The use of Amevive (Alefacept)®in moderate to Severe Psoriasis in Qatar

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Abstract:
Seven cases of severe psoriasis (PASI score exceeding 20) were treated with Amevive (Alefacept). They were started and maintained on 15 mg IM weekly doses for 12 weeks. PASI score and CD4 count were reported on weekly basis. The response rate ranged from 60-70% reduction in PASI score. Improvement continued without further treatment in most cases after discontinuation of therapy. Follow up of the same cases reached one year.

Introduction:
Psoriasis is now widely recognized as an immune-mediated disease of the skin with T cells playing a central role in its pathogenesis
Alefacept is the first biologic therapy approved for the use in patients with moderate to severe chronic plaque psoriasis. It is a fully human LFA-3/IgG1 fusion protein [1]
It has a dual mechanism of action that results in inhibition of T-cell activation and selective reduction of memory T cells [2]
Alefacept is a member in the biologic treatment family which is included in table 1. This family of the biologic treatments is growing by time.

Table 1

Generic name	Trade name
(alefacept)	**AMEVIVE®**
(etanercept)	**ENBREL®**
(infliximab)	**REMICADE®**
(efalizumab)	**RAPTIVA®**
(adalimumab	**HUMIRA®**

Patient and method:
Seven patients with severe psoriasis were treated with Alefacept (Amevive)®.

Patient Selection:
Male or female, excluding pregnant or lactating women, More than 18 years of age, Qatari, because the medicine is expensive, having moderate to severe psoriasis Plaque Type; PASI scores more than 10. Neither pustular, erythrodermic nor palmoplantar were included.
Duration of the disease should be more than two years, with history of more than one systemic treatment, regardless the type of response, including MTX, Retinoides and cyclosporine.
Patients discontinued all systemic treatment at least for four weeks prior to alefacept therapy. Patients should have a history of trial of photo-chemo-therapy; PUVA, NB-UVB and BB-UVB. Patients should also be naive to biologic treatments
All topical and systemic treatments were discontinued except for emollients and hydroxyzine. Other exceptions will be mentioned for each patient individually.
An evaluation sheet had been filled for all patients including:
Identification of patient; name, file number, age, sex, nationality, and weekly record both of PASI and CD 4+ T Cells count.
Other routine investigations were already done prior to alefacept treatment because these patients had a history of systemic treatments and were investigated accordingly. At the end of the treatment these routine investigations were repeated especially in patients with previous abnormal results.
Data analysis and discussion will include only six patients, because the seventh patient was irregular on treatment and will be discussed separately.
All patients were given Alefacept intramuscularly (IM) 15 mg weekly in the right and left sides of gluteal region alternatively
PASI score and CD 4+ T Cells count were reported on weekly or biweekly basis in all patients
All patients were photographed before and after treatment

Results:
Table two:

Pt.	Age	Sex	Mean PASI before	Mean PASI After	Mean CD4 Before	Mean CD 4 After
1	38	M	35.7	3.84	699	461
2	18	F	39.2	5.16	1467	1102
3	36	M	33.3	6.6	1041	811
4	30	M	44.3	9.84	508	338
5	51	M	60.6	12.7	616	614
6	48	F	38.9	5.04	1295	1130
Mean	36.8		42	7.2	938	666
		2 F/ 4 M				

Table two shows age, sex, mean PASI score and mean CD 4+ T Cells count and values before and after treatment

Age:
The mean age of patients was 36.8 year, the youngest was18 year female and the eldest 51-year male (Table 2)

Sex:
Patients were 2 females; (one third of the pts 33.3%) and 4 males (two thirds 66.6%)

PASI (charts 1-3) & (Table 2)
During treatment with alefecept there was neither steady nor regular improvement, but by taking the mean PASI scores for all patients the graph was more regular.
Mean PASI score before treatment was 42 (The lowest was 33.3 and the highest was 60.6).
Mean PASI score after treatment was 7.2 (The lowest was 3.84 and the highest was 12.7).
Mean PASI score reduction per week was 3.16 & this equaled almost 6.1% mean improvement per week

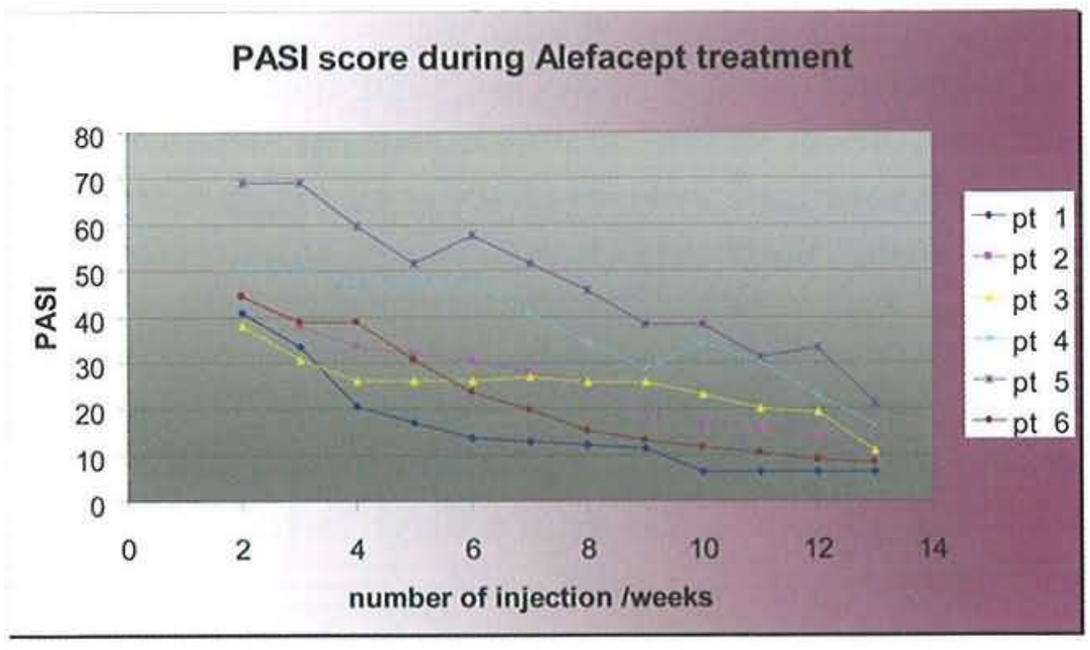


Chart 1 PASI score changes during treatment

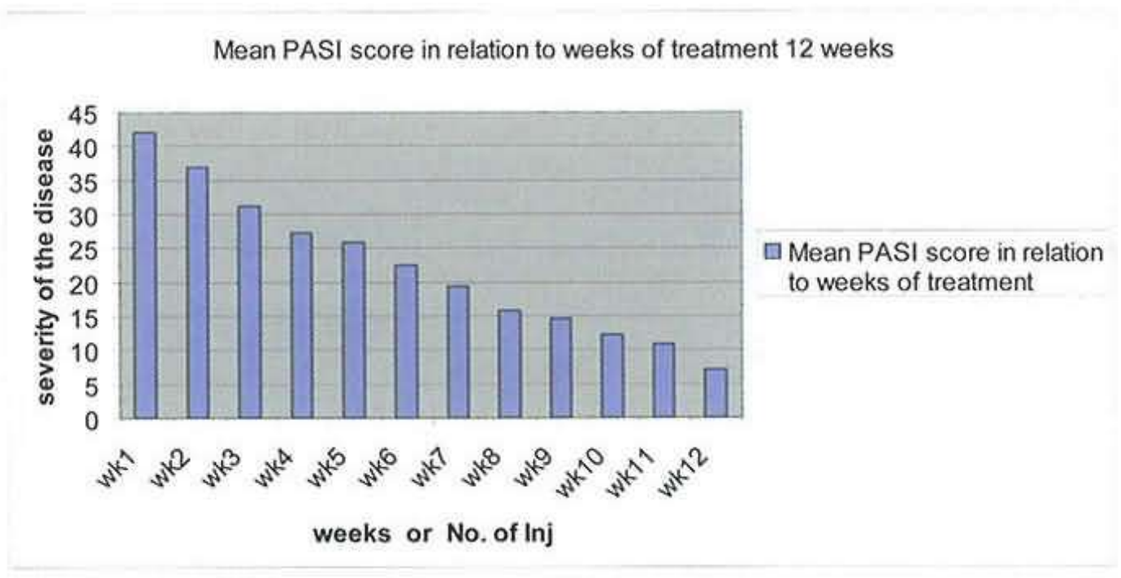


Chart 2 Mean PASI score in relation to weeks

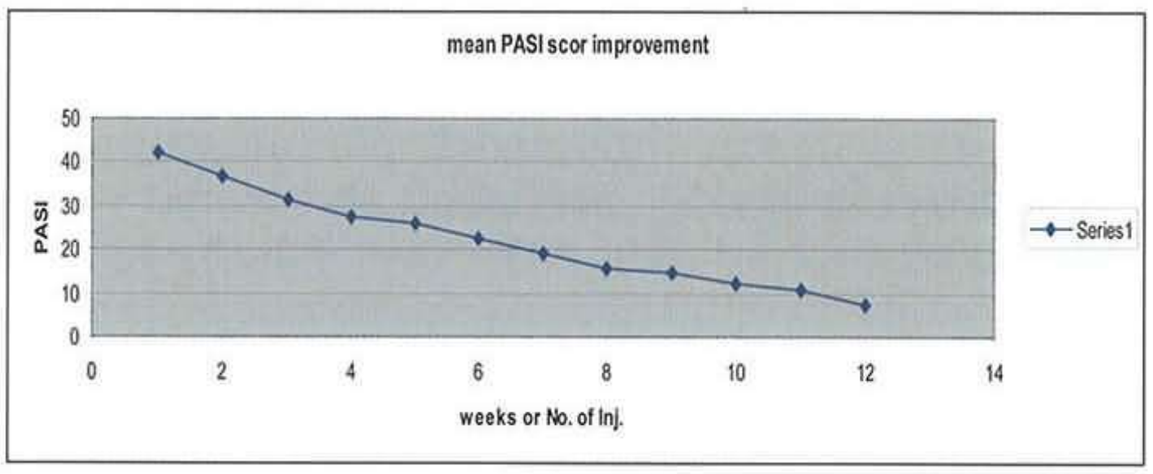


Chart 3 Mean PASI score improvement

Improvement: (Table three) & Chart 4
Mean percentage of improvement per week was almost 6.1 % of the remaining lesions. Three out of the six patients went abroad after discontinuation of treatment and were lost for further evaluation the remaining three showed stability or even further improvement for few weeks after the course had finished

Table three: Mean improvement of PASI

Weeks	wk1	wk2	wk3	wk4	wk5	wk6	wk7	wk8	wk9	wk10	wk11	wk12
Mean improvement of PASI	0	6.9	11.9	25.8	34.9	38.4	46.5	54.1	62.2	65	70.7	74.1

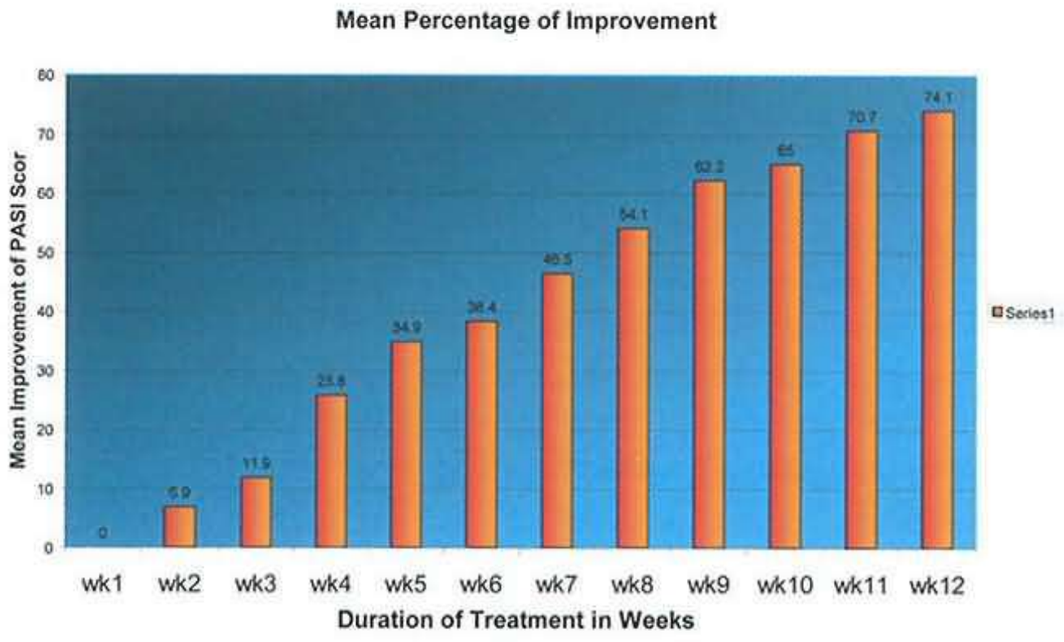


Chart four: Mean percentage of improvement

PASI score was not the only evaluating aid. Patients who had itching showed marked reduction in pruritus, concomitant or even previous to the clinical improvement, in addition to that the quality of life was markedly improved in most patients, particularly the females

CD 4⁺ T Cells (Chart 5 & table 2)
Mean CD 4+ T Cells count before treatment was 938 (range from 508- 1467).
Mean CD 4+ T Cells count after treatment was 666 (range from 461- 1130).
There was no relation between the level of CD 4+ T Cells count and the severity of the disease. Also there was no relation between the changes in the level of CD 4+ T Cells count and improvement of the disease.
CD 4+ T Cells count was variable from one week to another going almost always down and sometimes up but generally speaking there was gradual decline in the mean level of CD 4+ T Cells count.
In the whole period of the treatment regardless the initial level of CD 4+ T Cells count there was what looks like 30% reduction in the mean level of CD 4+ T Cells count. None of the patients showed reduction of CD 4+ T Cells count below 250

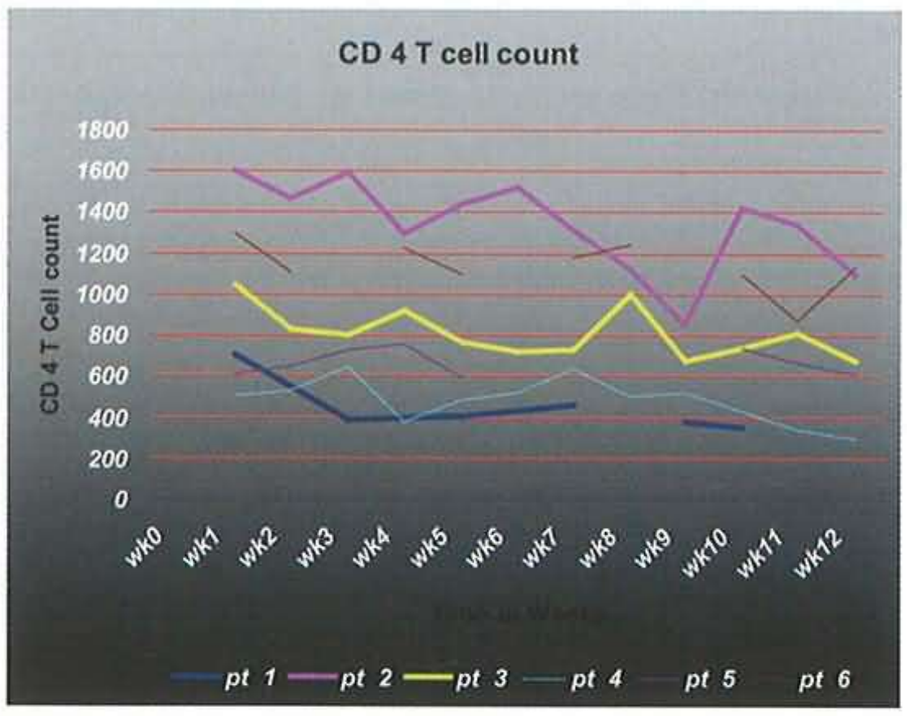


Chart five: CD 4+ T Cells count during alefacept treatment

Duration of the disease and age of onset before Alefacept treatment: (Table 4)

The mean duration of the disease before alefacept treatment was 15.3 years (range from 22-8years).
The mean age of patients before alefacept treatment was 21.5 years (range from 4-42 years).

Table 4: Duration of the disease and age of onset before Alefacept treatment

Pt.	Duration of Ps. Years	Age of onset
1	22	16
2	14	4
3	8	28
4	21	9
5	9	42
6	18	30
Mean	15.3 Y	21.5

Previous treatments and any relation (Table 5)

History of treatments prior to alefacept treatment showed that most patients had either systemic, phototherapy or combined treatments with mean of three treatments for a patient.
There was neither positive nor negative relation between type of these treatments and response to alefacept.

Table 5 Mean of three systemic and or phototherapy prior to amevive

RX.> PT.	MTX	Retin oids	CyA	BB-UVB	PUVA	NB-UVB	RE-PUVA	TOT
1		Y		Y		Y	Y	4
2	Y	Y	Y	Y	Y			4
3	Y							1
4	Y	Y	Y		Y		Y	4
5	Y		Y					2
6	Y		Y		Y	Y		4
	5/6	3/6	4/6	2/6	3/6	2/6	2/6	21/6
MEAN								3.1

Investigations

Routine investigations including CBC liver function tests (LFT) kidney function tests (KFT) Cholesterol triglycerides and fasting blood sugar (FBS) had been already done for all patients prior to alefacept treatment because these patients had a history of previous systemic treatments, phototherapy or combined therapy as mentioned above and were investigated accordingly. At the end of the treatment these routine investigations were repeated especially in patients with previous abnormal results and were almost unchanged suggesting that alefacept did not affect the side effects of previously given systemic treatments

Concomitant treatments:

All topical and systemic treatments were stopped during alefacept treatment except for emollients; mainly plane vaseline and/or Aquaderm. Hydroxyzine tab 10 mg also was allowed once at night only when needed
Patient number 2 had been applying calcipotriol mainly on the forearms which showed faster remission than before and faster than other non treated sites topically.
Patient number 4 was allowed to continue using Hydrocortisone butyrate topically (Locoid Lipocream) only on the forarms and it was very fast in improving these areas compared to other sites and faster response than before amevive.

Table of the side effects related to number of patients :

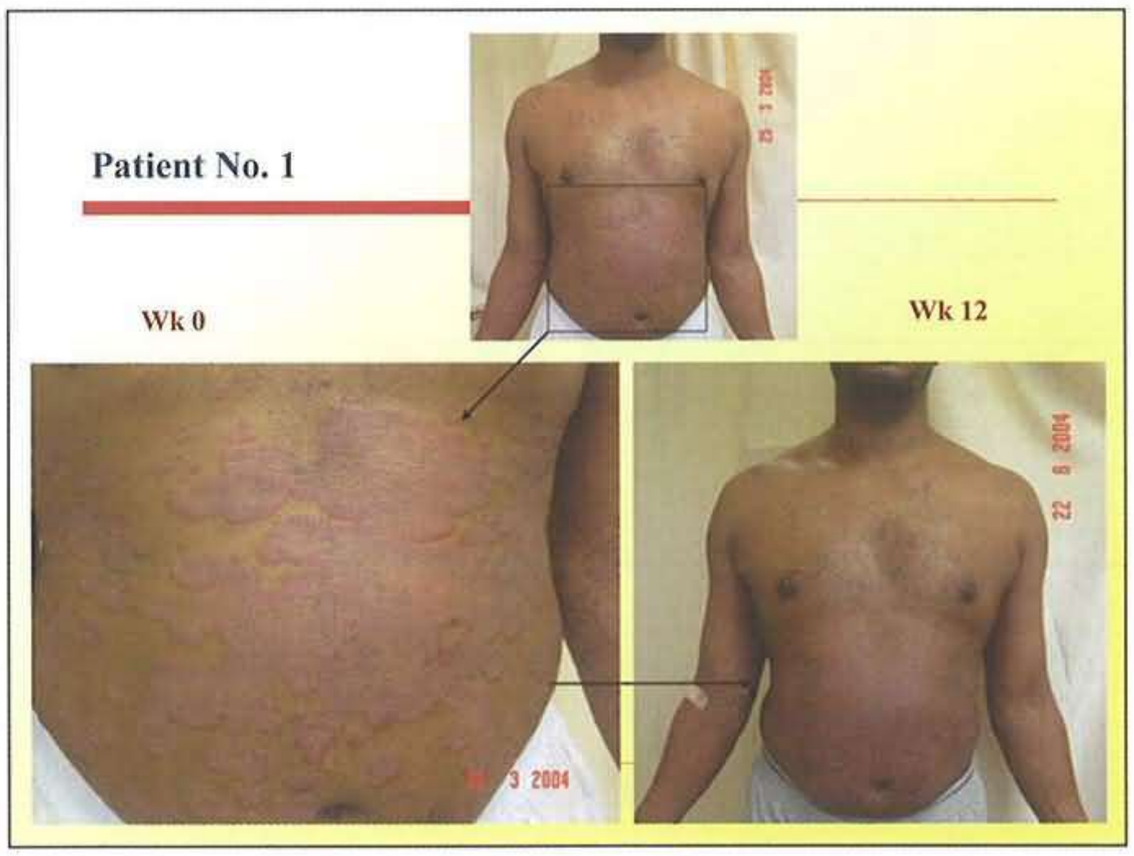
Side effects	No. of pt.s
Mild dizziness 1-2 days after the injection (3 times only)	1/6
Sore throat and low grade fever (2days after 2nd injection)	1/6
Severe hair loss started with the first injection (should be investigated in more patients)	1/6
Cold after the 11th injection	1/6
Sweating & mild burning (after 1st injection)	1/6
Transient headache for few hours (after 3rd injection)	1/6

Individual Patients assessment and special notes:

Patient No. 1

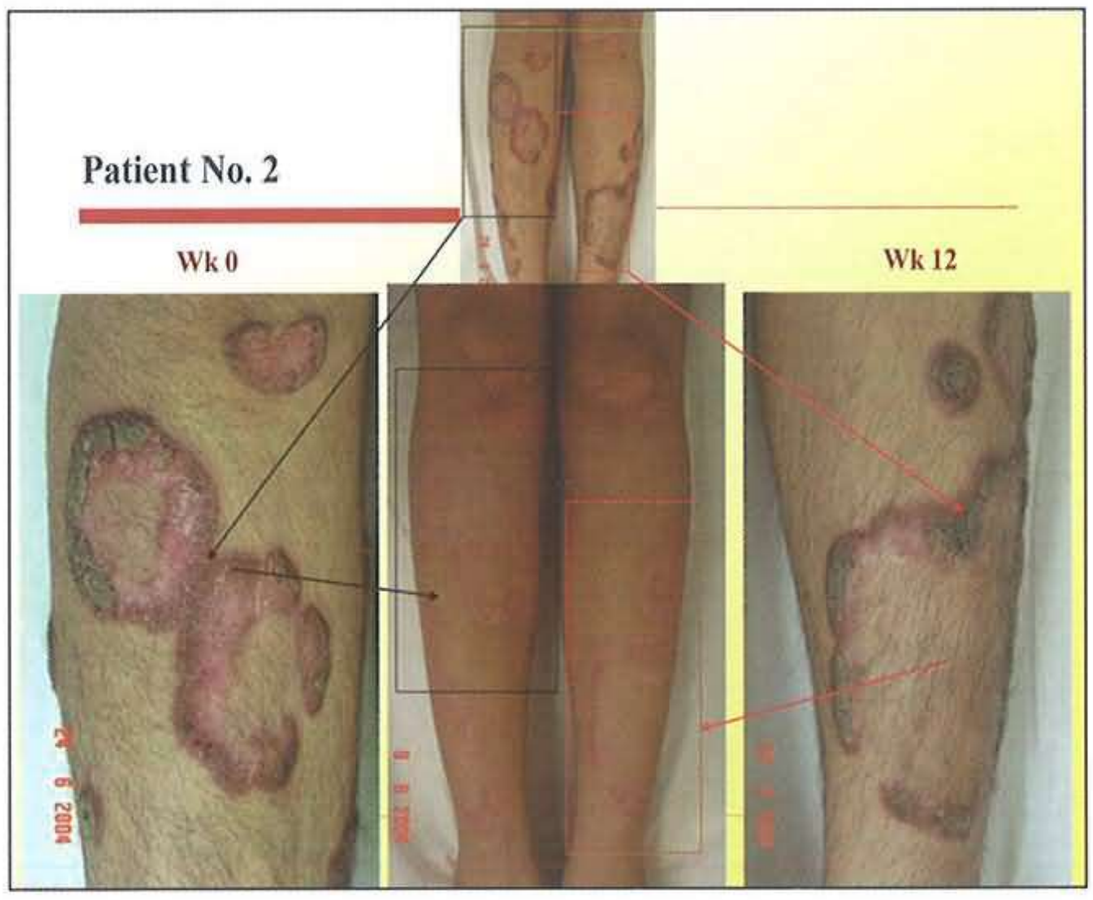
The first patient showed 20% of improvement 1 week after the first injection; this could be due to the psychological belief that what he was using is new and expensive.

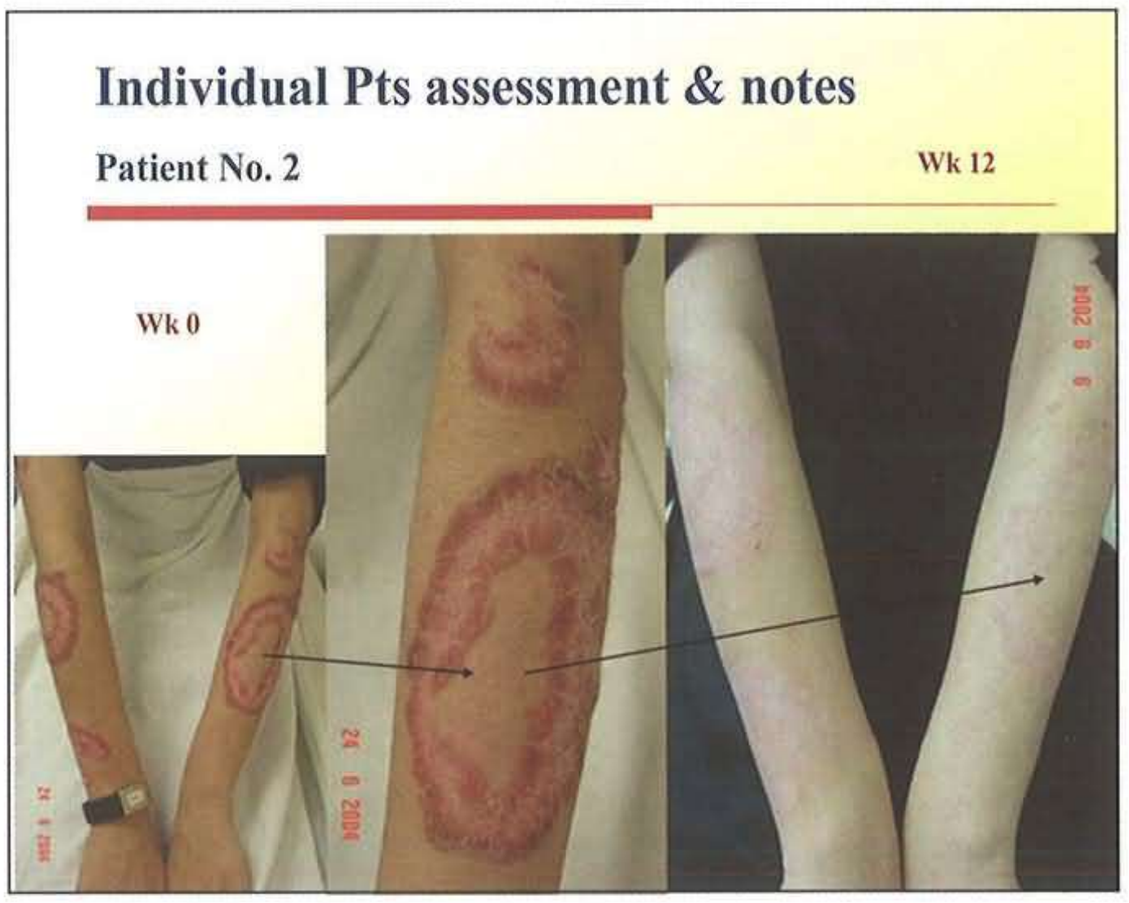
Same patient showed marked reduction of both erythema and pruritus after only one week, and after one more week pruritus disappeared completely. Patient had transient headache for few hours after the third injection

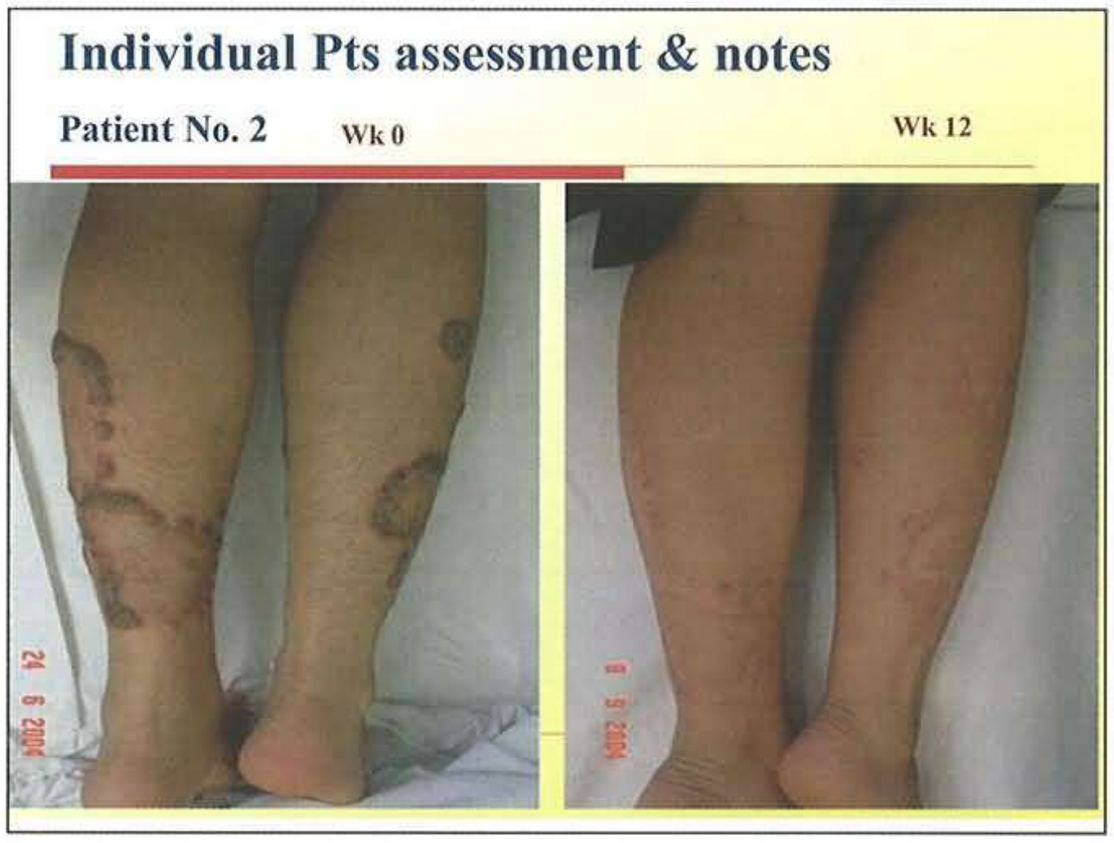


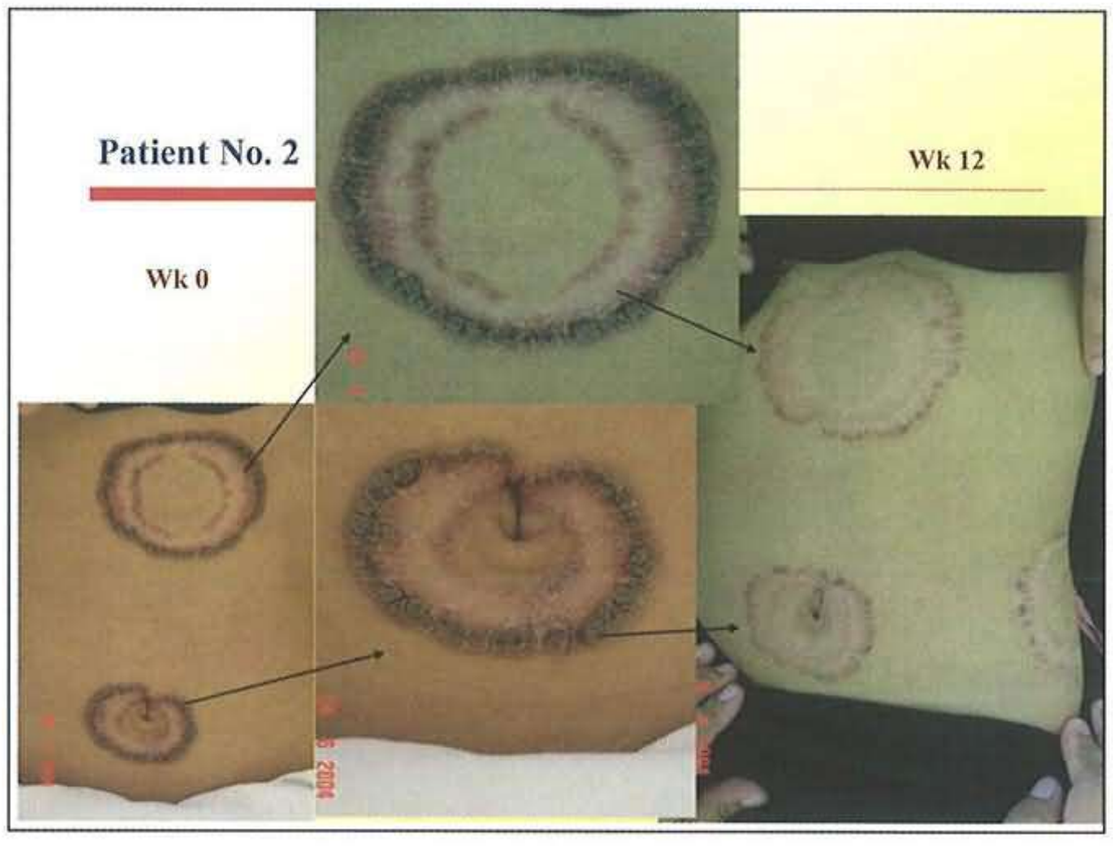
Patient No. 2

Patient applied calcipotriol topically with faster remission than before and faster than other sites. There was mild dizziness one to two days after the injection, this happened only three times out of twelve. CD 4 was declining for four weeks but it increased after patient's father had died.

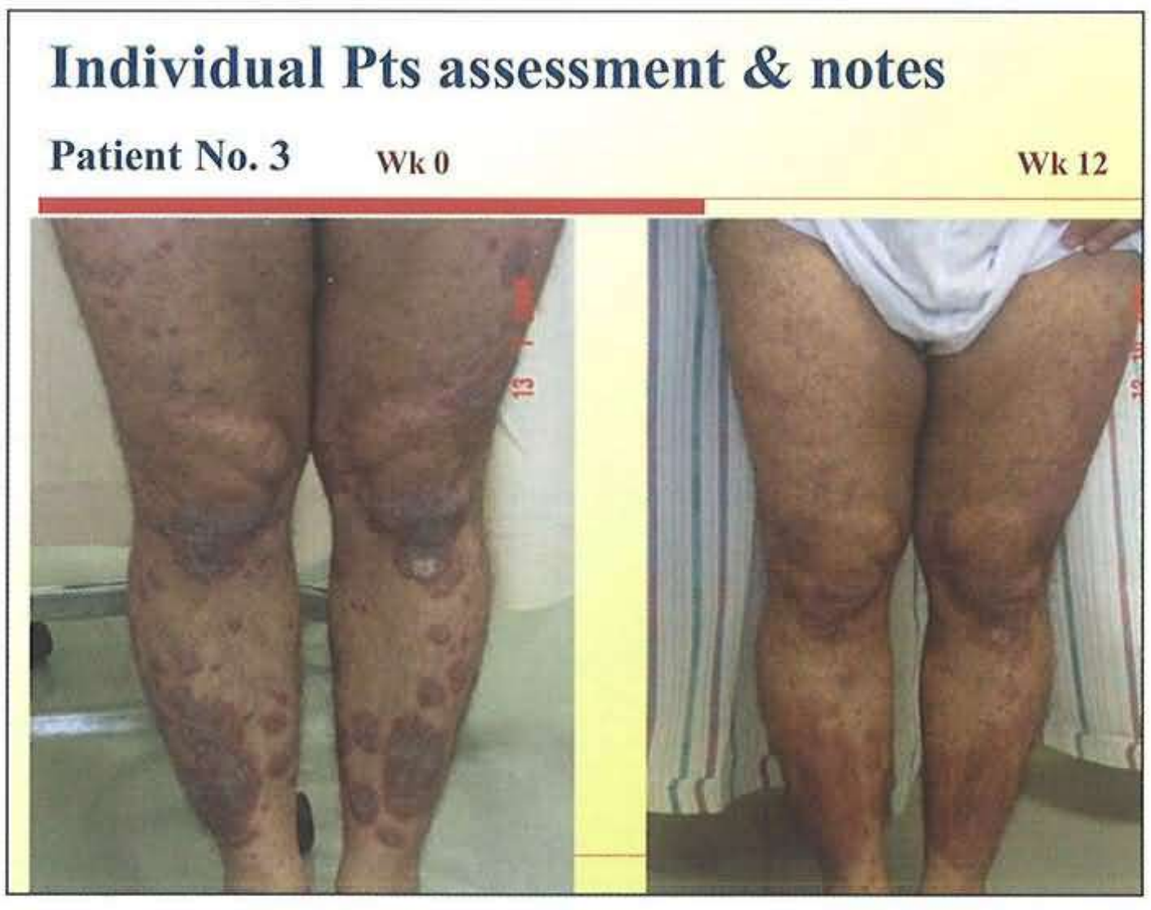


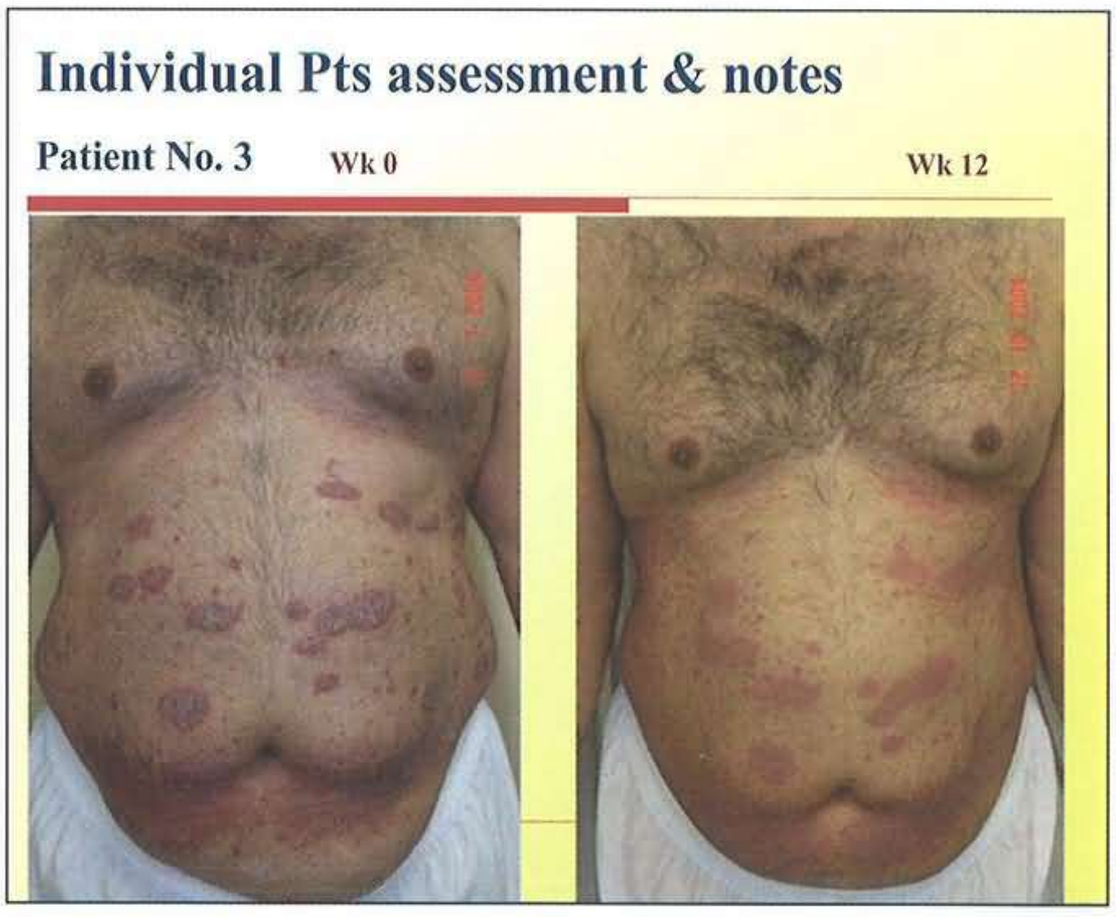






Patient No. 3:
Patient had mild unchanged vitiligo (limited to the hands) during alefacept treatment



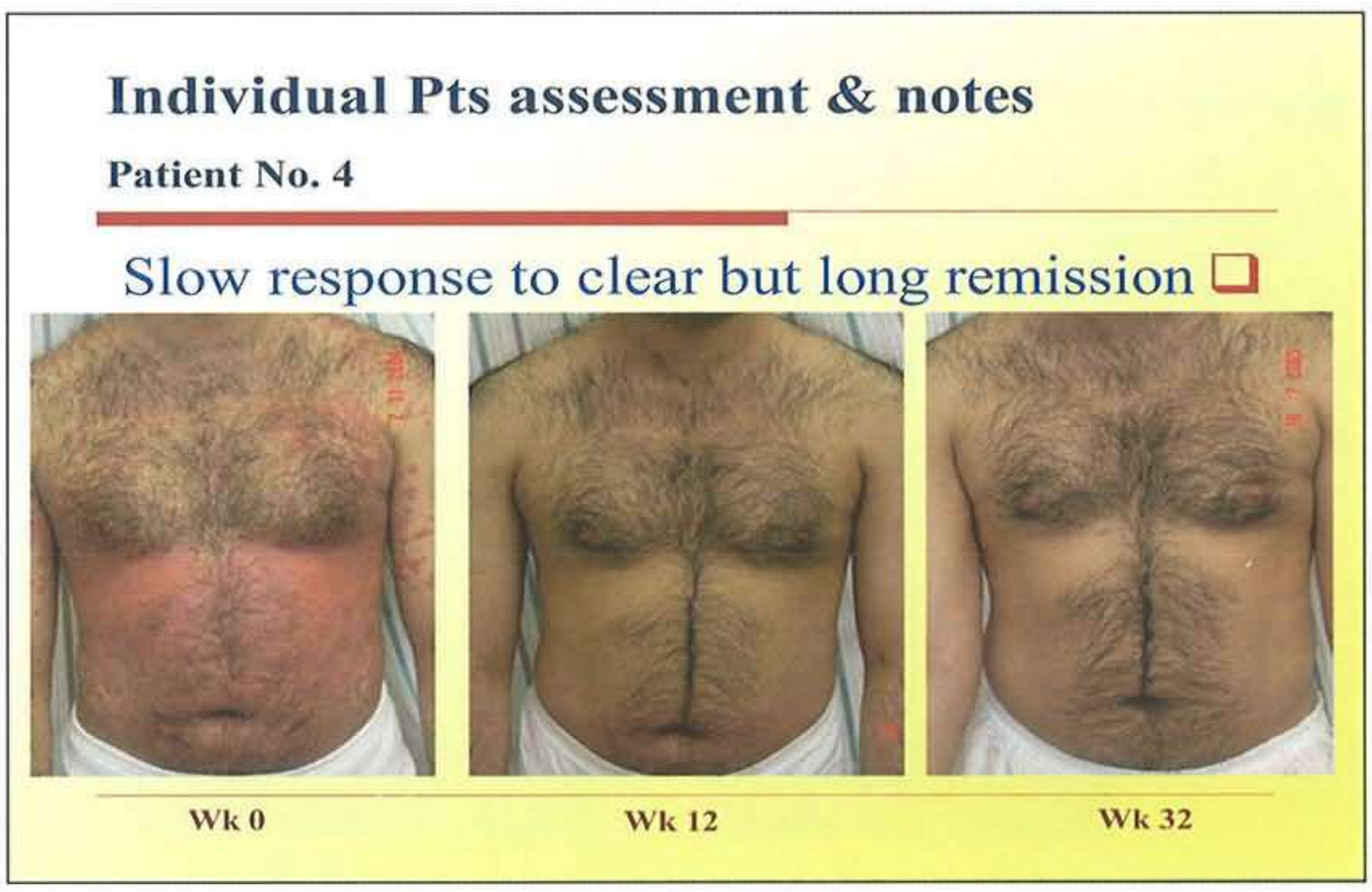


Patient No. 4

Because of sore throat and fever patient missed one injection. This was followed by increase in the CD 4.

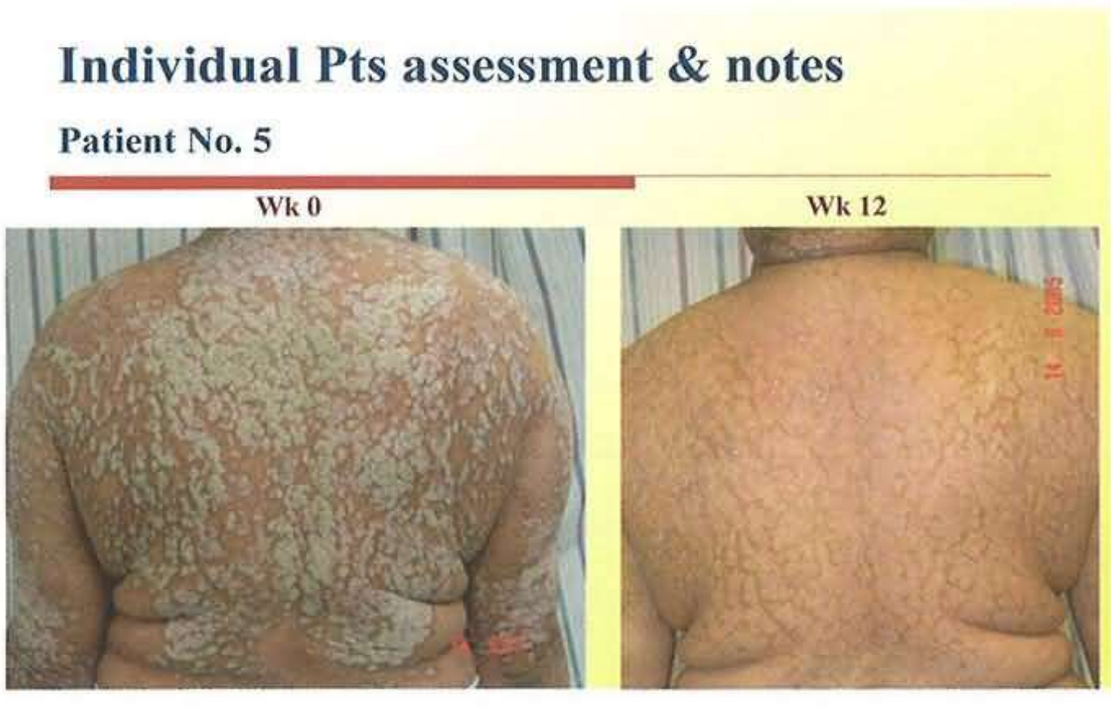
Clearance period after discontinuation of treatment lasted for 15 weeks after discontinuation of alefacept treatment, except for legs. Before alefacept patient had severe pruritus. This pruritus responded late and improved after the eleventh injection.

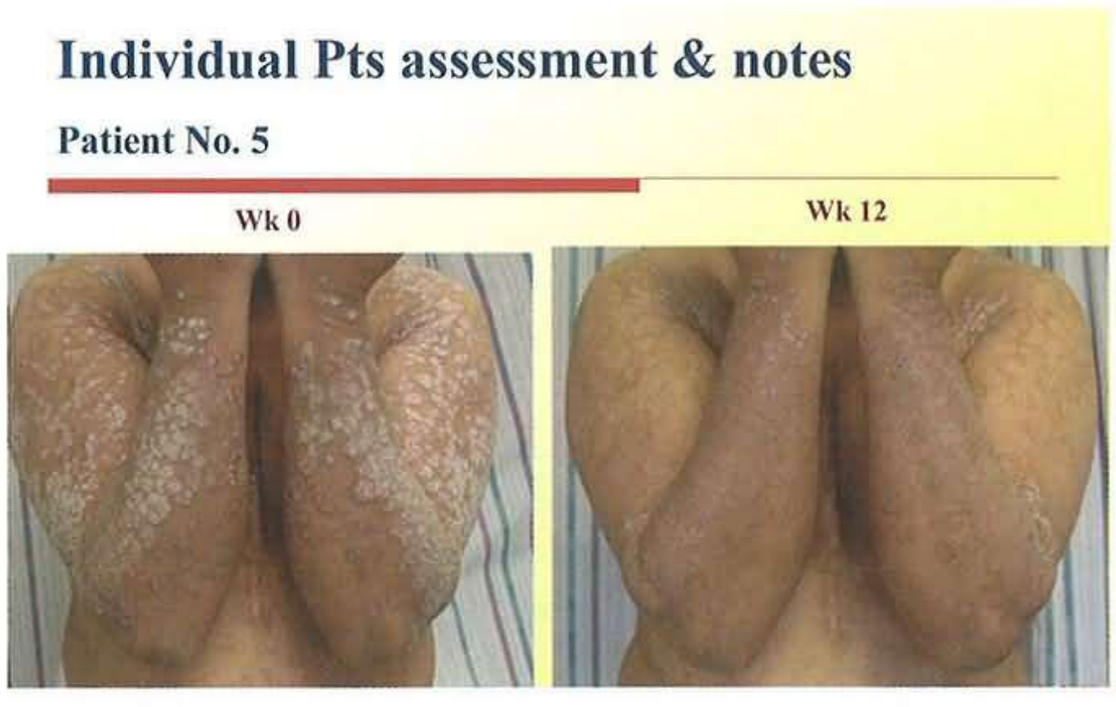
Patient stated that he had severe hair loss started with the first injection, but on examination it was that of male pattern alopecia. Topical hydrocortisone butyrate (Locoid) was very fast in improving the forearms during alefacept treatment.



Patient No. 5

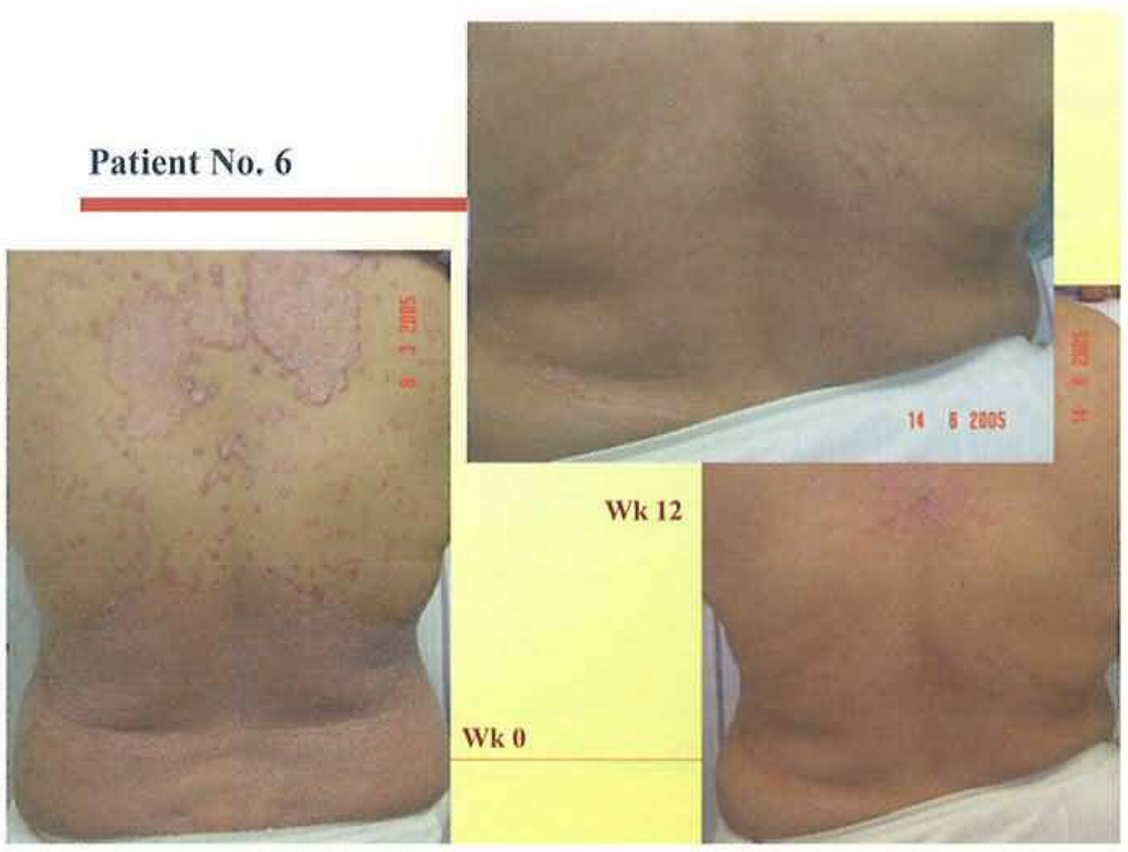
Patient is known cardiac on aspirin, he had also controlled hyperlipidemia on treatment. Checking drug-drug inter action there was no inter action among (nifedipine, aspirin and amevive). Because of common cold, the eleventh injection was postponed for a week. Erythema started to improve after the 6th injection while scales needed two more weeks

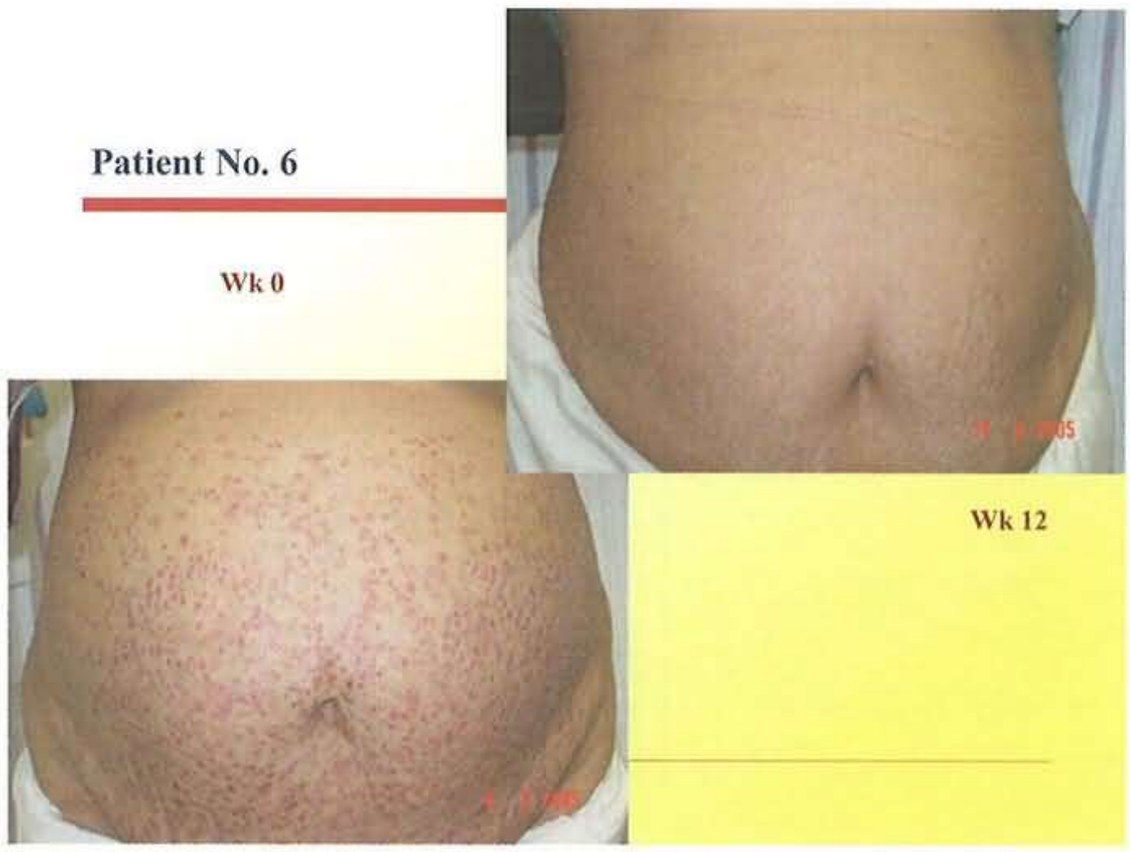


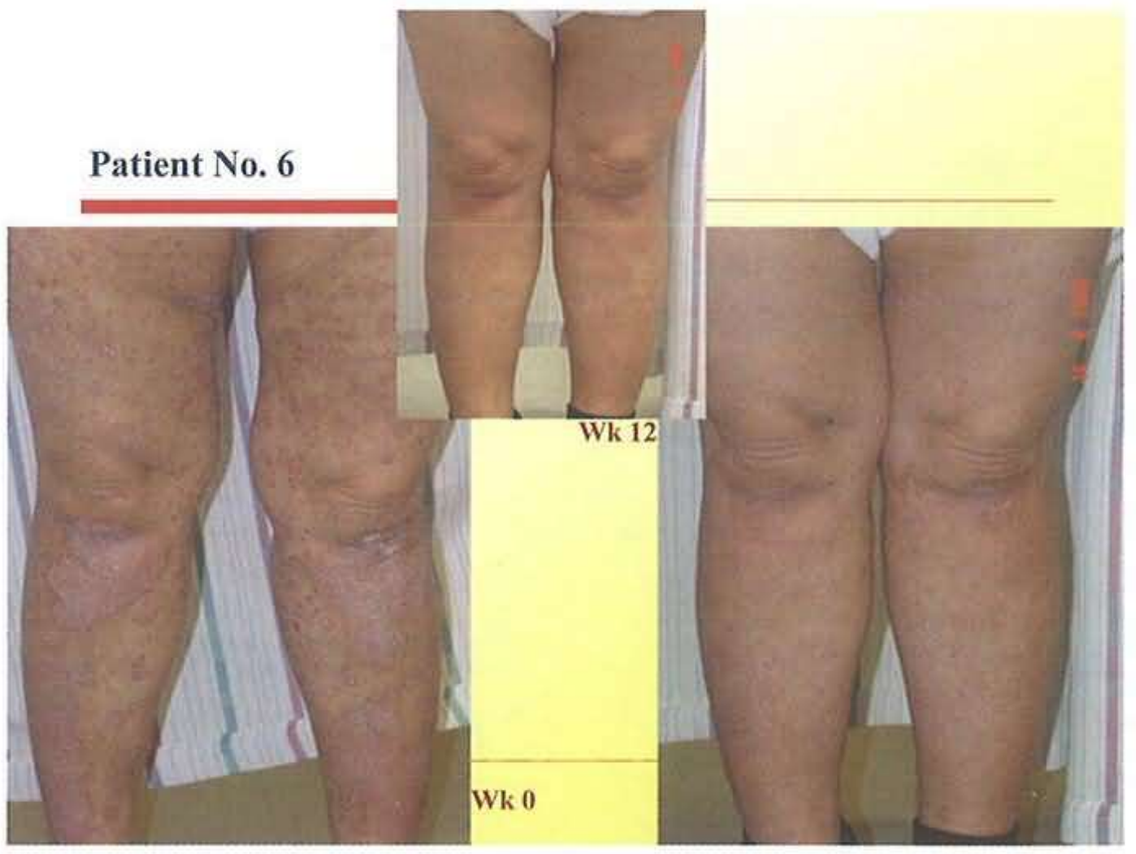


Patient No. 6

Patient had moderate to severe psoriasis with flexural sub-mammary and nail psoriasis. Erythema started to improve after the 2nd injection. Scales were less after the 6th injection. Patient had occasional sweating and mild burning sensation at the site of the injection. Most of lesions disappeared after the 10th injection.







Patient No. 7

The seventh pt took seven injections then he was abroad for ten weeks. He resumed treatment for another 5 injections but improvement was not as expected which means that intermittent treatment might reduce efficacy.

Discussion:

Generally speaking all patients tolerated the treatment.

Some patients had minor complaint after first injection but disappeared later on, such as transient headache for few hours after the injection. Three patients (50%) went abroad on completing the course and were followed up by phone.

Our patients are expecting a lot, and they consider 80% improvement as no change.

Alefacept was the first biologic to be approved in the United States for the treatment of adult patients with moderate to severe chronic plaque psoriasis. Alefacept is a recombinant, fully human dimeric fusion protein that selectively targets the memory effector (CD45RO+) T-cell population implicated in the pathogenesis of psoriasis [3].

Activated memory T cells, expressing CD2, are key components in the pathogenesis of psoriasis. Alefacept binds to CD2, blocks co-stimulatory signaling, and selectively induces apotosis of pathogenic T cells [4].

We used the intramuscular rout of administration in a dose of 15 mg weekly for twelve weeks followed by a 12-week observation period, although the drug may be administered at a fixed dose of 7.5 mg by 30-second IV bolus once weekly for 12 weeks followed by a 12-week observation period [5].

The mean age of our patients was 36.8 year, the youngest was18 year female and the eldest 51-year male. Alefacept data from multiple-course clinical trials were examined to evaluate the safety of alefacept in the elderly and diabetic populations. Overall, alefacept appears to be equally well tolerated in these special patient populations [6].

We used alefacept in a dose of 15 mg weekly although higher doses are studied [7].

In our patients all topical and systemic medications had been stopped for at least two weeks before alefacept was started, in an attempt to evaluate the efficacy of alefacept alone.

A safe and effective strategy for transitioning patients with psoriasis from cyclosporine to alefacept therapy [8], And Alefacept in combination with tapering doses of methotrexate in patients with psoriasis [9] were discussed in the literature

In all our patients we used alefacept for twelve one course only for evaluation, later on and for larger number of patients we may use it for extended courses as long as 16 weeks [10], and for several courses , because the improvement of psoriasis will be much more and correlated with the number of courses [11]. In the literature some patient completed the ninth course [12].

We used calcipotriol in one patient only which was applied to limited small areas, the treated sites showed faster and better response consistant with other poster presentations [13].

Alefacept was also reported to be safe and more effective if combined with Narrow band UVB [14].

In the whole period of the treatment of our patients regardless the initial level of CD 4+ T Cells count there was what looks like 30% reduction. Reductions in CD4+ T-cell counts with alefacept have been predictable, with no cumulative effects noted after multiple courses of treatment. There has been no increased incidence of infections [15].

Alefacept is considered an immunosuppressive as it appears to induce dose-dependent reductions in CD4+ and CD8+ T-lymphocyte counts. CD4+ T lymphocytes must be monitored in all patients receiving the drug and dosing withheld if these counts fall below 250 cell/μL.

The data suggest that alefacept is not associated with an increased risk of infection and patients will respond to vaccination during therapy [3].

Finally adverse events in the placebo and active treatment arms did not differ. It is concluded that alefacept significantly improves psoriasis and produces durable clinical improvement with a very favorable safety profile [4].

Conclusion:

In a group of small number of patients

- Alefacept was effective in the treatment of moderate to severe chronic plaque type psoriasis
- It was effective in patients who were tried on more than one systemic treatment
- Mean reduction in PASI score was 74% (12th and 16th week)
- Variable post therapeutic clearance (up to 4 Months)
- Mean CD 4 T cell was reduced by 30% but did not go below 250
- Alefacept treatment did not affect other routine investigations
- Combined topical treatment with either rcalcipotriol or hydrocortisone butyrate gave faster improvement on localized exposed lesions
- A list of recorded transient side effects
- Intermittent treatment will reduce efficacy
- Other etiological factors of psoriasis should be considered in any treatment.

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