) used calcitriol. One hundred and ten (82.7%) patients used 1 topical agent, 21 (15.8%) used 2 topical agents, and 1 (0.8%) used ≥3 topical agents. Topical agents were applied for mean (SD) of 51 (26) days for mild potency corticosteroids; 53 (30) days for moderate potency corticosteroids; 56 (22) days for potent corticosteroids; 49 (23) days for very potent corticosteroids; 45 (40) days for vitamin D analogues; and 54 (24) days for combination vitamin D analogue plus potent topical corticosteroid agents.

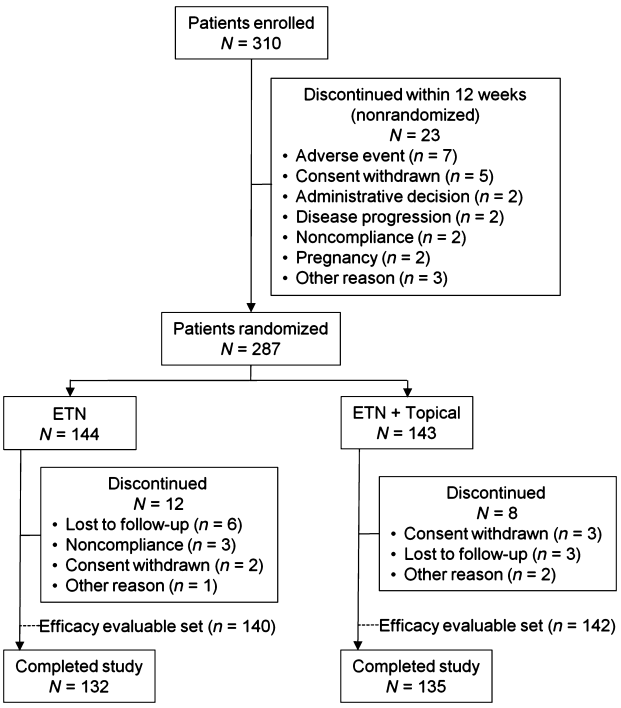

Figure 1 Patient disposition.

Changes in PASI scores and PASI responses

The percentage change from week 12 in PASI score was similar between treatment arms at weeks 16, 20, and 24 (Table 2). For the primary endpoint, the difference (95% CI) between treatment arms in change in PASI score from week 12 to week 24 was 16.2% (−3.5%, 35.8%). The difference (95% CI) between treatment arms in mean percentage change in PASI score from week 12 to week 24 was -8.9 (−66.0, 48.1) in patients with prior TNF-blocker exposure and 21.2 (0.3, 42.1) in patients without prior TNF-blocker exposure. The difference (95% CI) between treatment arms in mean percentage change in PASI score from week 12 to week 24 was 17.0 (−10.0, 44.1) in patients with BMI ≤30 kg/m^2 and 15.3 (−13.9, 44.5) in patients with BMI >30 kg/m^2. Proportions of patients achieving PASI 50, PASI 75 and PASI 90 responses were similar between arms (Fig 2).

Changes in sPGA

Similar proportions of patients in each treatment arm achieved sPGA status of clear/almost clear (score of 0/1) at weeks 12, 16, 20 and 24 (Table 3). At week 24, percentage (95% CI) of patients with sPGA response of clear/almost clear was 53.5% (45.3%, 61.7%) for etanercept and 45.4% (37.2%, 53.6%) for etanercept+topical.

Changes in BSA

Improvements in psoriasis-affected BSA were similar between treatment arms from week 12 to weeks 16, 20 and 24 (Table 4). At week 24, percentage change in psoriasis-affected BSA from week 12 was 15.6% (−4.4%, 35.6%) for the etanercept arm and 10.7% (−9.3%, 30.7%) for the etanercept+topical arm.

Safety

Approximately two-thirds of all patients reported ≥1 treatment-emergent AE (Table 5). There were a total of 138.1 patient-years of etanercept exposure across all 310 patients with a total of 603 AEs. The event rate was highest in the

Table 1 Demographics and disease characteristics at baseline

	ETN* 50 mg BIW *N* = 144	ETN 50 mg QW + Topical† *N* = 143	Non-randomized‡ *N* = 23	All patients *N* = 310
Sex, *n* women (%)	46 (31.9)	49 (34.3)	14 (60.9)	109 (35.2)
Age, mean years (SD)	45.7 (13.1)	46.3 (14.6)	36.6 (11.2)	45.3 (13.9)
Race, *n* white (%)	120 (83.3)	130 (90.9)	22 (95.7)	272 (87.7)
BMI, mean kg/m^2 (SD)	30.4 (7.8)	30.4 (6.8)	29.4 (7.2)	30.3 (7.3)
Tobacco use, *n* (%)				
Current	42 (29.2)	53 (37.1)	11 (47.8)	106 (34.2)
Former	44 (30.6)	35 (24.5)	5 (21.7)	84 (27.1)
Never	58 (40.3)	55 (38.5)	7 (30.4)	120 (38.7)
Duration of psoriasis, mean years (SD)	19.7 (13.1)	19.9 (12.7)	21.6 (12.4)	20.0 (12.9)
Prior TNF blocker therapy, *n* (%)	23 (16.0)	18 (12.6)	2 (8.7)	43 (13.9)
Psoriatic arthritis, *n* (%)	28 (19.4)	36 (25.2)	3 (13.0)	67 (21.6)
PASI, mean score (SD)	17.8 (6.5)	17.1 (6.4)	15.0 (4.7)	17.3 (6.4)
Psoriasis-affected BSA, mean% (SD)	23.0 (14.2)	22.3 (13.9)	17.2 (7.7)	22.2 (13.8)
sPGA score, *n* (%)				
0 or 1	0	0	0	0
2	7 (4.9)	17 (11.9)	1 (4.3)	25 (8.1)
3	103 (71.5)	86 (60.1)	15 (65.2)	204 (65.8)
4	33 (22.9)	37 (25.9)	7 (30.4)	77 (24.8)
5	1 (0.7)	3 (2.1)	0	4 (1.3)

*Patients received ETN 50 mg BIW for 12 weeks and continued on 50 mg BIW for 12 weeks.
†Patients received ETN 50 mg BIW for 12 weeks followed by 50 mg QW plus topical agents as needed to clear for 12 weeks.
‡Patients received ETN 50 mg BIW during the first 12 weeks but discontinued the study before they could be randomized to a treatment arm.
BIW, twice weekly; BMI, body mass index; BSA, body surface area; ETN, etanercept; PASI, Psoriasis Area and Severity Index; QW, once weekly; SD, standard deviation; sPGA, static physician global assessment; TNF, tumour necrosis factor.

Table 2 Percentage changes in PASI score

Mean percentage change in PASI score* (95% CI)	ETN 50 mg BIW *N* = 140	ETN 50 mg QW + Topical *N* = 142	Difference between ETN and ETN + Topical
Week 12 to week 16	16.0% (4.4%, 27.6%)	4.8% (−6.8%, 16.4%)	11.2% (−5.1%, 27.6%)
Week 12 to week 20	19.8% (6.5%, 33.1%)	3.2% (−10.1%, 16.5%)	16.6% (−2.2%, 35.3%)
Week 12 to week 24	17.0% (3.1%, 30.9%)	0.9% (−13.0%, 14.8%)	16.2% (−3.5%, 35.8%)

*Least squares means from repeated measures models over postrandomization time points.
BIW, twice weekly; CI, confidence interval; ETN, etanercept; PASI, Psoriasis Area and Severity Index; QW, once weekly.

non-randomized group. The most commonly reported AEs were nasopharyngitis (n = 44; 14.2%), injection site reaction (n = 33; 10.6%) and headache (n = 28; 9.0%). No fatal events occurred.

Discussion

Patients who received etanercept 50 mg QW with topical medications had similar PASI scores, PASI responses, sPGA status and percentage of psoriasis-affected BSA compared with patients receiving etanercept 50 mg BIW. These results are consistent with a small, open-label study that reported clinical benefit of adding topical calcipotriene 0.005% and betamethasone dipropionate 0.064% in patients who lost their initial response with transition from the 50 mg BIW initial dose of etanercept to maintenance dose of 50 mg QW.[1] Patients who stayed on etanercept 50 mg BIW achieved clinical benefit for up to 24 weeks of monotherapy. The proportion of patients receiving 50 mg BIW who achieved PASI 50, PASI 75 or PASI 90 responses at weeks 12 and 24 was similar to results from patients receiving etanercept 50 mg BIW up to 24 weeks in a phase 3, double-blind, placebo-controlled trial of etanercept.[5]

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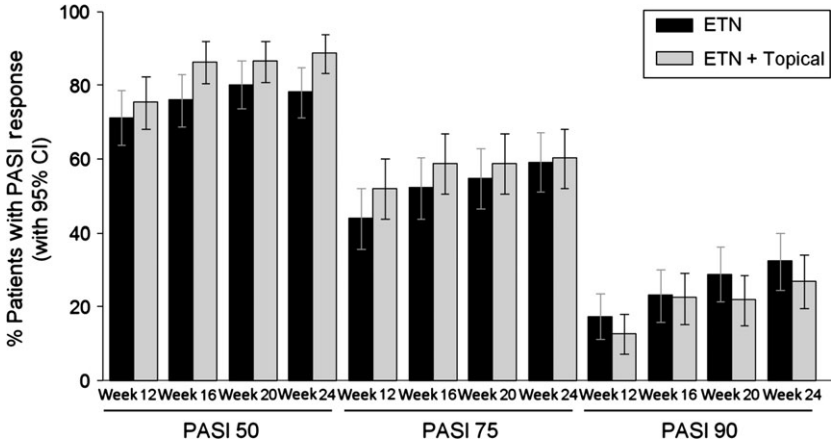

Figure 2 PASI responses. The proportion of patients with PASI 50, PASI 75 and PASI 90 responses are shown for patients receiving ETN 50 mg BIW only (black bars) and ETN 50 mg QW plus topical therapy (gray bars) at weeks 12, 16, 20 and 24. Last observation carried forward (LOCF) imputation was used for missing data; results with multiple imputations were similar (data not shown). Error bars represent 95% CIs. ETN, etanercept; PASI, Psoriasis Area and Severity Index; CI, confidence interval; BIW, twice weekly; QW, once weekly.

Table 3 sPGA responses of clear or almost clear (score of 0 or 1)

Patients with sPGA status of clear/almost clear*	ETN 50 mg BIW *N* = 144		ETN 50 mg QW + Topical *N* = 143	
	n/N	% (95% CI)	*n/N*	% (95% CI)
Week 12	58/143	40.6 (32.5, 48.6)	65/142	45.8 (37.6, 54.0)
Week 16	70/139	50.4 (42.0, 58.7)	70/139	50.4 (42.0, 58.7)
Week 20	73/142	51.4 (43.2, 59.6)	69/141	48.9 (40.7, 57.2)
Week 24	76/142	53.5 (45.3, 61.7)	64/141	45.4 (37.2, 53.6)

*Last observation carried forward (LOCF) imputation was used to impute missing data; results using multiple imputations were similar.
BIW, twice weekly; CI, confidence interval; ETN, etanercept; QW, once weekly; sPGA, static physician global assessment; *n*, number of patients with sPGA status of clear/almost clear; *N*, number of patients with assessment.

adjunct therapy (PRISTINE) study compared patients who initiated etanercept at 50 mg BIW for 12 weeks and then received a maintenance dose of 50 mg QW (BIW/QW group) with patients who received the 50 mg QW dose (QW/QW group) throughout the study.[2] Patients were allowed to use any topical medication after week 12. At week 24, 59.9% in the QW/QW group and 78.2% of the BIW/QW group achieved PASI 75 response. Mean percentage improvement in the QW/QW and BIW/QW groups, respectively, was 58.5% and 74.1% at week 12 and 70.7% and 81.3% at week 24. Only 23% of patients receiving BIW/QW dosing and 28% of patients receiving QW/QW dosing elected to use topical medications through week 24. In contrast, 92% of patients in the etanercept+topical arm of our study used topical medications. This difference in rates of topical medication usage could be related to instructions provided to patients (topical medications were used as needed in PRISTINE, but were used as needed to clear in REFINE) and source of topical medications (provided by patients in PRISTINE and by the sponsor in REFINE).

Patients in the adalimumab in combination with topical Treatment [Calcipotriol/Betamethasone] in subjects with moderate to severe psoriasis and insufficient response to classic systemic treatment (BELIEVE) study received adalimumab with either topical calcipotriol betamethasone or vehicle for 4 weeks and then topical therapies as needed for 12 weeks.[6] A greater proportion of patients receiving adalimumab plus topical calcipotriol betamethasone achieved PASI 75 response at weeks 2 ($P < 0.001$) and 4 ($P = 0.02$), but patients on adalimumab monotherapy showed better clinical responses after week 4 through week 16. In contrast, patients in REFINE did not initiate topical therapy until they had received etanercept for 12 weeks and patients on etanercept monotherapy did not achieve greater clinical benefit than patients using topical medications.

Table 4 Percentage change in psoriasis-affected BSA

Mean percentage change in psoriasis-affected BSA* (95% CI)	ETN 50 mg BIW *N* = 140	ETN 50 mg QW + Topical *N* = 142	Treatment difference
Week 12 to week 16	18.8% (7.4%, 30.1%)	12.8% (1.6%, 24.1%)	5.9% (−10.1%, 21.9%)
Week 12 to week 20	22.9% (7.8%, 38.0%)	16.0% (1.1%, 31.0%)	6.9% (−14.4%, 28.1%)
Week 12 to week 24	15.6% (−4.4%, 35.6%)	10.7% (−9.3%, 30.7%)	4.9% (−23.4%, 33.2%)

*Least squares means from repeated measures models over postrandomization time points.
BIW, twice weekly; BSA, body surface area; CI, confidence interval; ETN, etanercept; QW, once weekly.

Table 5 Adverse events

	ETN* 50 mg BIW *N* = 144	ETN 50 mg QW + Topical† *N* = 143	Non-randomized‡ *N* = 23
All treatment-emergent AEs, *n* (%)	92 (63.9)	95 (66.4)	17 (73.9)
Serious AEs	1 (0.7)	0	3 (13.0)
Leading to DC from IP	1 (0.7)	0	10 (43.5)
Leading to DC from study	0	0	8 (34.8)
All treatment-related AEs, *n* (%)	39 (27.1)	34 (23.8)	10 (43.5)
Serious AEs	0	0	1 (4.3)
Leading to DC from IP	0	0	6 (26.1)
Leading to DC from study	0	0	6 (26.1)

*Patients received ETN 50 mg BIW for 12 weeks and continued on 50 mg BIW for 12 weeks.
†Patients received ETN 50 mg BIW for 12 weeks followed by 50 mg QW plus topical agents as needed to clear for 12 weeks.
‡Patients received ETN 50 mg BIW during the first 12 weeks, but discontinued the study before randomization to a treatment arm.
AEs, adverse events; BIW, twice weekly; DC, discontinuation; ETN, etanercept; IP, investigational product; QW, once weekly.

Together, these results support the use of topical medications in combination with TNF blocker therapies in patients with psoriasis.

A limitation of the study was the short duration of treatment (12 weeks of etanercept plus topical therapies), which may not accurately reflect long-term results as adherence with topical therapies may decrease with time.[7,8]

Treatment responses were similar between patients on etanercept 50 mg BIW and those on 50 mg QW who used topical medications as needed to clear. Patients who received the lower dose of 50 mg QW at week 12 and those who stayed on etanercept 50 mg BIW were both able to maintain their clinical response through week 24.

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