MABp1 Targeting IL-1α for Moderate to Severe Hidradenitis Suppurativa Not Eligible for Adalimumab: A Randomized Study

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Patients with moderate to severe hidradenitis suppurativa failing adalimumab therapy, or those ineligible to receive it, remain a population with an unmet need. Twenty patients not eligible for adalimumab were randomized to receive 12 weeks of blind treatment with placebo or MABp1, a true human antibody targeting IL-1α. Hidradenitis suppurativa clinical response score at week 12 was the primary endpoint. The primary endpoint was met in 10% and 60% of placebo- and MABp1-treated patients, respectively (odds ratio = 13.50, 95% confidence interval = 1.19–152.51). Clinical efficacy was maintained at 24 weeks in 0% and 40%. Improvement in the visual analog scale was reported by 20% and 85.7%, respectively, of patients failing previous anti-TNF treatment. Ultrasonography showed decreased neovascularization and lesion skin depth in the MABp1 group. MABp1 treatment was associated with decrease of circulating IL-8 and of stimulated production of IL-8 by whole blood. Whole blood production for hBD-2 was negatively associated with changes on ultrasonography in the placebo group but not in the MABp1 group. MABp1 is a promising treatment for patients with hidradenitis suppurativa not eligible for adalimumab. Inhibition of neovascularization and modulation of the production of IL-8 and hBD-2 are suggested mechanisms of action.

Journal of Investigative Dermatology (2018) **138,** 795–801; doi:10.1016/j.jid.2017.10.030

INTRODUCTION

Hidradenitis suppurativa (HS) is increasingly being recognized as a common condition. A large epidemiological survey in France has reported 0.97% disease prevalence (Révuz et al., 2008). The two PIONEER studies that led to the registered indication of adalimumab for the treatment of moderate to severe HS used the HS Clinical Response (HiSCR) score after 12 weeks as the primary efficacy outcome (Kimball et al., 2016). The HiSCR takes into account the total inflammatory lesion count, that is, the sum of inflammatory nodules and abscesses of the body. A positive HiSCR score is defined as at least a 50% decrease of the total inflammatory lesion count from the baseline before start of treatment and the absence of new abscess or fistula formation (Kimball et al., 2014). Positive HiSCR score with adalimumab was reported in 41.8% of patients in the PIONEER I study and 58.9% of patients in the PIONEER II study (Kimball et al., 2016). Analysis of both studies showed loss of efficacy at the range of 50% after 36 weeks of treatment. These data highlight the need for the development of additional therapies, because many patients will experience primary or secondary failure of adalimumab.

IL-1β and IL-1α were increased in the pus of the lesions of all Hurley III-stage HS patients (Kanni et al., 2015), providing evidence for the participation of IL-1α in the inflammatory process of HS. Excess release of preformed IL-1α from the cytosol of damaged or stressed cells leads to the recruitment of hematopoietic cells to the site of the inflammation through endothelial activation and disruption of the vascular wall (Dinarello et al., 2012; Di Paolo & Shayakhmetov, 2016). In a recent small-scale, double-blind, randomized clinical trial, daily treatment with 100 mg of anakinra that blocks both IL-1β and IL-1α for 12 weeks led to a positive HiSCR score in 7 of 9 patients, compared with 3 of 10 patients treated with placebo (Tzanetakou et al., 2016).

MABp1 is a first-in-class true human monoclonal antibody cloned directly from human B lymphocytes that specifically targets and neutralizes IL-1α. In a large pivotal randomized phase III trial in metastatic colorectal cancer treatment, MABp1 resulted in improvement of cancer-associated symptoms, including muscle loss, fatigue, anorexia, and pain in 33% of patients, compared with 19% of placebo-treated comparators (Hickish et al., 2017). Additionally, there were no obvious toxicities observed. The observed efficacy of anakinra in HS and the elevated concentrations of IL-1α in the lesions generate the hypothesis that MABp1 may also be a promising agent for patients with HS, including those who are not eligible for treatment with adalimumab.

The purpose of this clinical study was to evaluate the safety and the efficacy of MABp1 compared with placebo in patients with moderate to severe HS for whom initial treatment with agents blocking TNF-α had failed or who, although

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Abbreviations: AE, adverse event; CI, confidence interval; HiSCR, hidradenitis suppurativa clinical response score; HS, hidradenitis suppurativa; OR, odds ratio; SAE, serious adverse event

Received 30 April 2017; revised 25 October 2017; accepted 26 October 2017; accepted manuscript published online 10 November 2017; corrected proof published online 17 February 2018

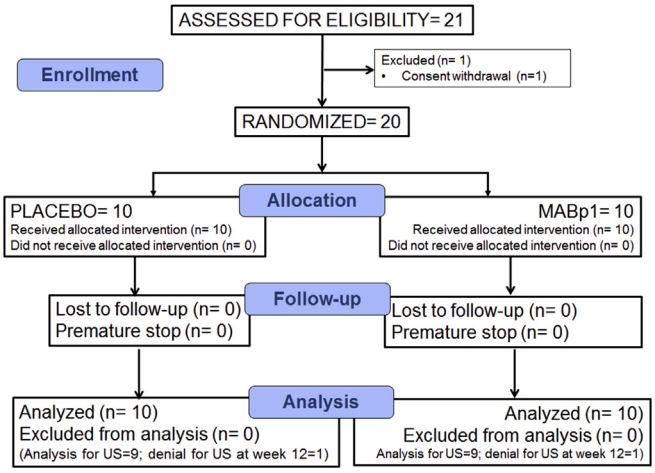

Figure 1. Study flow chart. US, ultrasonography.

treatment naïve, could not receive adalimumab treatment because of a contraindication.

RESULTS

Participant flow

The study was conducted between December 2015 and January 2017. The trial ended at the end of follow-up of the last patient. The study flow chart is shown in Figure 1. Ten patients were allocated to placebo and 10 to MABp1. Baseline characteristics are provided in Table 1. Follow-up ultrasonographic assessment was available for nine patients in each arm. Ultrasonographic findings showed patients assigned to receive MABp1 to have more severe disease than those in the placebo group. Expanded baseline characteristics, including affected skin areas, are provided in Supplementary Table S1 online.

Analysis: Primary study endpoint

Sixty percent of patients allocated to treatment with MABp1 achieved positive HiSCR at week 12 compared with 10% of the placebo group (Figure 2a). The odds ratio (OR) for positive HiSCR under MABp1 was 13.50 (95% confidence interval [CI] = 1.19−152.51; P = 0.035). The total inflammatory lesion count, which is the basic component of the HiSCR score, was decreased during the first 12 weeks of treatment (Figure 2b).

Analysis: Secondary endpoints

The clinical efficacy of MABp1 was maintained until week 24, that is, 12 weeks after stop of treatment. At that time point, no patients treated with placebo had a positive HiSCR score (0%), compared with 4 out of 10 patients (40%) treated with MABp1. Treatment with MABp1 was also accompanied by better patient-reported outcomes. Decrease of the visual analog scale score was found in 30% (3 of 10) and in 70% (7 of 10) allocated to placebo and MABp1, respectively. Subanalysis showed that this was 40% (2 of 5) and 33.3% (1 of 3), respectively, among anti-TNF−naïve patients and 20% (1 of 5) and 85.7% (6 of 7) of patients for whom previous treatment with anti-TNF had failed.

The median time to the first HS exacerbation was 7 weeks in the placebo group and 11 weeks in the MABp1 group. This time did not differ significantly between groups (log-rank = 1.98, P = 0.159). However, when subanalysis was done among anti-TNF−naïve patients, it was found that the median time until a new HS exacerbation was 4 weeks with placebo treatment and 18.5 weeks with MABp1 treatment (log rank test = 4.46, P = 0.035).

In one previous randomized clinical trial, decrease of disease activity was considered as a significant outcome (Tzanetakou et al., 2016). That decrease was found in all patients treated with MABp1 and who achieved positive HiSCR at weeks 12 and 24 (Table 2). The changes of all assessed scores in relation to previous exposure to anti-TNFs are shown in Supplementary Figures S1−S3 online. Decrease of at least two of the assessed scores (Physician Global Assessment, disease activity, modified Sartorius score, visual analog scale for pain, and Dermatology Life Quality Index) at week 12 was found in 40% of patients allocated to placebo and 80% of patients allocated to MABp1 (80%) (OR = 14.50, 95% CI = 0.96−218.99, P = 0.054). Subanalysis showed that this occurred in 60% (3 of 5) and 100% (3 of 3), respectively, of anti-TNF−naïve patients and 20% (1 of 5) and 71.4% (5 of 7) among patients for whom previous treatment with anti-TNFs had failed.

Significant changes in variables on skin ultrasonography included total lesion vascularity and total lesion depth, which is the sum of the grading of vascularity and the sum of the greatest depth of all involved skin areas, respectively. Both variables were decreased after treatment with MABp1 (Figure 3a and b). More than 20% decrease of total lesion depth was selected as a cutoff point (see Supplementary Figure S4 online), and it was found in 22.2% of patients allocated to placebo compared with 77.8% of patients treated with MABp1 (OR = 12.25, 95% CI = 1.33−113.06, P = 0.027). The effect was pronounced among patients for

Table 1. Baseline characteristics of enrolled patients

Characteristics	Placebo (n = 10)	MABp1 (n = 10)	*P*-Value
Reason for study enrolment, n (%)			
Primary failure of anti-TNFs	2 (20)	5 (50)	—
Secondary failure of anti-TNFs	3 (30)	2 (70)	—
Could not receive anti-TNFs	5 (50)	3 (30)	0.612[1]
History of tumor	1 (10)	1 (10)	—
Unwillingness to self-inject	4 (40)	2 (20)	—
Baseline disease severity			
Hurley stage II/III, n/total	2/8	0/10	0.474[1]
DLQI, mean ± SD	21.2 ± 4.8	20.0 ± 7.2	0.666[2]
VAS in mm, mean ± SD	55.0 ± 28.4	77.0 ± 36.5	0.150[2]
VAS for pain in mm, mean ± SD	48.0 ± 37.6	74.0 ± 34.6	0.130[2]
Disease activity, mean ± SD	228.1 ± 154.9	298.7 ± 125.3	0.277[2]
Modified Sartorius score, mean ± SD	124.9 ± 73.7	195.6 ± 97.9	0.085[2]
PGA score, mean ± SD	4.50 ± 0.70	4.70 ± 0.48	0.470[2]
Ultrasonography findings, mean ± SD			
Total lesion vascularity[3]	6.60 ± 3.23	10.70 ± 3.94	0.021[2]
Total lesion elasticity[3]	8.10 ± 4.81	14.50 ± 7.41	0.034[2]
Total lesion depth in cm	5.19 ± 0.97	6.20 ± 0.67	0.467[2]

Abbreviations: DLQI, Dermatology Life Quality Index; PGA, Physician Global Assessment; SD, standard deviation; VAS, visual analog scale.
[1]By Fisher exact test.
[2]By Student *t* test.
[3]See Patients and Methods section for explanation of vascularity and elasticity scoring.

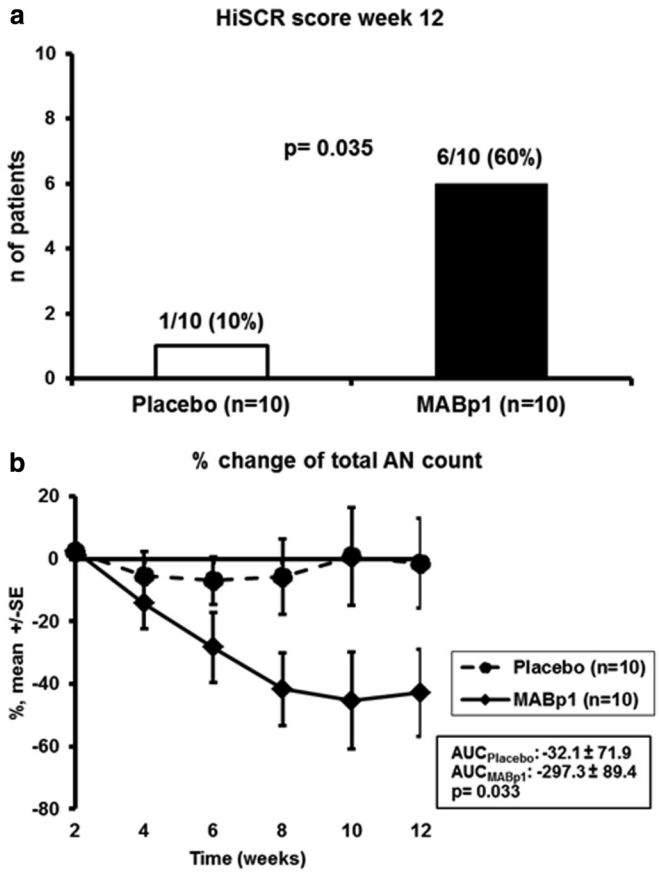

Figure 2. Primary study endpoint. (**a**) Hidradenitis Suppurativa Clinical Response (HiSCR) score at week 12 for each study group. *P*-value of comparison between the two groups by the Mantel-Haenszel test is provided. (**b**) Percent change of the total AN (sum of inflammatory nodules and abscesses) count over patient visits until week 12. The areas under the curve (AUC) are provided and are compared by the Student *t* test. SE, standard error.

whom previous anti-TNFs had failed (Figure 3c). Characteristic examples are provided in Figure 3d and 3e.

Analysis: exploratory endpoints

Serum IL-1α was below the lower limit of detection in the sera sampled from all patients both before and at the end of blind treatment. Pus was sampled before treatment from six patients allocated to the placebo group and seven patients allocated to the MABp1 group. Mean ± standard error concentrations of IL-1α were 697.2 ± 440.4 pg/ml and 772.0 ± 221.7 pg/ml, respectively ($P = 0.412$ by the Mann-Whitney *U* test).

Treatment with MABp1 was accompanied by decrease of serum IL-8 (Figure 4a). More than a 30% decrease of IL-8 at week 12 was selected as a cutoff point (see Supplementary Figure S5 online). The OR for this cutoff point for MABp1 was 13.50 (95% CI = 1.19–152.51, $P = 0.035$) (Figure 4b). This was consistent with change in levels of IL-8 produced from whole blood stimulated with heat-killed *Staphylococcus aureus*, which was significantly lower among patients treated with MABp1 than patients treated with placebo (Figure 4c). The capacities of whole blood to produce both IL-1α and hBD-2 were positively associated in placebo-treated patients (Figure 4d). Among these same patients, the capacity for hBD-2 production was negatively correlated with the change in the skin depth of lesions on ultrasonography (Figure 4e). These correlations did not exist in MABp1-treated patients, which suggested an hBD-2–associated mode of action of MABp1 in HS that is mediated through the inhibition of IL-1α.

Table 2. Decrease of baseline disease activity among groups of treatment at weeks 12 and 24 in relation to HiSCR score

Treatment Group	Disease Activity	HiSCR(−), n (%)	HiSCR(+), n (%)	*P*-Value
Week 12				
Placebo	Increase	6 (100)	0 (0)	0.400
	Decrease	3 (75)	1 (25)	—
MABp1	Increase	4 (100)	0 (0)	0.005
	Decrease	0 (0)	6 (100)	—
Week 24				
Placebo	Increase	6 (100)	0 (0)	NC
	Decrease	4 (100)	0 (0)	—
MABp1	Increase	5 (100)	0 (0)	0.048
	Decrease	1 (20)	4 (80)	—

Abbreviations: HiSCR, Hidradenitis Suppurativa Clinical Response; NC, cannot be calculated because of zero values.

Safety

In total, 43 HS exacerbations were recorded as adverse events (AEs) during the study period, 24 in the placebo group and 19 in the MABp1 group ($P = 0.353$). Four exacerbations required hospitalization and were reported as serious adverse events (SAEs), two in the placebo group and two in the MABp1 group ($P = 1.00$). No AE or SAE was related to the study drug. No other clinical or laboratory AE or SAE was recorded.

DISCUSSION

This study suggests that MABp1 could be a major advance in the management of HS for patients ineligible for adalimumab therapy. Lack of eligibility for adalimumab was defined as refractoriness to previous treatment with adalimumab or other anti-TNFs or medical history that made the use of adalimumab unlikely, such as past history of cancer or unwillingness to self-inject. Patients enrolled in this study had higher Dermatology Life Quality Index and greater modified Sartorius scores at baseline compared with those enrolled in the PIONEER studies (Kimball et al., 2016). Furthermore, 8.4–16.6% of study populations in the PIONEER studies had a history of previous surgery for HS, whereas this was the case for all 20 enrolled patients in this study. This generates hope that MABp1 may be even more effective when tested in a population with less severe disease, including anti-TNF–naïve patients.

Using an HiSCR score that is an established primary efficacy endpoint for response to treatment, we found that 60% of patients responded to MABp1 compared with only 10% of the placebo group. Analysis of the secondary outcomes showed that MABp1 was superior to placebo in maintaining clinical efficacy at 24 weeks, that is, 12 weeks after stop of treatment. Main other secondary outcomes like decrease in self-assessed HS severity and improved ultrasonography findings were met. The interpretation of findings should take into consideration the fact that patients assigned to treatment with MABp1 had more severe disease than placebo comparators, as evidenced by the greater modified Sartorius score and ultrasonographic measurements at baseline.

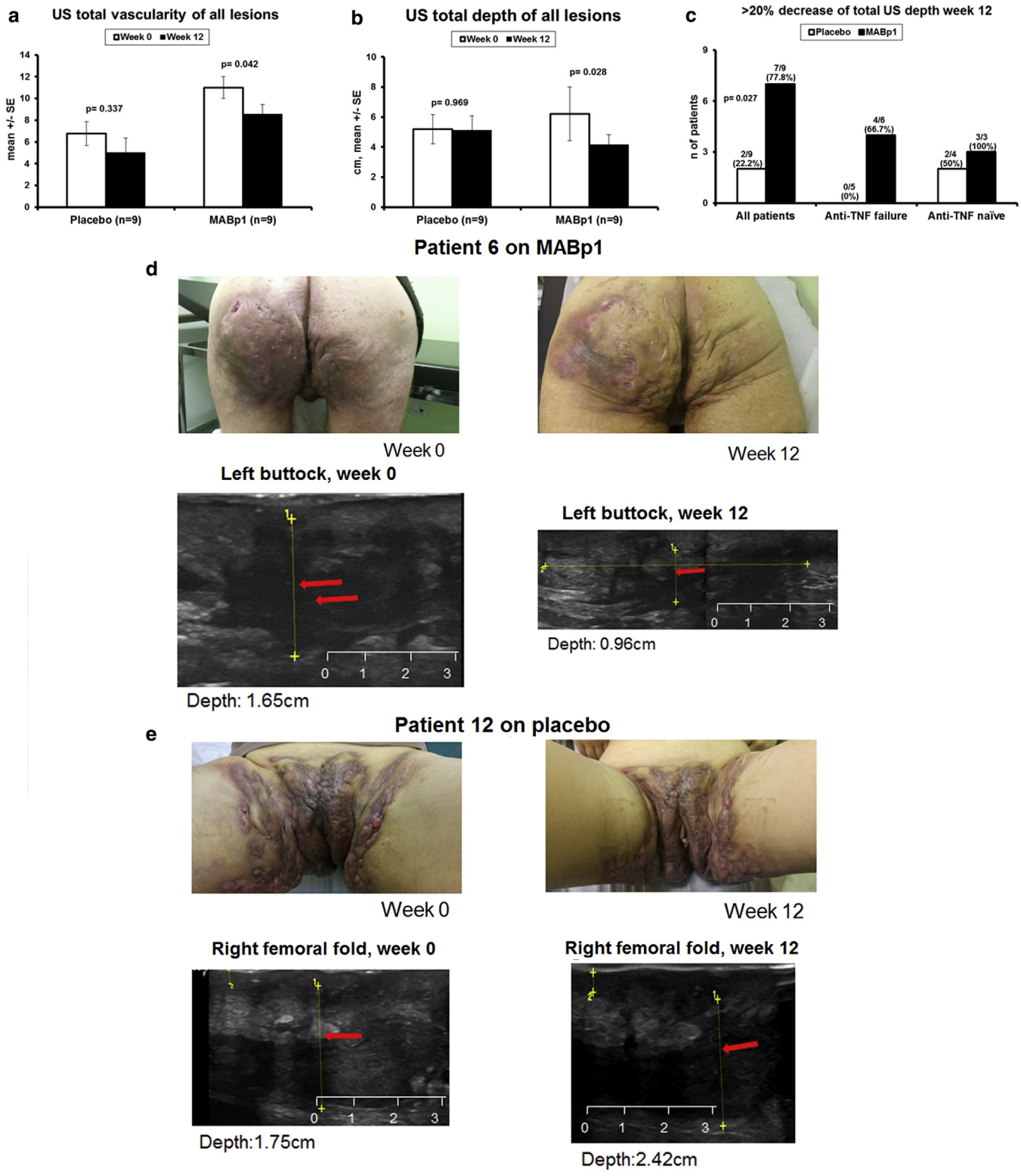

Figure 3. Ultrasonography (US) changes over treatment. (**a**) Total measurement of vascularity and (**b**) total measurement of depth of all lesions before and after treatment with placebo or MABp1. *P*-values represent comparisons before treatment and at the end of treatment separately within each group by the Wilcoxon ranked sum test. (**c**) Achievement of more than 20% decrease of total US depth of all lesions after 12 weeks of treatment with placebo or MABp1. Data are provided for all patients and separately for patients for whom previous anti-TNF treatment failed and for anti-TNF–naïve patients. The *P*-value of comparison by the Mantel-Haenszel test is provided. (**d**) Decrease of the depth of the lesion of the right buttock of patient 6 under treatment with MABp1 evidenced both by clinical improvement and by US. (**e**) Increase of the depth of the lesion of the femoral folds of patient 12 under treatment with placebo evidenced both clinically and by US. Red arrows indicate the US depth of the lesion. Scale is in centimeters. US, ultrasonography.

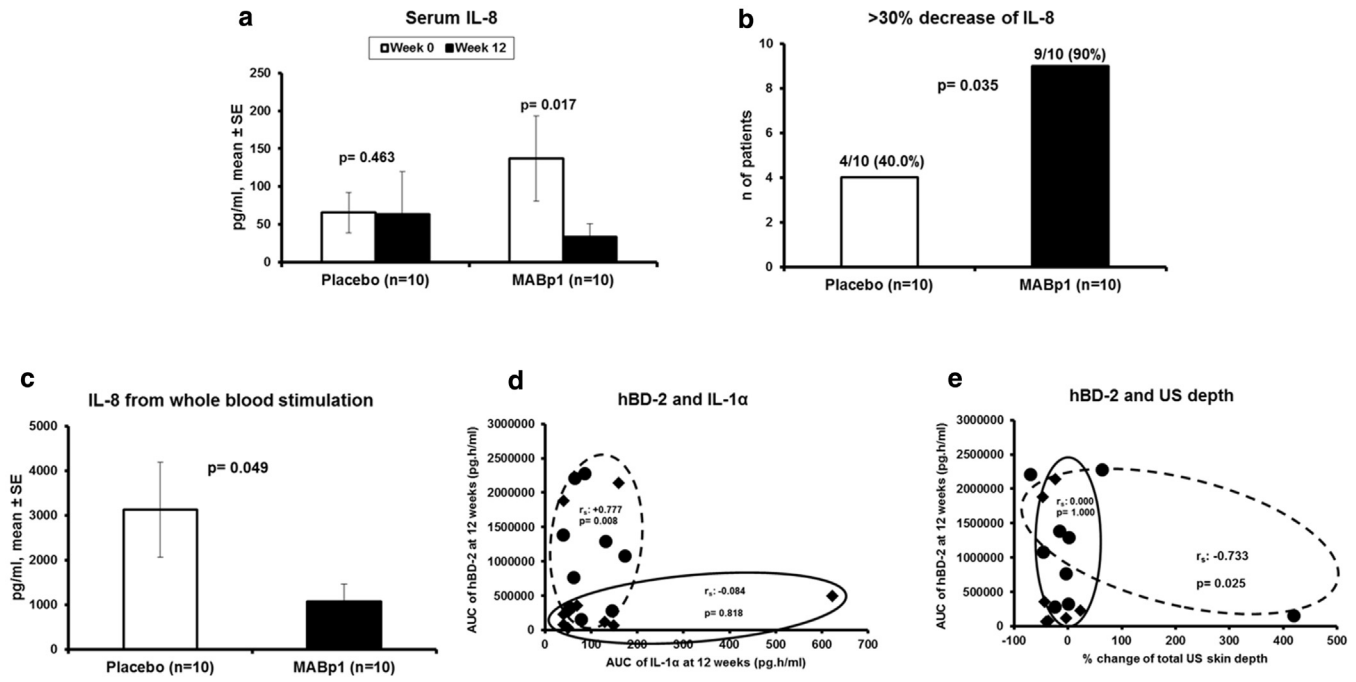

Figure 4. Exploratory study endpoints. (**a**) Serum measurements of IL-8 over treatment. *P*-values indicate statistical comparisons between groups of treatment at the indicated time intervals by the Wilcoxon ranked sum test. (**b**) Comparison between the frequency of placebo-treated and MABp1-treated patients achieving more than 30% decrease of serum IL-8 after 12 weeks of treatment. The *P*-value of comparison by the Mantel-Haenszel test is provided. (**c**) Comparative production of IL-8 from whole blood of placebo-treated and of MABp1-treated patients after 24 hours of stimulation with one heat-killed isolate of *Staphylococcus aureus*. *P* value represents comparison between the two groups by the Mann-Whitney *U* test. (**d**) Correlation of the whole blood production capacity for the production of hBD-2 and of IL-1α at the end of the 12-week of treatment. The capacity is provided as the AUC of whole blood stimulated for 48 hours with one heat-killed isolate of *S. aureus*. The dashed cloud indicates the correlation between hBD-2 and IL-1α for placebo-treated patients, and the solid cloud indicates the correlation between hBD-2 and IL-1α for MABp1-treated patients. The Spearman correlation coefficient and the *P*-value are provided separately for the correlations for placebo-treated patients and for MABp1-treated patients. (**e**) Correlation of whole blood production capacity for the production of hBD-2 and the change of total skin depth by US at the end of 12weeks of treatment. The capacity is provided as the AUC of whole blood stimulated for 48 hours with one heat-killed isolate of *S. aureus*. The dashed cloud indicates the correlation between hBD-2 and the change of total skin depth by US for placebo-treated patients, and the solid cloud indicates the correlation between hBD-2 and the change of total skin depth by US for MABp1-treated patients. The Spearman coefficient of correlation and the *P*-value are provided separately for the correlations for placebo-treated patients and for MABp1-treated patients. AUC, area under the curve; SE, standard error; US, ultrasonography.

The enrolled patient population consisted of two subpopulations: those refractory and those naïve to previous anti-TNF treatment despite noneligibility for adalimumab. The results suggest that responses to MABp1 may differ. Specifically, the time to new HS exacerbation was prolonged among naïve patients, whereas decreases of visual analog scale score and of the lesion depth on ultrasonography were more common among patients refractory to previous anti-TNF treatment.

One major difficulty in the design and conduct of randomized clinical trials in HS is the selection of the most appropriate clinical outcome. In a recent meta-analysis of seven randomized clinical trials, it is proposed that outcomes of a study in HS should report on 10 endpoints: quality of life, pain, lesion count, Physician Global Assessment, patient global self-assessment, recurrence rate, overall satisfaction with treatment, impairment of function, cosmesis, and duration of recovery (Ingram et al., 2016). Although our study was powered for the HiSCR score, the other scores evaluated during follow-up were also improved, albeit at a nonsignificant level. These observations illustrate the need for a larger study population to show statistical benefit from MABp1 treatment in the other measures of efficacy. Decrease of disease activity, a score that takes into consideration the dimensions of the affected skin areas and the intensity of skin inflammation, followed the achievement of HiSCR score among patients treated with MABp1. However, HiSCR score has two main limitations. The first limitation is the inconsistency both within the same observer over serial time intervals and between different observers at the same time, particularly when the lesions are vast in number. The second limitation is that HiSCR score does not take into consideration the change of frequency of HS exacerbations between visits and the patient's perception of his/her disease.

Our study used skin ultrasonography and serum IL-8 as markers of response to treatment. These markers may also reflect the mechanism of action of MABp1 involving either inhibition of neovascularization or modulation of the dysregulated innate immune responses.

The enrolled study population is small to allow full recognition of responders from nonresponders through the use of receiver operating characteristic curves. Despite this limitation, decreases on ultrasonography in lesion depth and vascularization appeared to be a sign for improvement. Because IL-1α is a potent inducer of the production of vascular endothelial growth factor, its neutralization by MABp1 may inhibit angiogenesis associated with the pathobiology of HS lesions.

Dysregulation of the innate and immune responses is considered to be the backbone of the pathobiology of HS (Kelly et al., 2014). Former studies of our group have shown an excess capacity for whole blood of HS patients to produce hBD-2 after stimulation with *S. aureus* that colonizes skin microbiota (Giamarellos-Bourboulis et al., 2016). Findings from patients enrolled in this trial suggest that when placebo treatment is administered, IL-1α signaling stimulates the production of hBD-2, thus impeding the healing of lesions, as assessed by the unchanged depth of the affected skin lesions. When patients are treated with MABp1, these effects cease to exist through the neutralization of IL-1α. It is also probable that hBD-2 responses among MABp1-treated patients are affected by the decreased production of IL-8 from whole blood that is a chemoattractant for neutrophils (Révuz, 2009; Shimizu et al., 1993).

This study opens insights in the management of HS. Inhibition of IL-1α through MABp1 is a promising alternative treatment strategy for patients not eligible for adalimumab or for whom it has failed. Inhibition of neovascularization and modulation of the production of IL-8 and hBD-2 are the suggested mechanisms of action. Although MABp1 showed a good safety profile, this study is small, and its findings may not be representative of what may occur in a larger population or even in a subsequent small study.

PATIENTS AND METHODS

Study design

This prospective, double-blind, 1:1 randomized, placebo-controlled study was conducted at the Outpatient Department of Immunology of Infectious Diseases of Attikon University Hospital. The study had a first treatment phase of 12 weeks and a second follow-up phase of 12 weeks. The protocol was conducted according to the Helsinki Declaration. Patients were enrolled after written informed consent. The protocol was approved by the Attikon Ethics Committee, the National Organization for Medicines of Greece (license IS-48/15), and the National Ethics Committee of Greece (license 46/00-01/15) (EudraCT number 2015-002321-20; ClinicalTrials.gov NCT02643654, registered 20 December 2015). Adult patients with Hurley II- or III-stage HS with at least three inflamed nodules and with primary or secondary failure of previous anti-TNF treatment or not eligible to receive adalimumab because of medical history or unwillingness to self-inject were included. Although not strictly defined in the protocol, primary failure of anti-TNF treatment was set as lack of efficacy after at least 3 months of treatment with agents blocking TNF-α, secondary failure of anti-TNF treatment as loss of clinical efficacy in a patient initially responding to an agent blocking TNF-α, and non-eligibility for medical history as past history making a patient not eligible to start treatment with adalimumab. Concomitant antimicrobial treatment was allowed. Written informed consent was provided by the patients.

Main exclusion criteria were latent tuberculosis, chronic infections by hepatitis B and C viruses and by HIV, active bacterial infections, systemic lupus erythematosus, neutropenia, pregnancy or lactation, recent vaccination, demyelinating disorders, serum creatinine level above 1.5 mg/dl, liver biochemistry levels at more than two times the upper normal limit, and medical history of cardiolipin syndrome. The first patient was enrolled on December 22, 2015 and the follow-up of the last patient was completed on January 12, 2017. The study was unblinded after database lock.

Screening and blind treatment

Once a patient was considered eligible for the study, the following screening procedures were done: (i) history and physical examination; (ii) skin tuberculin test; (iii) chest x-ray scan; (iv) serology tests for HIV and hepatitis B and C viruses; and (v) white blood cell count, serum creatinine level, and liver biochemistry tests. Patients were randomly assigned (1:1) to receive blind treatment at a final volume of 100 ml dispensed into 0.9% normal saline with 1-hour infusion every 14 days for a maximum of seven infusions. Blind treatment was either placebo or 7.5 mg/kg of MABp1. The study drug and identical placebo were provided by XBiotech (Austin, TX), which built the randomization sequence. Investigators, nurses, and patients were blinded to the study drug.

Follow-up

At weeks 0 (baseline), 2, 4, 6, 8, 10, 12 (end of treatment), 16, 20, and 24, individual lesions were counted and HiSCR, Physician Global Assessment, disease activity, and modified Sartorius were scored (Giamarellos-Bourboulis et al., 2008; Kimball et al., 2012, 2014; Sartorius et al., 2009). Any HS exacerbation defined as a typical HS flare-up (Zouboulis et al., 2015) was recorded. Patients were self-assessed for HS and pain severity using a visual analog scale from 0 mm (absent) to 100 mm (worst ever felt). At weeks 0, 12, and 24, patients completed the Dermatology Life Quality Index. Patients were asked to report any AEs and SAEs. For the efficient capture of AEs and SAEs two strategies were followed. First, enrolled patients were explicitly told at the baseline visit that for every sudden onset of an event they should immediately refer to the study personnel. Patients were given phone numbers of the study physicians so that the study physicians could arrange their referral to the internal medicine facility that is run at the same study site. Second, on each follow-up visit, patients were asked for the occurrence of any symptoms or for the need for any medication other than the medications needed for an HS exacerbation in the between-visits time using a symptom-targeted questionnaire. HS exacerbations requiring hospitalization were reported as SAEs; those not requiring hospitalization were reported as AEs.

At weeks 0 and 12, (i) 10 ml of whole blood was sampled from one forearm vein for whole blood cell counting, biochemistry testing, cytokine serum measurement, and ex vivo stimulation and (ii) ultrasonography was performed by the same expert, blinded to the allocated treatment, using a standard technique (brightness mode and color Doppler ultrasonography). A high-resolution, 7- to 12-MHz linear transducer was used on an HDI 3500, ATL (Philips, Mentor, OH) echo Doppler unit, and it was gently placed by pad gel over all involved skin areas in a perpendicular direction to the surface. Evaluable findings were the largest skin depth, vascularity, and skin elasticity of lesions. Vascularity was scored using the resistance index from 0 (none) to 3 (intense) and elasticity as 1 = cold, 2 = moderate and 3 = hot. The greatest values for each body lesion were calculated and added to provide the respective value per patient per visit.

All data were recorded to a case report form. All study procedures and case report forms were monitored by a blinded study monitor. All study procedures were audited for good clinical practice from August 28–30, 2017, by an independent auditor.

Study endpoints

The primary study endpoint was the clinical efficacy of MABp1 in moderate to severe HS assessed by positive HiSCR score at week 12. The effects of MABp1 at week 24, severity scores, time to first HS exacerbation, and ultrasonography findings were the secondary endpoints; they were analyzed separately for patients for whom previous anti-TNF treatments had failed and anti-TNF–naïve

patients. The effects on IL-8 and on the production of IL-1α, IL-8, and hBD-2 were exploratory endpoints.

Study power

The study was powered on the assumption that 60% of MABp1-treated patients would achieve a positive HiSCR score; the efficacy of placebo was set to 10% as described for anakinra treatment (Tzanetakou et al., 2016). To show difference at the 10% level with 80% power, 10 patients should be assigned into each arm.

Laboratory analysis

Whole blood was stimulated with one heat-killed isolate of *S. aureus* coming from a patient, as described previously (Giamarellos-Bourboulis et al., 2016). Concentrations of hBD-2, IL-1α, and IL-8 in culture supernatants and IL-1α and IL-8 in serum were measured by an enzyme immunosorbent assay. The lower limits of detection were 6 pg/ml for hBD-2 (Cusabio Biotech Co., Wuhan, China), 1.6 pg/ml for IL-1α (eBioscience, Affymetrix, Santa Clara, CA), and 5 pg/ml for IL-8 (R&D Systems, Minneapolis, MN). Blood potential for hBD-2 and IL-1α production at week 12 was expressed by the area under the curve of both variables over time of incubation calculated by the liner trapezoidal rule. Pus was sampled from 13 patients before study enrollment, as described previously (Kanni et al., 2015); IL-1α in pus was measured by the described immunosorbent assay.

Statistical analysis

Comparisons were done by the Fisher exact test for qualitative variables and by the Student *t* test or the Mann-Whitney *U* test for qualitative variables. Quantitative variables within the same group were compared by the Wilcoxon rank sum test. ORs and 95% CIs were calculated by the Mantel-Haenszel statistics. Percent changes were plotted over study visits, and areas under the curve were compared. Time to new exacerbation was compared by the log rank test. Cutoffs of IL-8 and ultrasonographic changes associated with more than 80% sensitivity for positive HiSCR score after receiver operating curve analysis were defined. Nonparametric correlations according to Spearman were done. Any *P*-value less than 0.05 was considered significant.

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CONFLICT OF INTEREST

EJG-B has received honoraria (paid to the University of Athens) from AbbVie, Biotest, Brahms GmbH, and The Medicines Company; has received compensation as a consultant for Astellas Greece and for XBiotech (paid to the University of Athens); and has received independent educational grants (paid to the University of Athens) from AbbVie and Sanofi. He is funded by the FrameWork 7 program HemoSpec (granted to the University of Athens). TK has received honoraria from XBiotech. JS and MS are employees of and hold stock and/or stock options for XBiotech. JS holds patents related to anti-IL-1α therapy.

ACKNOWLEDGMENTS

This study was supported in part by XBiotech (Austin, TX) and the Hellenic Institute for the Study of Sepsis.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2017.10.030.

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