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ORIGINAL ARTICLE

Adalimumab treatment in Japanese patients with generalized pustular psoriasis: Results of an open-label phase 3 study

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ABSTRACT

A phase 3, multicenter, open-label, 52-week study investigated the efficacy and safety of adalimumab 80 mg at week 0 followed by adalimumab 40 mg every other week (option to escalate to 80 mg when necessary) in Japanese patients with generalized pustular psoriasis (GPP). Adults (aged 15–75 years) with GPP, total skin score (overall erythema area, erythema area with pustules, and edema area) of 3 or more, and erythema with pustules (skin score, ≥1) based on the 2014 Japanese Dermatological Association severity index of GPP were enrolled. The primary efficacy end-point was clinical response at week 16 (non-responder imputation), defined as achieving remission (total skin score, 0) or improvement from baseline (reduction of ≥1 point from a baseline total skin score of 3 or ≥2 points from a baseline total skin score of ≥4). Of 10 enrolled patients (mean disease duration, 10.6 years), seven patients, including three with the dose escalated to 80 mg every other week before week 15, achieved clinical response at week 16, and five achieved clinical response at week 52. Mean change from baseline total GPP score was −4.6 at week 16 (*n* = 8) and −6.0 at week 52 (*n* = 5); change in total skin score was −3.1 (*n* = 8) and −4.2 (*n* = 5), respectively. Nine patients experienced one or more adverse events and three experienced serious adverse events. The most common adverse events were nasopharyngitis, pruritus and hypoalbuminemia. In conclusion, adalimumab was effective and well tolerated for up to 52 weeks in the treatment of Japanese patients with GPP.

Key words: adalimumab, generalized pustular psoriasis, Japanese patient, prospective clinical trial, tumor necrosis factor-α inhibitor.

INTRODUCTION

Generalized pustular psoriasis (GPP) is the most severe type of psoriasis, characterized by pyrexia, skin redness over the entire body, and multiple sterile pustules occasionally leading to fatal systemic symptoms.[1] Among Japanese patients with psoriasis, only 2.3% were affected by GPP between 2009 and 2012.[2] Systemic treatments for GPP recommended by Japanese guidelines are limited to etretinate, cyclosporin, methotrexate and tumor necrosis factor-α (TNF-α) inhibitors.[3] Recently, the interleukin (IL)-17 inhibitors brodalumab, ixekizumab and secukinumab were approved to treat GPP in Japan.[4–6] Among the TNF-α inhibitors, only infliximab was approved to treat GPP in Japan at the time of this research, with approval granted in 2010.[7] Additional treatment options for GPP are needed.

Adalimumab has been shown to be efficacious in Japanese patients with moderate to severe chronic plaque psoriasis and is approved for that indication in Japan.[8,9] Case studies[10–12] and post-marketing surveillance[13] in Japan suggest that adalimumab may improve GPP; however, the efficacy of adalimumab for the treatment of GPP had not been previously tested in a prospective clinical trial. The objective of this study was to investigate the efficacy, safety and pharmacokinetics of adalimumab in Japanese patients with GPP.

METHODS

Study design

This was a phase 3, multicenter, open-label, 52-week study (ClinicalTrials.gov, NCT02533375; Fig. 1) of adalimumab 80 mg

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at week 0 followed by adalimumab 40 mg every other week (EOW; last dose at week 50) by s.c. injection, with the option to escalate to 80 mg EOW at week 8 or later if necessary to achieve a clinical response (CR). CR was defined as either remission (total skin score, 0) or improvement from baseline (reduction of ≥1 point from a baseline total skin score of 3 or ≥2 points from a baseline total skin score of ≥4) (Table 1) with reference to the Japanese Dermatological Association (JDA) severity index of GPP in the GPP Medical Practice Guideline 2014.[3] The 52-week treatment period was preceded by a 30-day screening period and followed by a 70-day follow-up period. The study was conducted at seven hospitals in Japan. Patients visited the clinic during screening, baseline (week 0), and at weeks 2 and 4 and then every 4 weeks through week 52, as well as at an unscheduled visit if they discontinued the study prematurely. The study drug was administrated either in the clinic or, after training for self-injection, in the patient's home.

The study was conducted in accordance with Good Clinical Practice, the Declaration of Helsinki and applicable regulations. The study protocol and associated documents were reviewed before the study by an institutional review board at each study site. All patients provided written informed consent before any study-related procedures.

Patients

Patients with GPP (15–75 years of age) diagnosed at least 60 days before screening, with a total skin score of 3 or more and erythema with pustules (skin score, ≥1), but total GPP score of less than 14 in the JDA severity index of GPP in the GPP Medical Practice Guideline 2014 were enrolled. Patients were required to have had an inadequate response to a prior approved treatment for GPP or to be intolerant of or have a contraindication to approved treatments; however, patients could have previously received infliximab if they had discontinued its use because of documented loss of response or development of intolerance. Female patients could not enroll if pregnant or breastfeeding and had to use effective contraception, unless they had no child-bearing potential during the study and for 150 days afterward. Eligible patients had no active tuberculosis, based on a laboratory test and chest X ray; any patients with latent tuberculosis were to complete 2 weeks or more of prophylactic treatment before baseline. All patients were tested for the presence of hepatitis B virus surface antigen or antibodies against the hepatitis B virus and were excluded if the test was positive. Patients with drug-induced GPP, erythrodermic psoriasis, guttate psoriasis, subcorneal pustular dermatosis or any active skin condition (other than footpad trichophytosis) that could have interfered with study assessments of GPP were ineligible for enrollment.

Cyclosporin was not allowed after week 8 of the study. A stable dose of concomitant etretinate (≤20 mg/day), methotrexate, azathioprine or salazosulfapyridine was permitted during the study. Oral corticosteroids were allowed at a dose of 10 mg/day or less at baseline but had to be discontinued by week 4. Patients could not receive psoralen plus ultraviolet A (PUVA) phototherapy, narrowband ultraviolet B (UVB) phototherapy or the "strongest" topical corticosteroids, such as clobetasol propionate and diflorasone diacetate (per Japanese classifications) for 14 days before baseline and during the study. Granulocyte and monocyte adsorption apheresis was not allowed within 28 days of baseline and during the study. Anti-TNF-α agents other than infliximab had to have been discontinued 28 days or more before baseline; infliximab had to have been discontinued more than 42 days before baseline. Any prior exposure to adalimumab was an exclusion criterion. Treatment of GPP with any investigational agents was prohibited for 28 days or five half-lives of the agent before baseline (whichever was longer) and during the study.

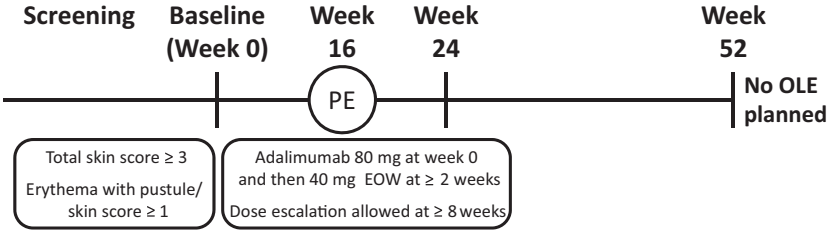

Figure 1. Study design. EOW, every other week; OLE, open-label extension; PE, primary efficacy end-point.

Table 1. Clinical response categories

Total skin score at baseline	Reduction in total skin score					Increase in total skin score
	Total skin score, 0	Δ≥3	Δ2	Δ1	Δ0	
4–9	Remission	Improvement	Improvement	Minimal Improvement	Unchanged	Worsened
3	Remission	Remission	Improvement	Improvement	Unchanged	Worsened

Shaded boxes indicate reductions in total skin score that define clinical response.

Ustekinumab was prohibited during the study and for 84 days before baseline.

Assessments

Efficacy

The total skin score, systemic/laboratory score, Physician Global Assessment (PGA) and Psoriasis Area and Severity Index (PASI) were assessed at clinic visits at screening; baseline (week 0); weeks 2, 4, 8, 12, 16, 24, 36 and 52; and at any unscheduled visit due to premature study discontinuation. The Dermatology Life Quality Index (DLQI) and 36-Item Short Form Health Survey (SF-36) scores were assessed at baseline (week 0) and weeks 8, 16, 24, 36 and 52 or at premature study termination.

The total skin score ranges from 0 (none) to 9 (severe) (Table 2) and includes three components (overall erythema area, erythema area with pustules, and edema area), each based on measurements in four anatomical areas that are summed to give the total affected body surface area (head [including neck, 10%], upper extremities [20%], trunk [including axillae and genitals, 30%] and lower extremities [including buttocks, 40%]).[3] The systemic/laboratory score ranges from 0–8 and has four components: pyrexia, white blood cell (WBC) count, C-reactive protein (CRP) concentration and serum albumin concentration (Table 2). The total GPP score is the sum of the total skin score and the systemic/laboratory score, and therefore has a range of 0–17. The total GPP score is categorized by the JDA severity index as follows: mild (0–6), moderate (7–10) and severe (11–17) (Table 2).

The PGA in this study was scored by the investigator, based on the degree of erythema, edema and pustulation, on a 6-point scale ranging from 0 (no evidence) to 5 (most severe). The score for each of the three skin symptoms was averaged to give a mean PGA score of 0 (clear), 1 (minimal), 2 (mild), 3 (moderate), 4 (severe) or 5 (very severe).

The DLQI[14] and SF-36 version 2[15,16] were completed by the study patients. The DLQI is a 10-item instrument for which the answer to each question about the effect of skin problems may be 0 ("not relevant" or "not at all"), 1 ("a little"), 2 ("a lot") or 3 ("very much"); the total DLQI may range from 0 (best) to 30 (worst). The SF-36 is a 36-item instrument that assesses health and well-being, including physical and mental components; each score is scaled to a range from 0 (worst) to 100 (best).

Safety

Safety was assessed by adverse events (AEs), vital signs and laboratory findings. AEs were collected throughout the study and until 70 days after discontinuation of adalimumab administration and were coded with the Medical Dictionary for Drug Regulatory Activities (MedDRA®) version 19.1. Study investigators rated the severity of each AE and recorded their opinion of whether it had a reasonable possibility of being related to study treatment. Vital signs were measured at every clinic visit. Laboratory tests were conducted at screening; baseline (week 0); weeks 2, 4, 8, 12, 16, 24, 36 and 52; and any unscheduled visit due to premature study discontinuation. Laboratory abnormalities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, translated into Japanese by the Japan Clinical Oncology Group (version 9 April 2013).

Pharmacokinetics and immunogenicity

Blood samples for analysis of adalimumab concentrations in serum were taken at baseline (week 0); weeks 2, 4, 8, 12, 16, 24, 36 and 52; and any unscheduled visit due to premature study discontinuation. Blood samples for analysis of anti-adalimumab

Table 2. Severity assessment criteria from the Medical Practice Guideline for generalized pustular psoriasis[3]

Evaluation of skin score (0–9)†				
	Severe	Moderate	Mild	None
Erythema area (overall)‡	3	2	1	0
Erythema area with pustules§	3	2	1	0
Edema area§	3	2	1	0

Evaluation of systemic/laboratory test score (0–8)¶			
Score	2	1	0
Pyrexia, °C	≥38.5	<38.5 to ≥37	<37
White blood cell count, per μL	≥15 000	>15 000 to ≥10 000	<10 000
CRP, mg/dL	≥7.0	>7.0 to ≥0.3	<0.3
Serum albumin, g/dL	<3.0	3 to <3.8	≥3.8

Total GPP score†† and JDA severity index of GPP			
	Severe (11–17)	Moderate (7–10)	Mild (0–6)

†Skin score (total skin score) is defined as the sum of the scores for the three components. ‡Percentage of body surface area (severe, ≥75%; moderate, ≥25% to less than 75%; mild, <25%). §Percentage of body surface area (severe, ≥50%; moderate, ≥10% to less than 50%; mild, <10%). ¶Systemic/laboratory test score is defined as the sum of the scores for the four components. ††Total GPP score is defined as skin score + systemic/laboratory test score. CRP, C-reactive protein; GPP, generalized pustular psoriasis; JDA, Japanese Dermatological Association.

antibodies (AAAs) were collected at baseline; weeks 8, 16, 24, 36 and 52; and any unscheduled visit due to premature study discontinuation. Additional blood samples were taken directly before any dose escalation. Blood samples were drawn before any dosing with adalimumab at the clinic visit.

Trough concentrations of adalimumab in serum were analyzed by a study sponsor affiliate (AbbVie Deutschland, Ludwigshafen, Germany) using a validated electrochemiluminescence immunoassay. The lower limit of quantitation (LLOQ) was 50 ng/mL in undiluted serum or 5 ng/mL in 10-fold diluted serum. The assay included quality control samples supplemented with adalimumab 7.50, 375 or 750 ng/mL. The coefficients of variation were 4.7% or less, and the mean analytical bias ranged from 3.2–12.5% of the theoretical values.

Concentrations of AAAs were analyzed by the same facility (AbbVie Deutschland) if the adalimumab concentration in serum was 2 μg/mL or less. AAAs were detected with a validated double-antigen immunoassay. The LLOQ was 10.3 ng/mL in undiluted serum. The assay included quality control standards (rabbit AAAs) with concentrations of 3, 10 and 20 ng/mL. The coefficients of variation were 14.9% or less, and the mean analytical bias ranged between −8.5% and 4.0% of the theoretical values. Tests to confirm the specificity of AAAs were performed for samples with an initially detected concentration of 20 ng/mL or more.

Statistical analysis

The primary efficacy end-point was achieving CR at week 16, using non-responder imputation; CR was defined as either remission (total skin score, 0) or improvement from baseline (reduction of ≥1 point from a baseline total skin score of 3 or ≥2 points from a baseline total skin score of ≥4) (Table 1). Other efficacy end-points over time, using observed data, included the following: the categorical end-points of proportions of patients achieving CR; remission; PGA of clear or minimal; JDA severity score improvement of one grade or more; and improvement in PASI of 50% or more, 75% or more, or 90% or more (PASI-50, PASI-75 and PASI-90, respectively); and the continuous end-points of changes from baseline in total GPP score, total skin score and its components, systemic/laboratory score and its components, PASI, DLQI and SF-36 score.

The efficacy analysis included all patients who complied with Good Clinical Practice, received one dose or more of adalimumab and had one or more post-treatment efficacy assessments. The safety analysis included all patients who received one or more doses of adalimumab. Efficacy and safety were also analyzed in the subgroups of patients who had dose escalation or AAAs. The primary efficacy end-point was also analyzed in patients based on prior exposure to infliximab. The pharmacokinetic analysis included all patients who received one or more doses of adalimumab and had one or more post-dose samples for the determination of adalimumab serum concentration.

A population sample size of 10 patients was chosen to provide 91.2% power, assuming a 50% response rate for the primary efficacy end-point, to detect the difference from a 10% threshold response rate, using a one-sample χ^2-test for a one-sided significance level of 2.5%. However, no statistical testing was planned. Descriptive statistics were calculated for demographic characteristics, baseline disease measures, and assessments of efficacy and safety. Concentrations of adalimumab were summarized from week 16 to week 52; AAA concentrations by week 52 were listed by the patient. All analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient disposition and characteristics

A total of 10 patients with GPP were enrolled and received adalimumab; the median compliance with planned injections

Table 3. Demographic and baseline disease characteristics

Characteristic	Patients (n = 10)
Men, *n* (%)	7 (70)
Age, mean ± SD, years	49.8 ± 13.3
Weight, mean ± SD, kg	70.7 ± 12.5
GPP duration, mean ± SD, years	10.6 ± 12.6
Prior treatments for GPP, *n* (%)	
PUVA	1 (10)
Narrowband UV-B	2 (20)
GMA	2 (20)
Infliximab	3 (30)
Total GPP score, mean (range)	7.5 (5–11)
Total skin score	5.5
Erythema score	2.2
Erythema with pustules score	1.7
Edema score	1.6
Systemic/laboratory test score	2.0
Pyrexia score	0.3
WBC score	0.5
hs-CRP score	0.9
Serum albumin score	0.3
JDA severity index of GPP, *n* (%)	
Mild	3 (30)
Moderate	6 (60)
Severe	1 (10)
PASI, mean ± SD	28.3 ± 16.0
PGA, *n* (%)	
Clear	0
Minimal	0
Mild	4 (40)
Moderate	3 (30)
Severe	3 (30)
Very severe	0
DLQI, mean ± SD	10.8 ± 5.1
SF-36, mean ± SD	
Physical Component Summary	36.0 ± 12.2
Mental Component Summary	43.8 ± 9.5

DLQI, Dermatology Life Quality Index; GMA, granulocyte and monocyte absorbent apheresis; GPP, generalized pustular psoriasis; hs-CRP, high-sensitivity C-reactive protein; JDA, Japanese Dermatological Association; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; PUVA, psoralen plus ultraviolet A; SD, standard deviation; SF-36, 36-Item Short Form Health Survey; UV-B, ultraviolet B; WBC, white blood cell.

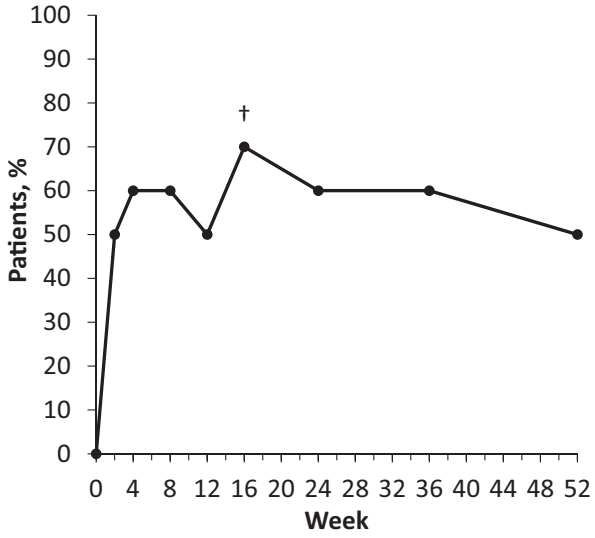

Figure 2. Clinical response. †Primary efficacy end-point was clinical response, defined as remission (total skin score, 0) or reduction of 1 point or more if baseline total skin score was 3, or 2 points or more if baseline total skin score was 4 or more, at week 16. Non-responder imputation.

was 100%. Five (50%) of the 10 enrolled patients completed the study through week 52; three patients discontinued prematurely because of lack of efficacy and two discontinued prematurely because of AEs. All 10 patients were included in the analyses of efficacy and safety. The eight patients with pharmacokinetic data at week 16 and beyond were included in the analyses of pharmacokinetics.

Most patients were men, with a mean age of 50 years (range, 22–70), and patients had a mean GPP duration of more than 10 years; four patients had received prior treatments, and most patients (60%) had moderate or severe GPP (Table 3). During this study, seven patients (70%) took one or more concomitant systemic medications to treat GPP (etretinate, $n = 3$; cyclosporin, $n = 2$; methotrexate, $n = 2$; oral corticosteroids, $n = 1$) and seven patients (70%) required topical corticosteroids to treat GPP.

Efficacy

Primary end-point

Seven patients (70% [95% confidence interval, 34.8–93.3%]) achieved the primary efficacy end-point of CR at week 16. CR rates reached 50% at week 2 and remained approximately stable thereafter through week 52 (Fig. 2). Five patients

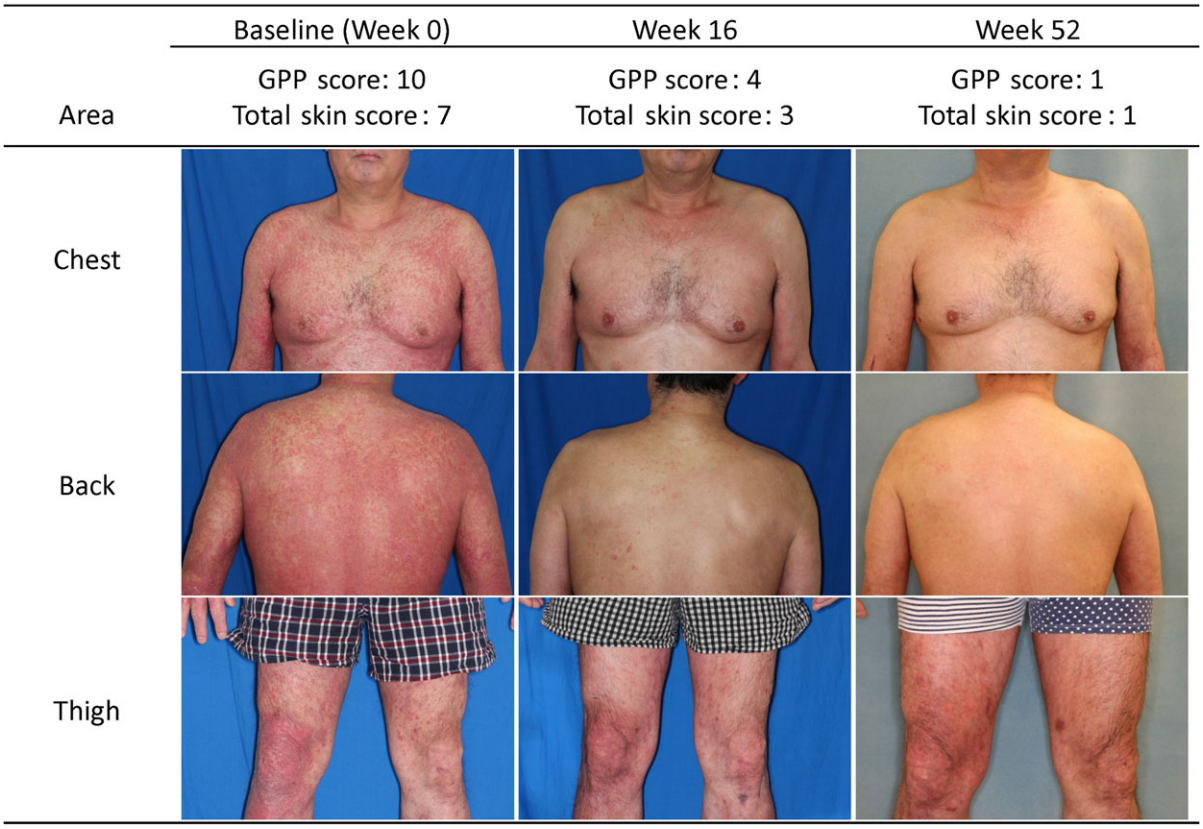

Figure 3. Skin lesions in a representative patient at baseline, week 16 and week 52. GPP, generalized pustular psoriasis.

increased their dose to adalimumab 80 mg EOW on or after week 8, and four of them before week 16; three of these four patients achieved CR at week 16. The one remaining patient discontinued the study before week 16. Of the three patients who previously received infliximab, two (67%) achieved CR at week 16; the one remaining patient discontinued the study because of lack of efficacy prior to week 16. Figure 3 shows skin lesions in a typical patient at baseline, week 16 and week 52.

Secondary end-points

The PASI-50 response rates increased between baseline and approximately week 4, then stabilized; PASI-75 and PASI-90 response rates increased more gradually (Fig. 4a). PGA and JDA response rates (Fig. 4b,c respectively) increased between baseline and approximately week 4, then stabilized. Total skin score, systemic/laboratory test score and total GPP score decreased from baseline until approximately week 4, then slowly decreased through week 52 (Fig. 5a). One patient achieved remission (i.e. total skin score, 0) at week 4. Components of the total skin score changed over time in parallel, with the greatest improvement in erythema with pustules, followed by edema and overall erythema (Fig. 5b). WBC count and high-sensitivity CRP levels improved over time, whereas pyrexia and serum albumin levels (whose scores were already low at baseline; Table 3) returned to baseline levels after small decreases at weeks 2 and 4 (Fig. 5c).

The PASI as a percentage of baseline values decreased rapidly during weeks 2 and 4, then remained approximately stable (Fig. 6a). DLQI and SF-36 scores (Fig. 6b,c respectively) improved from baseline to approximately week 16 and week 24, respectively, and were somewhat variable afterward. The Physical Component Summary of the SF-36 improved, on average, to a greater extent than the Mental Component Summary (Fig. 6c); the Physical Component Summary was more impaired than the Mental Component Summary at baseline (Table 3).

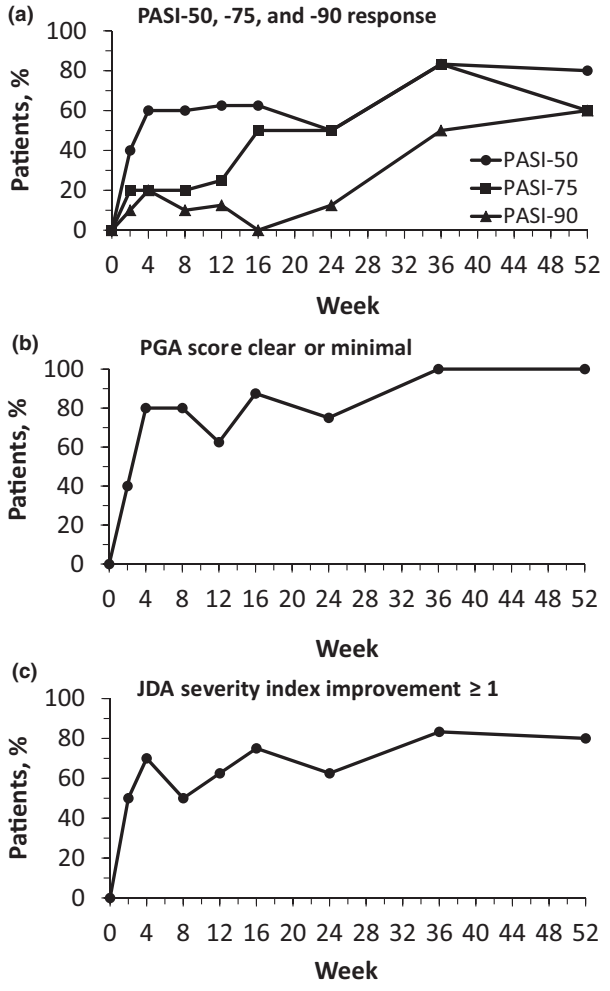

Figure 4. (a) PASI, (b) PGA and (c) JDA responses. Observed data. Responses defined as improvement from baseline in PASI of 50% or more (PASI-50), 75% or more (PASI-75) or 90% or more (PASI-90); achievement of 0/1 score (clear/minimal) in PGA; and improvement from baseline of one grade or more in JDA severity index. JDA, Japanese Dermatological Association; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment.

Safety

Nine patients (90%) experienced one or more AEs, and three (30%) had serious AEs (Table 4). Most patients (7/10, 70%) had only mild or moderate AEs; two patients had severe AEs. Two patients (20%) discontinued the study because of AEs. Seven patients (70%) had infections, of which two were serious. There were no AEs of opportunistic infection, tuberculosis, hepatitis B reactivation, malignancy, myocardial infarction, injection site reaction and death. The most common AEs were nasopharyngitis (n = 3), pruritus (n = 3) and hypoalbuminemia (n = 2).

Two of the three patients with serious AEs discontinued from the study prematurely as a result. One patient, a woman aged 55 years, experienced moderate bacterial enterocolitis, with a reasonable possibility of being related to adalimumab, and severe worsening of pustular psoriasis, considered unrelated to adalimumab. The AE of bacterial enterocolitis began on study day 47, adalimumab was withheld starting on day 64, and the patient was hospitalized on day 69. On day 82, the patient experienced worsening of GPP; on day 92, she was treated again with adalimumab, but the exacerbation of GPP continued, eventually leading to premature study discontinuation. A second patient, a man aged 70 years with a history of congestive heart failure (New York Heart Association Class II),[17] hypertension, diabetes mellitus, atrial fibrillation and coronary artery stenosis, experienced serious AEs of severe dehydration, cardiac failure and renal failure that were all considered unrelated to adalimumab and resulted in hospitalization. The serious AE of renal failure resulted in premature study discontinuation. A third patient, a man aged 22 years with a history of chronic sinusitis, experienced a serious AE of chronic sinusitis with moderate severity. On day 161 of the

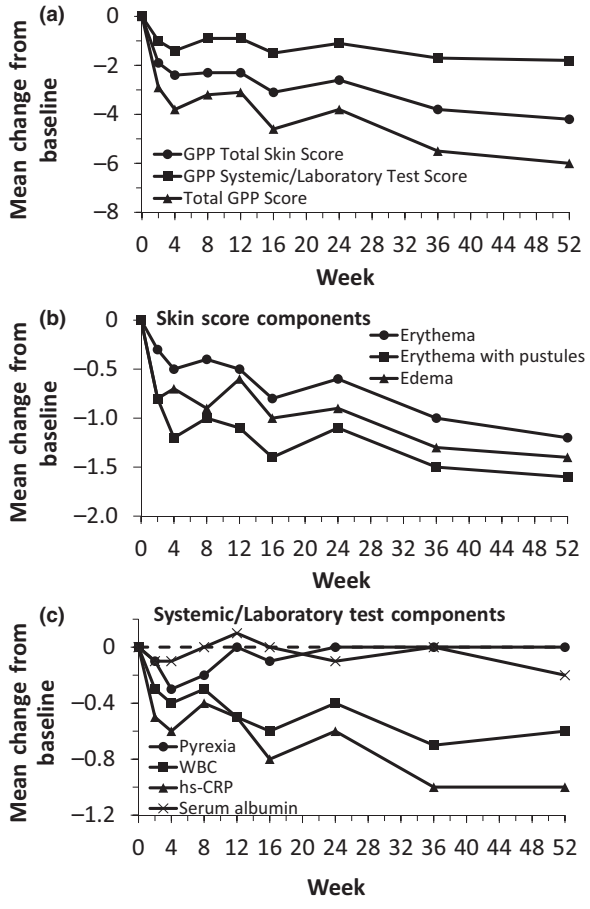

Figure 5. Change from baseline in (a) total skin score, systemic/laboratory test score and total GPP score; (b) skin score components; and (c) systemic/laboratory test score components. The values in (c) represent score components and not the actual systemic/laboratory test measurements. Observed data. GPP, generalized pustular psoriasis; hs-CRP, high-sensitivity C-reactive protein; WBC, white blood cell.

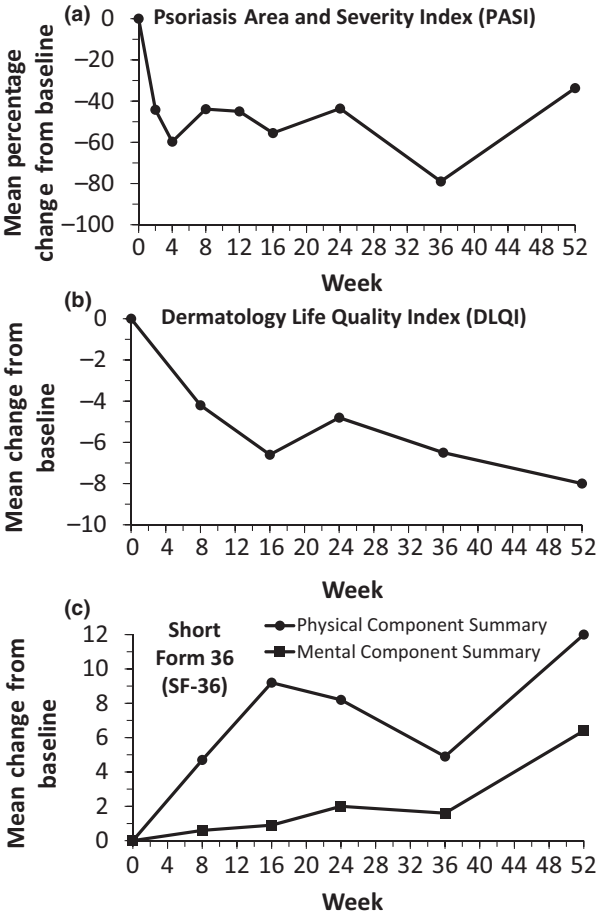

Figure 6. Percentage change from baseline in (a) PASI and change from baseline in (b) DLQI and (c) SF-36 Physical and Mental Component Summaries. Observed data. DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; SF-36, 36-Item Short Form Health Survey.

study treatment period, the patient underwent planned surgery to treat chronic sinusitis; he continued in the study and the AE was considered unrelated to adalimumab.

There were no clinically meaningful changes in mean laboratory values; shifts in laboratory values were sporadic and not clinically meaningful overall. No patients had hematology abnormalities of grade 3 or more during the study. Three patients had clinical chemistry abnormalities of grade 3 or more during the study. One patient had grade 3 hypocalcemia and grade 3 hypoalbuminemia on study day 92, which improved to grade 2 by day 106; this patient discontinued the study because of the serious AE of severe pustular psoriasis. A second patient had grade 3 hypertriglyceridemia at baseline, which increased to grade 4 at day 15, decreased to grade 3 at day 29, and then remained at grade 2 or 1 for the rest of the study and follow up (through day 365). The third patient had grade 3 high creatinine levels during post-treatment days 27–55 while receiving diuretics to treat the serious AE of renal failure, which resulted in discontinuation. Two patients had potentially clinically significant liver function abnormalities during the study. One patient had elevated alanine aminotransferase at baseline that persisted during most of the treatment period but was no longer elevated at post-treatment day 12. The same patient had elevated aspartate aminotransferase at days 29 and 57 and elevated bilirubin levels at baseline; both parameters normalized by day 85. The second patient had elevated alanine aminotransferase and aspartate aminotransferase at baseline, both of which normalized by day 106.

Dose escalation did not appear to affect the safety profile of adalimumab in this study.

Pharmacokinetics and immunogenicity

In the overall pharmacokinetic population, the mean concentrations of adalimumab in serum were 6–10 μg/mL between

weeks 16 and 52 (Table 5). The concentrations of adalimumab were 8–23 μg/mL in patients who had dose escalation and 4–7 μg/mL in patients without dose escalation; however, only one of the three patients with dose escalation continued in the study past week 24 and provided data for analysis of adalimumab concentrations for all time points. Three patients were positive for AAAs, one of whom discontinued the study before week 24 and so had no data for analysis of adalimumab concentrations. Serum adalimumab concentrations in patients with AAAs were low. Two of three patients with AAAs achieved CR at week 16; one of these patients completed the study and maintained CR, and the other two patients discontinued the study (before weeks 24 and 36). The number of patients with AAAs was too small to identify any effects on safety.

Table 4. Safety

Adverse event, *n* (%)	Patients (*n* = 10)
Any AE	9 (90)
Serious AE	3 (30)[†]
AE leading to discontinuation of adalimumab	2 (20)[‡]
Infection	7 (70)
Serious infection	2 (20)[†]
Congestive heart failure	1 (10)[§]
Worsening or new onset of psoriasis	2 (20)[¶]
Liver failure or other liver event	1 (10)[††]
AE in more than one patient	
Nasopharyngitis	3 (30)
Pruritus	3 (30)
Hypoalbuminemia	2 (20)

[†]Bacterial enterocolitis (reasonable possibility to be related to adalimumab) and worsening of pustular psoriasis (considered unrelated to adalimumab) in one patient; chronic sinusitis (considered unrelated to adalimumab) in one patient; dehydration, cardiac failure and renal failure (all considered unrelated to adalimumab) in one patient. [‡]Pustular psoriasis (considered unrelated to adalimumab) in the patient with bacterial enterocolitis, during a period of no treatment with adalimumab (treatment was restarted 10 days later); renal failure (considered unrelated to adalimumab) in the patient with dehydration and cardiac failure. [§]Male patient, age 70 years, with a history of congestive heart failure (New York Heart Association Class II), hypertension, diabetes mellitus and coronary artery stenosis (AE considered unrelated to adalimumab). [¶]Psoriasis (considered unrelated to adalimumab) in one patient; serious pustular psoriasis (considered unrelated to adalimumab) in one of the patients who discontinued. [††]Hepatic steatosis (considered unrelated to adalimumab) in one patient. AE, adverse event.

DISCUSSION

This was the first study to prospectively study the efficacy, safety and pharmacokinetics of the TNF-α inhibitor adalimumab for the treatment of Japanese patients with GPP. Forty percent of the patient population had received prior treatment for GPP, and 30% had previously received infliximab. In this study, adalimumab 40 mg EOW was effective in improving the symptoms of GPP and increasing quality of life. Escalation of the adalimumab dose to 80 mg EOW appeared to be a successful approach to achieving CR when the initial dose was insufficient. The efficacy of adalimumab in two of the three patients with prior treatment with infliximab suggests that switching to a different TNF-α inhibitor when the first is not effective is a feasible treatment strategy. The safety of adalimumab in the present study was in line with expectations from prior trials in larger populations of Japanese patients with psoriasis. Three patients developed AAAs, but there was not a clear relationship between AAAs and efficacy and safety.

The CR rate increased rapidly after baseline, thereafter remaining in the range of approximately 50–70%, in line with the anticipated 50% response rate by week 16. Other efficacy end-points followed a similar pattern over time, although achievement of the more stringent PASI-75 and PASI-90 responses followed a slower time course. The final PASI response rates and mean improvement in PASI in the present study were consistent with the results from prior studies in Japanese patients with psoriasis treated with adalimumab 40 mg EOW.[8,13,18] GPP skin symptoms improved more than systemic/laboratory tests; however, decreases in WBC counts and high-sensitivity CRP levels suggested a reduction in systemic inflammation. Patient quality of life improved, both in

Table 5. Concentrations of adalimumab in serum at weeks 16, 24, 36 and 52

	Mean ± SD (range) adalimumab concentration, μg/mL			
Analysis group	Week 16	Week 24	Week 36	Week 52
All patients (*n* = 8)	*n* = 8	*n* = 7	*n* = 5	*n* = 5
	5.7 ± 4.8 (0–13.5)	7.4 ± 6.5 (0–16.8)	9.2 ± 8.2 (0–22.5)	10.0 ± 8.7 (0–23.4)
By dose escalation[†]				
Yes (*n* = 3)	*n* = 3	*n* = 3	*n* = 1	*n* = 1
	7.8 ± 7.0 (0.1–13.5)	10.4 ± 9.0 (0.1–16.8)	22.5	23.4
No (*n* = 5)	*n* = 5	*n* = 4	*n* = 4	*n* = 4
	4.4 ± 3.4 (0–8.8)	5.0 ± 3.9 (0–9.3)	5.8 ± 4.0 (0–8.8)	6.7 ± 5.1 (0–12.2)
By presence of AAAs				
Yes (*n* = 2)	*n* = 2	*n* = 2	*n* = 1	*n* = 1
	0.04 (0–0.1)	0.1 ± 0.1 (0–0.1)	0	0
No (*n* = 6)	*n* = 6	*n* = 5	*n* = 4	*n* = 4
	7.6 ± 4.9 (2.8–13.5)	10.3 ± 5.2 (4.7–16.8)	11.5 ± 7.4 (7.3–22.5)	12.5 ± 7.6 (6.4–23.4)

[†]Dose escalation occurred at or after week 8. AAA, anti-adalimumab antibody; SD, standard deviation.

terms of skin-specific aspects (DLQI) and general condition (SF-36), particularly the Physical Component Summary of the SF-36.

The incidence and patterns of AEs in this study were not unexpected considering the 1-year length of the study and the complications that may arise from GPP itself. Three patients experienced serious AEs, but only one such event was considered to have a reasonable possibility of being related to adalimumab, and that particular event (moderate bacterial enterocolitis) did not lead to discontinuation. Although seven of 10 patients had infections, only two had serious infections, and only one (bacterial enterocolitis) was considered to be possibly related to adalimumab. Overall, the AE profile in the present study did not appear to differ substantially from that of adalimumab in previous studies in Japanese patients with psoriasis.[8,13,18]

In recent years, biologic agents (most commonly the TNF-α inhibitors infliximab and adalimumab and the IL-12 and -23 inhibitor ustekinumab) have been used more to treat psoriasis in Japan.[2] Other than the present clinical trial, only one other study has prospectively examined a biologic agent (the IL-17 inhibitor secukinumab) solely for the treatment of Japanese patients with GPP ($n = 12$).[19] Several studies in Japanese patients with various types of psoriatic disease included a subgroup with GPP, including two studies with infliximab ($n = 7$ in each study),[20,21] and one study each with the IL-17 inhibitors brodalumab ($n = 12$)[22] and ixekizumab ($n = 5$).[23] However, as with the present study, all of these trials had small populations, were open-label, and did not include a control group, thus limiting the ability to compare results.

Strengths of the present study include the prospective design focusing on a well-defined population of Japanese adult patients with confirmed GPP, a wide range of patient ages and treatment for up to a full year. The major limitation of the study was its open-label, single-treatment design without a comparator treatment; this could have led to bias, especially for subjectively scored end-points. However, the observed response for the primary end-point was approximately in line with expectations from calculations used to determine the sample size (70% vs 50%, respectively), and improvement was replicated across a variety of different efficacy end-points. Furthermore, the improvements with adalimumab were seen despite 40% of patients having received other prior treatments with inadequate results. As planned, the study population was small because of the low prevalence of GPP in Japan, as in other studies already noted. The study enrolled few women, which again was a result of the low frequency of GPP in that population. The results of this study may not be applicable to treatment lasting more than 1 year; however, because adalimumab has been approved to treat psoriasis in Japan since 2010,[24] there is already considerable experience with its long-term efficacy and safety, unlike the situation with newer biologic agents. The results of the present study may not be extended to pediatric patients or those who are not Japanese.

In conclusion, this study demonstrated that adalimumab was effective and well tolerated for up to 52 weeks in the treatment of Japanese patients with GPP, even in those who had not been responding to previous infliximab treatment, and no new safety risks were identified.

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