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Phase II randomized, placebo-controlled trial of *M. vaccae*-derived protein (PVAC®) for the treatment of psoriasis

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Abstract

The treatment effect against psoriasis of an antigen (delipidated, deglycolipidated form of *M. vaccae*-PVAC) was investigated. One hundred and sixty-five patients were enrolled in three arms (50 or 15 μg or placebo), each receiving a total of two intradermal injections (days 0 and 21). At week 12, a 75% decrease in psoriasis area and severity index was similar among the studied groups (13, 9 and 18%, $p = 0.429$). The overall incidence of adverse events was significantly higher in the PVAC treated groups when compared to placebo (98.2, 87.3 and 70.9%; $p < 0.001$) largely due to local reactions that were limited for the most part to grades 1 and 2 in severity and were self-limiting. Despite its overall safety, PVAC was not clearly indicated to be superior to placebo in the treatment of psoriasis in this study.

Keywords: Plaque psoriasis; Treatment; Immunotherapy; PVAC; Placebo

1. Introduction

Psoriasis is a common chronic inflammatory immune mediated disease of skin and joints characterized by erythematous papules and plaques covered by silvery white scales commonly localized on the elbows, knees, scalp, umbilicus, and lumbar area [1]. It affects 1–2% of the worldwide population [2]. Results from a population based study estimates that approximately 6.5 million US individuals have psoriasis [3]. Approximately one-third of patients with psoriasis have moderate or severe forms of the disease that require costly, and often harsh treatments [4–9]. The disease is characterized by chronic recurrent exacerbations and remissions and patients with psoriasis have reduced quality of life similar to patients with chronic diseases such as cancer, hypertension and diabetes [10]. Current therapies for psoriasis include topical and systemic therapies, which includes several immunosuppressive drugs and more recently potent T cell immunomodulators [11]. Psoriasis therapy is not optimal, and the selection of therapy depends on the extent and psychosocial impact of the disease [12]. Combination therapy is often employed aiming at synergistic efficacy while reducing dosages and side effects of the individual agents [13].

The vaccination with *Mycobacterium* species for clinical use in the treatment of psoriasis has been less driven by immunology theory than by empirical data [14–17]. The use of *Mycobacterium vaccae* in psoriasis was foreseen as early as the 1990s, when physicians tested autoclaved *M. vaccae* as a treatment for leprosy and saw that patients with concomitant psoriasis experienced clearing of their psoriatic

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lesions [14]. Following these interesting results Corixa, Genesis and Medicis developed a delipidated, deglycolipidated form of *M. vaccae*, designated as PVAC; an immunomodulator derived from killed *M. vaccae* and licensed from SR Pharma for the potential treatment of psoriasis. Preliminary reports in an open label clinical trial with PVAC revealed marked improvement (>50% reduction in the PASI score) in 13 out of 20 patients with moderate to severe plaque psoriasis [18]. In February 2001, phase II trials were conducted in the US, the Philippines and Brazil for the treatment of moderate-to-severe psoriasis. In January 2001, a New Drug Application (NDA) filing was expected to take place in 2003. In January 2002, Medicis and Corixa planned to initiate another phase IIb trial, and by June 2002, two studies in patients with mild-to-moderate plaque psoriasis had begun in the US and New Zealand, with the former designed to investigate the use of PVAC in combination with ultraviolet B (UVB) light [11,19]. The available results of the New Zealand randomized placebo-controlled trial of PVAC in 36 psoriatic arthritis (PsA) patients did not show efficacy as immunotherapy to alter the clinical activity of PsA although it showed enough safety to continue development [11,19,20].

Herein, we report the results of the trial conducted in Brazil with PVAC on the treatment of moderate-to-severe plaque psoriasis.

2. Methods

2.1. Study design

The trial was performed at two sites in Brazil (Salvador/Bahia and São Paulo/São Paulo), and was a controlled, parallel-group, double-blind study with three groups receiving fixed doses of study treatments at days 0 and 21. Patients were recruited from outpatient dermatologic clinics. The study was conducted between September 2000 and April 2002. Subjects were assigned to receive 0.1 ml intradermal injections of either 15 and 50 μg of PVAC or placebo (0.9 NaCl + 0.03% Tween) at days 0 and 21. Highly trained technicians with more than 10 years experience injecting PPD performed the intradermal injections at both sites (Salvador and São Paulo).

Patients were initially assessed at a screening visit to determine eligibility for the trial. Those patients using therapy for psoriasis at the time of screening were required to provide the proper washout (2–8 weeks) before entering the study. At the baseline visit (day 0) the patients were re-screened to assess current health status; psoriasis area and severity index (PASI) score [18,21]; global physician assessment; obtain baseline photograph; and provide standard laboratory testing. The first intradermal injection of PVAC or placebo was then given on this visit. Follow up was at 3, 6, 9 and 12 weeks (second infection given at 3 weeks). At each visit all clinical and laboratory evaluations were performed. The site of injection was covered by gauze for all subjects before clinical assessment and subjects were advised on each visit that there was no relationship between the size of the injection site reaction and psoriasis response in previous studies.

2.2. Subjects

Eligible subjects were men or women aged 18–70 years with stable plaque psoriasis comprising 10% or more of body surface and PASI over 12 for more than 6 months. Women of childbearing potential agreed to use adequate contraception throughout the study. All patients agreed not to use any known active anti-psoriatic therapies for the duration of the study including: topical agents such as corticosteroids, salicylates, anthralin, calcipotriene and tazarotene (except emollients); phototherapy or PUVA therapy (washout of 2 weeks); systemic agents such as corticosteroids (washout of 8 weeks); methotrexate, retinoids and cyclosporine (washout of 4 weeks); and other experimental therapies.

Subjects were excluded if they had any other form of psoriasis such as pustular, erythroderma or guttate forms and/or inflammatory arthritis. They were also excluded if they had any history of the following: (a) history of exfoliative dermatitis or prolonged exposure to the sun within 4 weeks prior to study randomization or intention of prolonged exposure to the sun during the study with this exposure thought likely (by the investigator) to modify the subject's disease; (b) severe hepatic or renal disease or other disease that would increase the risk of study participation to the subject; (c) history of active TB or treatment for TB in the past 5 years; (d) any disease states including but not limited to, AIDS and history of infection with HIV and patients with a positive anti-nuclear antibodies, that would impair evaluation of the test therapy or increase the risk of study participation to the subject. Tuberculin skin test (PPD) was not performed since the rate of PPD positive reaction in Brazil is greater than 30% [22,23]. The local ethics committee approved this study and all patients provided written informed consent prior to entering the study.

2.3. Assessments

2.3.1. Efficacy measurements

The primary outcome was the proportion of subjects with 75% or more improvement in PASI score at week 12 for the arm receiving 50 μg PVAC compared to placebo arm. Comparisons of the arms receiving 15 μg or placebo were supportive of the primary endpoint outcome. The secondary efficacy endpoints were actual value of PASI score at week 12, change in PASI between weeks 0 and 12; PASI at each visit; physician global assessment at week 12; and global score from investigators global assessment at week 12 (or termination).

Safety was monitored by physician examination, vital signs, laboratory tests and patient diaries. All possible adverse events were recorded, with details of severity and likely causality.

Table 1
Reason for exclusion from efficacy evaluable population

	Placebo ($N=55$)	PVAC 15 μg ($N=55$)	PVAC 50 μg ($N=55$)
Total number of patients excluded from efficacy evaluation population	6 (10.9%)	7 (12.7%)	3 (5.5%)
Reason for exclusion			
Did not receive two injections	5 (9.1%)	1 (1.8%)	1 (1.8%)
Did not complete week 12 visit	6 (10.9%)	7 (12.7%)	3 (5.5%)

2.4. Statistical analysis

All analyses were conducted independently of the manufacturers and suppliers of PVAC, and according to an intention to treat (ITT) principle with the use of two tailed tests and an α-value of 0.05. Initial measures such as age, sex, weight, race and site usage of prior systematic treatment, baseline PASI score, age of disease onset, and duration of disease were included as covariates in analyses. Statistical Analysis System (SAS) Institute, Inc. (Cary, NC; 1996) was used as the procedure for mixed models for continuous, ordinal and binary outcomes as indicated in Results.

3. Results

3.1. Baseline characteristics

One hundred and seventy-four patients were screened for entry into the study. Nine were not enrolled because they did not meet the entry criteria. All 165 randomized patients were included in the population for ITT analysis. All of them received at least one dose of the study medication according to the randomization schedule and were included in the safety analysis. A total of 149 patients met the inclusion/exclusion criteria, in the ITT analyzed population studied. These patients received both doses of study medication, and completed the week-12 termination visit. They were also included in the efficacy evaluable (EE) population. The reasons for exclusion of the 16 patients from the EE population are presented in Table 1. The treatment groups were comparable with respect to the number (%) of patients in each arm for the EE population ($p=0.507$).

3.2. Demographic and baseline disease parameter

Table 2 summarizes the demographic characteristics for the study population. There were no significant differences among the treatment groups with respect to age, gender and race ($p>0.139$).

Baseline disease parameter and history of prior treatment of the studied population is summarized in Table 3. Independent logistic regression models were used to investigate the relationship between the demographic characteristics and baseline disease parameter achieving >50% improvement in PASI score at any time. This revealed that the factors with a significant effect on achieving improvement were: patients with prior methotrexate treatment were less likely to respond ($p=0.043$), and patients who failed prior methotrexate or PUVA or cyclosporine treatment were less likely to respond ($p=0.022$).

Table 2
Demographic characteristics of the intention to treat population

	Placebo ($N=55$)	PVAC 15 μg ($N=55$)	PVAC 50 μg ($N=55$)	p-Value
Age				
Mean ± S.D.	41.9 ± 13.2	40.9 ± 11.9	43.4 ± 11.7	0.566[a]
Median	43	38	42	
Range	18-68	18-69	19-65	
Weight (kg)				
Mean ± S.D.	77.0 ± 18.6	73.7 ± 17.7	77.2 ± 15.2	0.488[a]
Median	73	74	77	
Range	47–122	43–130	49–123	
Gender				
Male	40 (72.7%)	34 (61.8%)	39 (49.1%)	0.419[b]
Female	15 (27.3%)	21 (38.2%)	16 (29.1%)	
Race				
Caucasian	17 (30.9%)	24 (43.6%)	27 (49.1%)	0.139[b]
Mixed	32 (58.2%)	26 (47.3%)	26 (47.3%)	
Black	6 (10.9%)	4 (7.3%)	1 (1.8%)	
Asian/Pacific Islander	0 (0.0%)	1 (1.8%)	1 (1.8%)	

[a] Analysis of variance.
[b] Chi-square test S.D. = standard deviation.

Table 3
Baseline disease characteristics of the ITT population

	Placebo ($N=55$)	PVAC 15 μg ($N=55$)	PVAC 50 μg ($N=55$)	p-Value
Baseline PASI				
Mean ± S.D.	18.5 ± 6.0	17.7 ± 5.4	17.5 ± 4.9	0.572[a]
Median	16	16	16	
Range	12–34	12–33	12–32	
<12	0 (0%)	0 (0%)	0 (0%)	
>20	17 (30.9%)	15 (27.3%)	15 (27.3%)	
Age of onset				
Mean ± S.D.	31.5 ± 14.8	26.5 ± 13.5	31.5 ± 12.4	0.073[b]
Median	28	26	31	
Range	4–65	2–59	6–56	
Years since onset				
Mean ± S.D.	10.4 ± 9.2	14.3 ± 9.9	11.9 ± 9.0	0.049[b]
Median	9	12	12	0.013[c]
Range	4–65	2–59	6–56	0.259[d]
				0.202[e]
<10	31 (56.4%)	18 (32.7%)	22 (40.0%)	
>30	3 (5.5%)	5 (9.1%)	2 (3.6%)	
Baseline % involvement				
Mean ± S.D.	32.2 ± 13.0	30.4 ± 13.2	31.1 ± 13.1	0.736[b]
Median	30	30	29	
Range	10–60	10–70	10–60	
Prior systemic treatment				
Yes	35 (63.6%)	29 (52.7%)	25 (45.5%)	0.139
No	20 (36.4%)	26 (47.3%)	30 (54.5%)	
No. of failed treatments				
0	15 (27.3%)	15 (27.3%)	16 (29.1%)	0.319
1	15 (27.3%)	15 (27.3%)	7 (12.7%)	
2–8	25 (45.5%)	25 (45.5%)	32 (58.2%)	

S.D. = standard deviation; PASI = psoriasis area and severity index.
[a] Analysis of variance.
[b] Kruskal–Wallis test.
[c] Pairwise comparison, placebo vs. 15 μg PVAC arm.
[d] Pairwise comparison, placebo vs. 50 μg PVAC arm.
[e] Pairwise comparison, 15 μg PVAC vs. 50 μg PVAC arm.

The treatment groups were not significantly different in terms of average baseline PASI ($p=0.572$) or percent body surface involvement ($p=0.736$). There was a trend on the average of age at disease onset in the PVAC 15 μg arm to be lower ($p=0.073$) (mean 26.5 years versus 31.5 years versus 31.5 years; 15 μg, 50 μg and placebo, respectively). The treatment groups were significantly different ($p=0.048$) in terms of years since onset. The average time since onset was significantly longer ($p=0.013$) in the PVAC 15 μg arm (mean = 14.3 years) than in the placebo arm (mean = 10.4 years).

Prior anti-psoriatic treatment regimens were similar between the treatment groups. The topical treatments used in the population were: no treatment (4.4%), coal tar (23.3%), corticosteroids (50.5%), anthralin (1.8%), cacipotriene (9.5%), salicylic acid (4.7%), tazarotene (0.7%) and other topical agents (5.1%). The systemic treatments used in the population were: no treatment (37.3%), methotrexate (24.5%), cyclosporin (2.0%), corticosteroids (18.6%), retinoids (13.7%) and other systemic agents (3.9%). There were no apparent differences between the treatment groups in the severity of the target lesions at the baseline (data not shown). For most patients, the target lesion was characterized by redness and elevated and palpable plaque thickness, with large scales on the lesion.

3.3. Efficacy evaluation

All 165 patients included for the ITT analysis received at least one injection and 158/165 (96%) received both injections. There were no apparent dose-related trends in terms of the percentage of patients who did not receive both injections. The efficacy evaluable population had the same results. A total of seven patients had an increase in the overall severity of psoriasis; five of these patients were in the placebo group. This difference was not statistically significant ($p=0.218$).

The primary efficacy variable was numerically in favor of PVAC 50 μg treatment, with 10 (18%) patients experiencing >75% improvement in PASI at week 12 compared to 5 (9%) in the PVAC 15 μg group and 13% (7) in the placebo group (Fig. 1) but the efficacy of the PVAC 50 μg was not different from the placebo group ($p=0.429$).

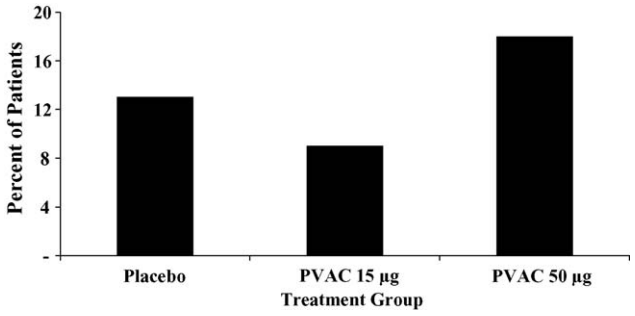

Fig. 1. Percent of patients achieving equal or more than 75% improvement of PASI and week 12.

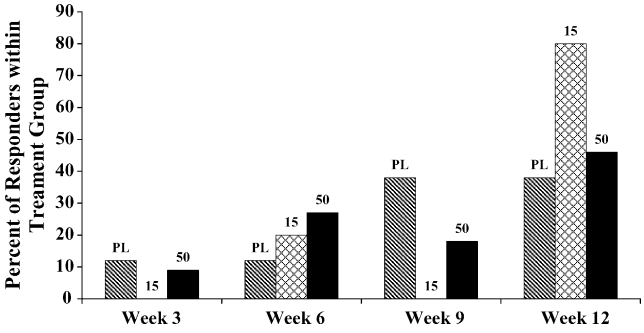

Fig. 2. Visit at which >75% improvement in PASI was first noted in the intention-to-treat population.

As indicated in Fig. 2, 75% improvement on PASI score was first evident for the majority of responders (12 of 22 responders) at or after the week 9 visit. At least 75% improvement in PASI score was evident on or before the week 9 visit for four patients in the placebo group. Three responders in the placebo group, four responders in the PVAC 15 μg group, and five responders in the PVAC 50 μg group had their first response at the week 12 visit.

Fig. 3 depicts the mean percent change in PASI of the ITT population over time.

3.4. Safety evaluation

The treatment groups were significantly different with respect to the percentages of patients with at least one adverse event. The overall incidences of adverse events were significantly higher in the PVAC 15 and 50 μg groups than in the placebo group ($p < 0.001$). The differences were attributable largely to differences among the groups in the percentages of patients with adverse events related to injection site reactions. The treatment groups differed significantly with respect to the percentage of patients who reported injection site erythema, inflammation, edema, pain, pigmentation changes and vesicles. With the exception of adverse events associated with injection site reactions, there were no significant differences among the treatment groups in terms of the incidence of specific adverse events classified by system organ class and preferred term. In general, adverse events were mild in all three treatment groups. Grade 3 or higher adverse events were reported for 3/55 patients (5%) in the placebo group (two cases of erythroderma, both considered probably related to

Table 4
Incidence of adverse events among the intention to treat population

	Placebo ($N = 55$)	PVAC 15 μg ($N = 55$)	PVAC 50 μg ($N = 55$)	p-Value[a,b]
At least 1 AE	39 (70.9%)	48 (87.3%)	54 (98.2%)	<0.001
At least 1 grade 3/4 AE	3 (5.5%)	1 (1.8%)	3 (5.5%)	0.551
GI disorders	11 (20.0%)	8 (14.5%)	10 (18.2%)	0.746
Nausea	6 (10.9%)	2 (3.6%)	3 (5.5%)	0.388[c]
General disorders and site conditions	18 (32.7%)	43 (78.2%)	49 (89.1%)	<0.001
Injection site dermatitis	3 (5.5%)	8 (14.5%)	11 (20.0%)	0.077
Injection site erythema	7 (12.7%)	29 (52.7%)	37 (67.3%)	<0.001
Injection Site induration	2 (3.6%)	8 (14.5%)	14 (25.5%)	0.005
Injection site inflammation	1 (1.8%)	8 (14.5%)	13 (23.6%)	0.003
Injection site edema	0 (0.0%)	4 (7.3%)	14 (25.5%)	<0.001
Injection site pain	3 (5.5%)	10 (18.2%)	19 (34.5%)	<0.001
Injection site pigmentation	0 (0.0%)	6 (10.9%)	4 (7.3%)	0.037[c]
Injection site vesicles	6 (10.9%)	25 (45.5%)	22 (40.0%)	<0.001
Malaise	6 (10.9%)	8 (14.5%)	7 (12.7%)	0.849
Pyrexia	2 (3.6%)	3 (5.5%)	7 (12.7%)	0.241[c]
Infections and infestations	14 (25.5%)	5 (9.1%)	6 (10.9%)	0.318[c]
Musculoskeletal, connective tissue and bone disorders	14 (25.5%)	7 (12.7%)	8 (14.5%)	0.166
Nervous system disorders	20 (36.4%)	20 (36.4%)	19 (34.5%)	0.974
Headache NOS	15 (27.3%)	18 (32.7%)	14 (25.5%)	0.679
Skin and subcutaneous tissue disorders	15 (27.3%)	18 (32.7%)	23 (41.8%)	0.266
Pruritus NOS	10 (18.2%)	13 (23.6%)	19 (34.5%)	0.134

AE, adverse event; GI, gastrointestinal; NOS, not otherwise specified.
[a] For overall comparison of treatment groups.
[b] Based on Chi-square test, unless otherwise indicated.
[c] Based on Fisher's exact test.

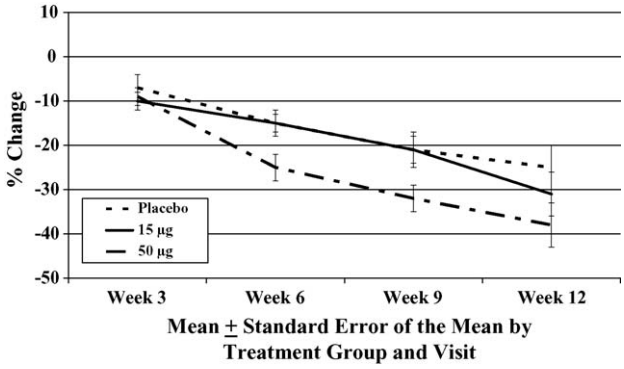

Fig. 3. Mean percent change in PASI of the intention-to-treat population. Mean ± standard error of the mean by treatment group and visit.

treatment), 1/55 patients (2%) in the PVAC 15 μg (exfoliative dermatitis considered possibly related) and 3/55 patients (5%) in the PVAC 50 μg group (ulceration at the injection site considered definitely related and two cases of hypertension, both considered unrelated to treatment). Only one patient (placebo group) experienced a grade 4 adverse event (hypertensive crisis considered unrelated to treatment). A total of 21 patients experienced one of more infections. The incidence of infections was higher in the placebo group (18%) than in either of the PVAC treatment groups (9% in the PVAC 15 μg group and 11% in the PVAC 50 μg group). However, the difference between the groups was not statistically significant ($p = 0.318$). Table 4 summarizes these data.

4. Discussion

In this study, we documented that no significant difference was noted in the modification of the PASI score between patients receiving PVAC at the doses given and those receiving placebo. Despite the similar incidence of serious adverse reactions among the groups studied, local and mild systemic reactions were significantly more frequent in the PVAC group as compared to the placebo group largely attributable to injection site reactions. These reactions, however, were low in severity, self-limiting and resolved without sequelae.

The ultimate measure of success in the clinical trial is determined by the "primary outcome". This is the key measure of success on which the study and statistical analyses are based. In psoriasis, PASI score of 75% improvement (termed "PASI75") at the 3-month visit is considered an effective response [21,24]. In this trial, 12 weeks was the time point to evaluate improvements. Intermediate time points were also important to evaluate the speed of clearance; however, similar levels of improvement were noted within all groups.

In a placebo-controlled study of immunotherapy with *M. vaccae* for chronic plaque psoriasis performed in Argentina, there was a significant improvement in PASI score in 19 of 21 patients in the immunotherapy group [15]. Nevertheless, the level of improvement did not achieve the PASI75, since the 1st 3-month improvement was 46.4 ± 21.4% and did increase the PASI score above 50% even at the 6-month evaluation. Three major randomized, placebo-controlled and partially blinded trials have been carried out in Africa to evaluate the efficacy of PVAC in the treatment of patients with multidrug-resistant tuberculosis [25]. Together these studies have shown that a single dose may not be sufficient. However, they have confirmed the mode of action of *M. vaccae* to be regulation of cell-mediated immunity with enhancement of Th1 and down-regulation of Th2, resulting in faster bacteriological conversion, reduction in erythrocyte sedimentation rate, recovery of body weight and resolution of radiological opacities, leading to better recovery from the disease even when it was given to patients receiving directly observed therapy, short-course (DOTS).

The study of PVAC in psoriatic arthritis among 36 patients randomized to receive either two intradermal injections of 50 μg of PVAC or placebo, and followed for 24 weeks according to the psoriatic arthritis response criteria (PsARC-improvement defined as a decrease of more than 30%; worsening defined as an increase of more than 30%), response at either 12 or 24 weeks was achieved by 9/18 (50%) in both PVAC and placebo ($p = 1$). However, change in the pain visual analogue score (PVS) over time significantly differed between the two groups. At 24 weeks the mean score of PVS for PVAC group had declined by 19.2 mm and increased 4.8 mm for the placebo group ($p = 0.0006$) [20]. Despite the lower median PASI score of the randomized population in this trial (2.8 and 2.5 PVAC versus placebo) compared to our study (16 both PVAC and placebo) the results were similar, which re-enforces the lack of efficacy of PVAC in the treatment of psoriasis.

The high rate of adverse events observed especially in the high dose (50 μg) may have been induced by the TNF-α effect of PVAC in patients with psoriasis. Heat-killed *M. vaccae* was studied in leprosy patients and 18 months later there was significantly improved blood flow and temperature sensation [26]. Differently from psoriasis, patients with leprosy present a predominant Th2 type of response, but TNF-toxicity is rare. It may be possible that the immunomodulatory effect of PVAC in TNF-α would not favor the control of inflammatory process noted in psoriasis.

Another interesting observation was the finding that patients with prior methotrexate or PUVA or cyclosporine treatments were less likely to respond to PVAC. The effects of PUVA therapy on a T cell subpopulation ($CD4^+CD25^+$) and the production of cytokines were evaluated in a pilot study. The results revealed that the production of INF-γ, TNF-α, IL-2, and IL-10 in psoriatic patients before PUVA application increased significantly compared with the control group. In patients after PUVA therapy there was decreased production of TNF-α and a decreased number of $CD4^+CD25^+$ cells in the blood compared with the same group of patients before the treatment [27].

In psoriasis, T cells play a role in the initiation and maintenance of psoriasis, but the next step in understanding the development of biologic agents is to learn how the

T cells induce the phenotypic changes [28]. The predominant cytokine profile in T cells from patients with psoriasis is the Th1 phenotype [29]. The Th1 cytokine profile seems to be necessary for psoriasis. The major cytokines produced by intraepidermal T cells are TNF-α, IL-2 and IFN-γ with some T cells producing IL-4 and very few cells producing IL-10 [30]. Interestingly, a larger population of lesional intraepidermal $CD8^+$ T cells produces more IL-2, IFN-γ and TNF-α than do the CD4 T cells [31,32]. It may be possible that the desirable immunomodulatory effect of the PVAC would only increase the Th1 cytokine stimulation and not the Th2 type. One of the possible mechanisms that is postulated for the role of T cells in psoriasis is the ability to induce keratinocyte hyperproliferation through secretion of relevant epidermal and keratinocyte growth factors and IL-1 [33]. Most studies with IL-10-secreting Tr1 cells and $CD4^+CD25^+$ T cells have focused on their ability to inhibit proliferation of responder cells [34]. Recently, several studies have demonstrated the important role of regulatory T (Treg) cells on the balance between regulatory and effector functions of T cells in psoriasis [27,30,34,35]. These studies have demonstrated the presence of inflammatory pathogenic effector T cells and enhanced proliferation of $CD4^+$ responder T cells. Most of these cells express CXCR3 but few are of the $CD25^{high}$, CTLA-4^+, $Foxp3^{high}$ phenotype as is characteristic of regulatory T (Treg) cells [35]. It appears that PVAC's immunomodulatory effect, if any, is not a consequence of stimulation of $CD24^+CD25^+$ cell proliferation.

Despite the negative results of this immunotherapy agent in the treatment of psoriasis, the immunomodulatory treatment approach for psoriasis is still rational [36]. Recently, several approaches to modulate cytokine responses with successful results it has been published. A double-blind placebo-controlled phase III trial exploring the effects of Etanercept (an anti-TNF-α agent) on clinical outcomes, fatigue, and depression in psoriasis, revealed that at week 12 the mean percentage of improvement in the dermatology life quality index (DLQI) was 69.1% in patients receiving Etanercept, compared with 22.1% in the placebo group ($p < 0.0001$; difference 47%, 95% CI 40–54) [37]. One pilot and two phase II trials with sc. IL-10 administration over 3–7 weeks in patients with moderate to severe psoriasis have suggest that IL-10 is of major importance in psoriasis and show that IL-10 administration represents a new therapeutic approach that is well-tolerated and may have clinical efficacy for psoriasis patients [38].

Finally, Alefacept is a recombinant, fully human fusion protein that selectively targets the memory T cell population implicated in psoriasis pathogenesis. The ability of Alefacept to induce lengthy disease remissions even in the absence of continued therapy was demonstrated [39]. Two courses of Alefacept conferred greater efficacy and duration of clinical improvement in psoriatic patients. This novel biologic agent is currently approved in the United States and under regulatory review in Europe for moderate to severe chronic plaque psoriasis.

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