DOI: 10.1111/j.1468-3083.2010.03610.x JEADV

ORIGINAL ARTICLE

Adjuvant triamcinolone acetonide injections in oro-pharyngeal pemphigus vulgaris

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Abstract

Background High-potency topical and perilesional/intralesional corticosteroids are becoming increasingly useful as adjuvant to treat autoimmune blistering diseases.

Objective We sought to evaluate the role of perilesional/intralesional triamcinolone acetonide (PITA) injections in reducing the time for first complete clinical remission and the total amount of systemic corticosteroids in oro-pharyngeal pemphigus vulgaris (OPV) patients, and also the compliance of PITA injections, in terms of satisfaction, pain and discomfort.

Methods Thirty-five OPV patients were treated with conventional immunosuppressive therapy (CIST) and received high potency topical corticosteroids (clobetasol and/or methylprednisolone) and/or PITA injections. Patients were grouped as follows: (i) a group of 16 patients was treated with PITA injections and (ii) a group of 19 patients without PITA injections.

Results Sixteen patients treated with PITA injections and 19 without PITA injections reached complete clinical remission within 126.6 days (SD: 41; 95% CI: 104.7–148.8) and 153.2 days (SD: 97.4; 95% CI: 106.2–200.1) ($P = 0.4$) respectively. The total amount of corticosteroids in patients treated with PITA and without PITA was 4894 mg (SD: 2832; 95% CI: 3385–6403) and 5312 mg (SD: 4009; 95% CI: 3380–7245) ($P = 0.4$) respectively. Patients treated with PITA reported a satisfaction score significantly higher than pain ($P = 0.0007$) and discomfort score ($P = 0.0006$).

Conclusion Perilesional/intralesional triamcinolone acetonide injections seems to represent a helpful clinical tool to successfully join CIST, in terms of shortening the time of complete clinical remission, reducing the total amount of corticosteroids and obtaining an acceptable compliance.

Received: 25 August 2009; Accepted: 14 January 2010

Keywords

oral mucosa, pemphigus vulgaris, remission, side-effects, topical corticosteroids, triamcinolone acetonide

Conflict of interest

Contents of the manuscript have not been previously published and are not currently submitted elsewhere. Authors have no conflict of interest to declare and all participated in the preparation of the manuscript.

Introduction

Pemphigus vulgaris (PV) is a potentially life-threatening autoimmune mucocutaneous blistering disease caused by a humoral response directed against keratinocyte desmosomal cadherins, such as Desmoglein 1 and 3 (Dsg1/3), resulting in an impairment of adhesive function with subsequent blister formation.[1]

Currently, conflicting data are present in the literature on which is the most effective and safest treatment option for PV.[2] Several lines of evidence have shown the pivotal role of systemic corticosteroids (CS) in the treatment of PV, even though the optimal dose regimen remains unknown.[2] As far as the oro-pharyngeal PV (OPV) is concerned, the treatment still remains a challenge because of the chronic nature of the disease[3] and the rough oral environment (poor oral hygiene, prosthesis, restorations, poor oral habits, smoking, alcohol consumption and so on) that makes oral mucosa very susceptible to PV and the most difficult and recalcitrant site to be managed. These might be the reasons why oral lesions in PV patients appear to be more resistant to treatment, healing much more slowly than cutaneous lesions[4] and then, slowing down the tapering of CS.

It has been shown that several topical CS are used as an adjuvant therapy to limit systemic CS-related adverse events.[3] Among them, triamcinolone acetonide has been used as a cream 0.1% or perilesional/intralesional injections in the remnant and recalcitrant

PV lesions.[4–6] Even though the role of perilesional/intralesional triamcinolone acetonide (PITA) injections seems to be useful in rapidly tapering CS,[4] data available are, however, scanty.

The primary outcomes of this longitudinal open-label trial were the evaluation of the efficacy of PITA injections in terms of time for first complete clinical remission either 'on' or 'off systemic therapy', and total amount of systemic CS up to the first complete clinical remission, comparing two groups of patients treated with and without PITA injections. The secondary outcomes were the evaluation of compliance of OPV patients treated with PITA injections in terms of pain, discomfort and satisfaction.

Materials and methods

Patients

This investigation was a single-centre longitudinal open-label trial, carried out between 1994 and 2007, at the Oral Medicine Unit, Federico II University of Naples, Italy. All patients provided their written informed consent before participating in the study.

Patients were recruited according to the detailed inclusion and exclusion criteria. The inclusion criteria were: (i) typical clinical findings with active bullous and/or erosive lesions on the oro-pharyngeal mucosa only, (ii) immunohistopathological findings exhibiting suprabasal detachment, with intercellular staining of IgG and/or C_3, (iii) serological evaluation via both indirect immunofluorescence (IIF) and enzyme-linked immunosorbent assay (ELISA), to detect the presence of anti-desmoglein 1 and 3 IgG antibodies, and (iv) OPV patients entered in complete clinical remission either 'on' or 'off systemic therapy' to calculate the exact amount of CS administered.

Conversely, the exclusion criteria encompass: (i) patients with mucocutaneous or cutaneous PV; (ii) OPV patients in partial clinical remission; (iii) patients with concomitant severe systemic diseases such as malignancies, infections, gastro-intestinal and coagulation disorders; (iv) patients with other concomitant autoimmune pathologies; (v) patients for whom the parenteral drug administration is contraindicated; (vi) patients allergic to local anaesthesia or CS or adjuvants; (vii) patients previously treated with different CS injections; (viii) patients treated with different therapies such as intravenous immunoglobulin therapy or anti-CD 20 monoclonal antibody (Rituximab); (ix) drug-addicted or alcoholic patients; (x) pregnant patients; and (xi) patients unable to give consent. Patients who developed one of these conditions during the treatment were automatically excluded from the study.

All patients were treated with conventional immunosuppressive therapy (CIST), made up of systemic CS and immunosuppressive agents (ISAs) and, except four, with topical CS, such as clobetasol (CB) and/or methylprednisolone (MT). PITA injections were scheduled for still present oro-pharyngeal lesions after 2–4 weeks of CIST. As some patients showed a low compliance (needle-fear and/or low pain threshold), two groups of patients were formed: (i) 16 patients received PITA injections; and (ii) 19 patients received solely CB and/or MT (Table 1).

Table 1 Patients' characteristics

	No. (%)
Total	35 (100)
Female treated with PITA	11 (31.4)
Male treated with PITA	5 (14.3)
Mean age at diagnosis (range)	F: 47.3 years (17–73)
	M: 50.8 years (28– 67)
Female treated without PITA	11 (31.4)
Male treated without PITA	8 (22.9)
Mean age at diagnosis (range)	F: 51 years (34–72)
	M: 36.8 years (25–52)
Patients	
In complete clinical remission at last control	35 (100)
In complete clinical remission at last control 'off-therapy'	13 (37.1)
In complete clinical remission at last control 'on-therapy'	21 (60)
Died*	1 (2.9)
Disease severity at onset†	
Mild	0 (0)
Moderate	6 (17.2)
Severe	29 (82.8)

*Patient died 3 years after achieving a complete clinical remission 'on therapy'.

†Mild: severity score ≤2; Moderate: 3 ≤ severity score ≤6; Severe: severity score ≤7.

Definition of disease severity and clinical remissions

Based on a previous model,[7] the severity of the disease was graded on a 0–10 scale based on the sum of the extent of the disease, and on the dosage of corticosteroids and adjuvants. The extent of the disease was graded on a 0–4 scale, based on the number of the different anatomical locations of oro-pharyngeal mucosa involved; there are 11 locations, i.e. (1) lips, (2) upper and/or lower fornices, (3) upper and/or lower gingiva, (4) hard palate, (5) soft palate, (6) cheeks, (7) tongue, (8) floor of the mouth, (9) pharynx, (10) larynx and (11) oesophagus. In the same way, we scored the corticosteroid therapy (0–4 score), by evaluating how many milligrams of prednisone were administered daily, to which was added a score of +1 or +2 based on how many milligrams of azathioprine or cyclophosphamide were given. Disease severity was classified as mild for a score of ≤2, as moderate for a score from 3 to 6, and severe for a score higher than 7. The scores were recorded at the first examination and then every 6 months.

The definition of complete and partial clinical remission 'on and off therapy', and 'failure of therapy' was based on the

Consensus Statement from the International Pemphigus Committee.[8] The duration of remission was classified as short if it lasted more than 1 month and less than 6 months, while it was classified as long if it lasted 6 months or more.[7]

Treatment protocol

After receiving a certain diagnosis of PV, approximately 1 week after the first visit, all patients were treated with a high dose of CS whose range varied from 75 mg to 100 mg of Prednisone per day (Deflazacort equivalent)[9] (Tables 2 and 3). The dose was reduced in increments of 5–25 mg every other day until a regimen of 100–0/90–0/75–0 (depending on the initial dose of corticosteroids administered to each patient) was reached, only when the activity of the disease was being controlled (maintenance phase).[4] The disease was said to be 'controlled' when there was a reduction of 75% of all oral lesions and an absence of new blisters.[10] At that point, if all oro-pharyngeal lesions continued to heal and no relapses occurred, the dose was progressively reduced to 50 mg twice a week.

Adjuvant therapy with ISAs envisaged the use of azathioprine ranging from 50 mg to 150 mg per day, or cyclophosphamide ranging from 50 to 100 mg daily (Tables 2 and 3), from the beginning of therapy or subsequently, if the patients did not show any remarkable improvement (> 75% reduction in the number of lesions within 2 months), or the disease relapsed after tapering the CS, or the patient developed contraindications to the use of systemic CS.

Topical CS were administered as follows: in widespread OPV lesions, MT was given as mouthwash four times a day at the dosage of 2 g dissolved in 500cc of saline solution per week. In localized OPV lesions, CB ointment 0.05% was given mixed 1 : 1 with orabase. In case of gingival lesions, CB was applied with custom-made, vacuum-formed, soft plastic applicator trays, covering the attached gingiva.[9]

Perilesional/intralesional triamcinolone acetonide injections were introduced at the dosage of 40 mg/mL diluted 2 : 1 with saline (i.e. 25 mg/mL) per four lesions at weekly interval for at least 2 weeks. A single investigator administered all the PITA injections.

In addition, all OPV patients were treated with topical alcohol-free chlorhexidine 0.2% rinse twice a day and were advised to undergo a weekly professional session of oral hygiene, to remove dental plaque, throughout the administration of TA injections.

All patients were clinically examined every week before remission, and every 2 weeks for 4 months after remission and bimonthly thereafter. The appearance of new lesions and/or the presence of pre-existing lesions were clinically evaluated, to establish whether or not a patient needed further injections. Patients who experienced a complete clinical remission of their oro-pharyngeal lesions after the first two sessions were not recalled anymore for further injections. In case of partial resolutions of these lesions, patients were seen every week to repeat the treatment until complete resolution of the lesions. Patients were monitored for any side-effects of the systemic and topical therapy.

Technique of TA injections

A 28-gauge needle on a 1-mL insulin syringe was used to inject 25 mg/mL of diluted TA [Triacort, Pharmatex Italia S.r.l., Milano, Italy; Kenakort, Bristol-Myers Squibb S.p.A, Sermoneta (LT), Italy; Triamvirgi, Fisiopharma S.r.l., Palomonte (SA), Italy].

Oral mucosa was anaesthetized with a local application of 2% lidocaine in gel, before performing injections. For gingival lesions, the upper and/or lower lip was stretched and everted, so as to show the gingival fornix. The needle was inserted along the mucogingival junction perpendicularly to inter-incisor line, not deeply in the fornix, in order to not disperse the drug in the submucosa, and not on the attached gingiva. It is necessary not to traumatize periosteum to avoid a painful inflammation. For oral lesions other than gingival sites, TA injections were administered perilesionally if their extent was less than 50%, and intralesionally if it was wider than 50%. TA should be always delivered in the sub-lesional area.

Patients were discharged home with the following therapy: chlorhexidine 0.2% rinse twice a day for 3 days and Acethaminophen (1000 mg p.o.) in case of unbearable pain.

Endpoints assessment

The primary outcomes, evaluated from the date of diagnosis, were: (i) the time to achieve the first complete clinical remission; (ii) the total amount of systemic CS until first complete clinical remission. The secondary outcomes, evaluated only in the PITA group, assessed the following variables after the treatment: (i) the perceived level of pain; (ii) the perceived level of discomfort; and (iii) the overall level of satisfaction.

A 11-point Numerical Rating Scale (NRS)[11] was used to evaluate pain intensity, discomfort and satisfaction experienced by OPV patients. The NRS asks a patient to rate her or his pain/discomfort/satisfaction by assigning it a numeric value, with 0 indicating no pain/ no discomfort/ no satisfaction and 10 representing the worst pain/discomfort imaginable/complete satisfaction (Fig. 1).

Statistical analysis

Kaplan–Meier survival analysis was applied for the mean time of complete clinical remission of oro-pharyngeal lesions and, then, a log-rank test was used to compare the time of complete clinical remission of these lesions between the two samples (with and without TA). Data were stratified according to the daily dosage of CS. Wilcoxon signed-rank test was applied to compare the level of satisfaction with pain and discomfort perceived by OPV patients. *P*-values of less than 0.05 were considered significant. Statistical analysis was performed using the Statistical Package for Social Sciences, version 16.0 (SPSS Inc., Chicago, IL, USA).

Table 2 Disease extent and disease severity at first visit, time of first complete clinical remission, systemic and topical treatment with triamcinolone (TA) injections in oropharyngeal PV patients

Pts	Age in years/Sex	Body weight (kg)	Disease extent at presentation	Disease severity at presentation	Time for first complete clinical remission (days)	CS* (mg) initial dose daily	Total CS (mg) up to the first complete remission	ISA† (mg) initial dose daily	Topical treatment‡	Sessions of TA injections	Short-term side-effects of TA
1	17/F	67	All	Severe	120	100	4875	0	MT + TA	3	None
2	25/F	62	2	Moderate	105	75	2310	0	CB + MT + TA	2	Gingival neovascularization and pellets
3	28/F	65	4	Severe	105	100	3300	100 AZ	CB + MT + TA	2	Gingival pellets and Candidiasis
4	43/F	70	All	Severe	180	100	7525	100 AZ	MT + TA	5	None
5	44/F	65	5	Severe	240	100	12455	100 AZ; 50 CY	CB + MT + TA	7	Candidiasis
6	45/F	63	3	Severe	90	90	2395	100	MT + TA	4	Gingival pellets
7	47/F	68	4	Severe	90	100	2650	100 AZ	MT + TA	5	None
8	58/F	59	2	Moderate	120	75	3520	0	TA	4	None
9	69/F	70	All	Severe	120	100	4785	150 AZ	MT + TA	5	None
10	72/F	85	3	Severe	180	90	9705	100 AZ	CB + MT + TA	8	Candidiasis
11	73/F	93	All	Severe	90	100	2600	100 AZ	TA	4	None
12	26/M	71	All	Severe	120	100	4785	100 AZ	MT + TA	6	None
13	48/M	85	All	Severe	135	100	5235	150 AZ	TA	3	None
14	54/M	66	4	Severe	90	100	2600	150 AZ	MT + TA	4	None
15	57/M	70	All	Severe	120	100	4785	150 AZ	TA	3	None
16	67/M	71	All	Severe	120	100	4785	100 AZ	MT + TA	5	None

*CS, Corticosteroids.

†ISA: AZ, azathioprine; CY, cyclophosphamide.

‡Topical treatments: CB, clobetasol; MT, methylprednisolone; TA, triamcinolone acetonide.

Table 3 Disease extent and disease severity at first visit, time of first complete clinical remission, systemic and topical treatment with clobetasol (CB) and/or methylprednisolone (MT) in oro-pharyngeal PV patients

Pts	Age in years/Sex	Body weight (kg)	Disease extent at presentation	Disease severity at presentation	Time for first complete clinical remission (days)	CS* (mg) initial dose daily	Total CS (mg) up to the first complete remission	ISA† (mg) initial dose daily	Topical Treatment‡	Short-term side-effects of CB and/or MT
1	34/F	67	5	Severe	360	100	13795	100 AZ; 50 CY	CB + MT	None
2	34/F	60	2	Moderate	90	75	1975	0	MT	None
3	40/F	63	3	Severe	360	90	12010	100 AZ	CB	None
4	44/F	69	All	Severe	120	100	4545	100 AZ	MT	Candidiasis
5	48/F	58	3	Severe	90	90	2395	100 AZ	MT	None
6	50/F	64	4	Severe	90	100	2400	100 AZ	MT	Candidiasis
7	52/F	63	2	Moderate	90	75	2175	0	MT	None
8	56/F	51	1	Severe	180	75	7265	100 AZ	CB	None
9	63/F	69	All	Severe	90	100	2600	100 AZ	MT	None
10	69/F	62	2	Moderate	90	75	1975	0	CB	Candidiasis
11	72/F	96	All	Severe	120	100	5025	100 AZ	CB + MT	Candidiasis
12	25/M	68	All	Severe	360	100	13795	0	MT	None
13	27/M	62	3	Severe	120	90	4005	100 AZ	MT	Candidiasis
14	28/M	64	2	Moderate	90	75	1975	0	MT	None
15	33/M	61	3	Severe	180	90	7850	100 AZ	MT	None
16	38/M	72	All	Severe	120	100	4785	100 AZ	MT	None
17	45/M	52	2	Severe	180	75	7365	150 AZ	MT	None
18	46/M	69	5	Severe	90	100	2600	100 AZ	CB	Candidiasis
19	52/M	57	3	Severe	90	90	2395	100 AZ	MT	Candidiasis

*CS, corticosteroids.

†ISA: AZ, azathioprine; CY, cyclophosphamide.

‡Topical treatments: CB, clobetasol; MT, methylprednisolone.

Please circle the answer

Secondary outcomes

1) On a scale of 0–10 how would you describe the pain you experienced during and after the treatment when you went home?

(No pain) 0 1 2 3 4 5 6 7 8 9 10 (Extremely painful)

2) On a scale of 0-10 how burdensome was your treatment in terms of cause you discomfort?

(For example, were you able to eat or drink or speak? Did you have difficult applying sterile gauze and/or massage to the treated lesion at home? Did your treatment restrict you in any other way?)

(No burdensome) 0 1 2 3 4 5 6 7 8 9 10 (Extremely burdensome)

3) On a scale of 0–10 how would you rate your overall level of satisfaction with the treatment received?

(For example, you may want to consider how successful the treatment was, how restrictive the treatment and aftercare was, and whether you had significant bruising after the treatment)

(Extremely unsatisfied) 0 1 2 3 4 5 6 7 8 9 10 (Extremely satisfied)

Figure 1 Secondary outcomes evaluated via a 11-point Numerical Rating Scale (NRS) questionnaire.

Results

Primary outcomes: time for first complete clinical remission and total amount of corticosteroids

Thirty-five patients suffering from OPV, 13 males and 22 females, were treated either with systemic or topical treatment. At the time of diagnosis, the mean age of 16 patients (11 females and 5 males) treated with TA was 47.3 years for females and 50.8 years for males, while the mean age of 19 patients (11 females and 8 males) treated with TA was 51 years for females and 36.8 years for males (Table 1). The average duration of the follow-up was 5.3 years.

At the last evaluation, of 35 patients (100%) in complete clinical remission, 13 (37.1%) were off-therapy and 21 (60%) were on-therapy [14 patients were on 5 mg of prednisone, five were on 10 mg of prednisone and two were on 25 mg of Prednisone twice a week]. One patient (2.9%) died following a stroke 3 years after clinical remission on therapy and was censored at the time she was last known to be alive (Table 1).

No patient had a mild form of the disease, while two of 15 patients (12.5%) treated with PITA and four of 19 patients (21%) treated with PITA had moderate form of disease. All the remaining patients had a severe form of the disease (Tables 1, 2 and 3). In the group of 16 patients treated with PITA, three patients also received CB and MT, eight received MT, whereas four patients were just given PITA injections because refused the alternative topical treatment (either CB or MT) due to a reduced domiciliary compliance (Table 2). Conversely, in the group of 19 patients, 13 patients received MT, four received CB and two received CB and MT (Table 3).

The number of sessions of PITA injections per patient varied from two to eight sessions (Table 2), with a total diluted amount of TA up to a maximum of 25 mg/mL per session.

Thirty-five patients experienced a complete remission, in which no oro-pharyngeal lesion was detected, and the disease was controlled using a dosage of 5–25 mg of prednisone twice a week. The course of remission in OPV patients showed that 16 patients (45.7%) treated with PITA injections and 19 patients (54.3%) treated without PITA injections progressed towards a complete clinical remission in a mean survival time of 126.6 days (SD: 41; 95% CI: 104.7–148.8) and 153.2 days (SD: 97.4; 95% CI:

Table 4 Overall assessment of primary outcomes in oro-pharyngeal PV patients. Comparison of overall mean survival time and corticosteroids (CS) amount in both groups treated with and without PITA injections

Treatment group	Survival time (days)	SD	SE (95% CI)	Significance
Patients with TA	126.6	41	10.2 (104.7–148.8)	$P = 0.40$
Patients without TA	153.2	97.4	22.3 (106.2–200.1)	
	Survival CS amount (mg)			
Patients with TA	4894	2832	708 (3385–6403)	$P = 0.40$
Patients without TA	5312	4009	919.8 (3380–7245)	

SD, standard deviation; SE, standard error; CI, confidence interval.

Table 5 Overall assessment of secondary outcomes in oro-pharyngeal PV patients treated with PITA injections

Secondary outcomes	Range score	Mean	SD	SE (95% CI)	Significance
Satisfaction	0–10	7.3	2.22	0.57 (6.1–8.56)	
Pain	0–10	3.9	2.37	0.61 (2.62–5.25)	$P = 0.0007$
Discomfort	0–10	2.9	2	0.52 (1.74–4)	$P = 0.0006$

SD, standard deviation; SE, standard error; CI, confidence interval.

106.2–200.1) respectively. These differences were not statistically significant ($P = 0.4$) with the log-rank test (Table 4). These data were confirmed and extended over the entire period of the follow-up. Moreover, the mean survival CS up to the first complete clinical remission was 4894 mg (SD: 2832; 95% CI: 3385–6403) in patients treated with PITA injections and 5312 mg (SD: 4009; 95% CI: 3380–7245) in patients treated without PITA injections ($P = 0.4$) (Table 4).

Secondary outcomes: pain, discomfort and satisfaction experienced by OPV patients treated with TA

A significant difference was found between the three variables, showing that OPV patients reported a satisfaction score of 7.3 (SD: 2.22; 95% CI: 8.42–6.18) that was higher than the pain [3.9 (SD: 2.4; 95% CI: 5.11–2.69)] and discomfort score [2.9 (SD: 2.03, 95% C.I.: 3.93–1.87)]. These results indicated that there was a significant difference between the level of satisfaction with pain ($P = 0.0007$) and discomfort ($P = 0.0006$) perceived by patients (Table 5).

Adverse events

In both groups, short-term adverse events (AEs) were reported, as they disappeared within 1 week. In patients treated with PITA, candidiasis was seen in three of 16 patients (18.7%), as well as the presence of yellowish gingival pellets, while gingival neo-vascularization in one patient (6.2%) (Table 2). Conversely, in patients treated without PITA, candidiasis was detected in seven of 19 patients (36.8%) (Table 3). In both groups, candidiasis was controlled by topical (nystatin oral suspension, 500 000 Units twice a day as mouthwash for 7 days) and, in a very few cases, by systemic treatment (fluconazole, 100 mg p.o. q.d., for 7 days).

Discussion

In the era before the advent of corticosteroids the vast majority of PV patients died from their disease, whereas currently the mortality rate is dramatically reduced to less than 10% and is mainly related to CS side-effects, which sometimes limit their use. Potent topical CS are becoming increasingly useful as adjuvant in these chronic conditions.[3,5]

Over the last 30 years, many different topical CS have been used for oral vesiculoerosive disease.[3,12–14] In case of PV, they have been advocated for controlling minor or mild form of PV, but their efficacy appeared limited.[1] Although the use of clobetasol 0.05% as monotherapy failed in two of three PV patients,[15] however, in some studies,[3,13] it showed to be more effective than other less potent topical drugs in terms of controlling pain and disappearance of lesions. Indeed, flucinonide 0.05% gave partial results, with a complete disappearance of signs and symptoms in about 50% (35 of 74) patients with oral vesiculoerosive disease.[12] Other different topical CS used in combination with systemic CS and immunosuppressant agents in PV patients were halobetasol 0.05% ointment compounded 1 : 1 with orabase and dexamethasone elixir 0.1 mg/mL as mouthwash.[14] In addition to topical CS, other topical agents used in PV were cyclosporine,[16] and tacrolimus, which was considered, on the one hand, a useful adjuvant therapy for mucosal pemphigus vulgaris[17,18] but, on the other hand, an agent of limited use.[4]

Triamcinolone injections have been recommended in the treatment of remnant OPV lesions,[6] and resistant or new PV lesions in patients whose systemic medication is being tapered, although the use of both topical and perilesional injection showed a more effective control of the disease in the treatment of pemphigus foliaceus and bullous pemphigoid.[5] A good response with a complete remission after 9 months of follow-up has been reported in an OPV patient by using 0.1% TA cream with occlusive therapy.[19]

To the best of our knowledge, no study has been previously performed to evaluate the efficacy of PITA injections in addition to systemic therapy in terms of clinical remission and total amount of CS administered to OPV patients.

Despite the notion that oral lesions represent a challenge, given that they heal more slowly in mucocutaneous PV patients,[4] it appears that it is possible to induce a complete clinical remission more successfully in OPV patients treated with PITA injections than in OPV patients treated with different topical CS. The drop of mean survival time of complete clinical remission (126.6 instead of 153.2 days), and mean survival CS amount (4894 instead of 5312 mg), comparing both groups treated with and without PITA,

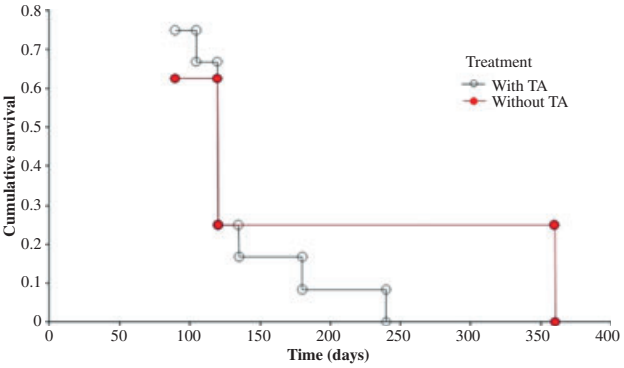

Figure 2 Kaplan–Meier cumulative survival curve for the mean time of complete clinical remission of oro-pharyngeal pemphigus vulgaris patients treated with and without TA (CS daily dosage of 100 mg).

respectively, was not considered statistically significant (log-rank test result on Kaplan–Meier survival comparison: $P = 0.4$) (Table 4) (Fig. 2). Nevertheless, the overall mean value of the time for the first complete clinical remission in patients treated with PITA is 27 days less than in patients treated without PITA. These differences are clinically relevant but statistically not significant, perhaps because of the sample size.

The major drawbacks of CS injections have been reported to be mucosal and cutaneous atrophies,[4,20] when given in concentration of 10–20 mg/mL.[4,5] Even though we used PITA injections at a higher concentration, i.e. up to a maximum of 25 mg/mL per session, none of our patient developed such side-effects. Considering that one of the factors involved in CS-induced atrophy appears to be the presence of CS crystals, it is likely that in our patients, the dilution of TA had relied on the resuspension and redistribution of poorly soluble TA crystals. Indeed, it has been demonstrated that the use of serial saline injections may represent a safe, relatively rapid, cost-effective and non-complicated therapeutic tool to CS-induced atrophy by fostering the gradual disappearance of CS crystals from the tissue.[21]

Whether the efficacy and AEs of PITA injections for OPV patients may vary with different concentrations remains unknown and, thus, further evidence is required. Moreover, it is remarkable to underline that it is not always possible to administer TA as perilesional injections, which would be preferable to avoid pain, infections and excessive bleeding. This is very often a result of the wide extent of the lesions and narrow space, which impede to move the syringe properly. In such cases, the drug has to be delivered intralesionally.

Short-term side-effects of topical CS in both groups were mild and controlled by topical treatment. They are summarized in Tables 2 and 3. Three patients developed several yellowish pellets localized in the gingival fornices (Fig. 3), for which no biopsy was taken, because they disappeared within few days after the administration of TA. One possible explanation for this might be that an accumulation of the drug occurred, because of its crystalline powder form, acting as a depot.[22] Conversely, the major advantage of these procedures has consisted in its practical nature, in terms of time, money, handiness, and, perhaps, long-lasting permanence in tissues.

In spite of all AEs reported by OPV patients, we have tried to understand better their overall compliance in receiving PITA injections, by quantifying pain, discomfort and satisfaction via a specific scale.[11] A limitation of our study was that the score of these three variables was taken at the end of the treatment, when the patient had a global view, and unfortunately, the results might have been influenced by whether the treatment had given satisfactory results in a shorter period. NRS was used to measure these outcomes as this method was found to be more useful than Visual Analogue Scale (VAS) and Verbal Rating Scale (VRS).[11]

The data of the secondary outcomes analysed via a 11-point NRS by Wilcoxon signed-rank test showed that the level of satisfaction vs. pain and discomfort perceived by OPV patients was statistically significant ($P < 0.001$) (Fig. 4). This implies that, despite a very mild pain and discomfort caused by PITA injections, clinicians involved in the management of OPV patients should be encouraged in performing this kind of procedure, considering their benefits. The most frequent complaint reported was a burning and swelling sensation, which did not impede patients to perform their common daily activities such as eating, speaking, drinking or driving, and did not last over 15 min after PITA injections.

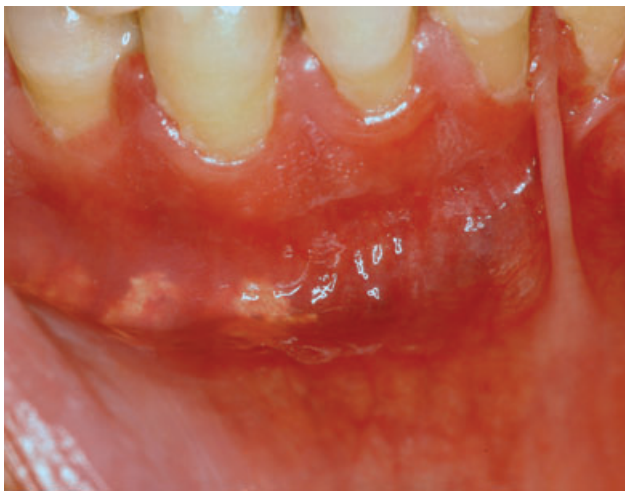

Figure 3 Presence of yellowish pellets in the gingival fornix. Marginal and attached gingival mucosa appeared healed after the administration of perilesional TA injections.

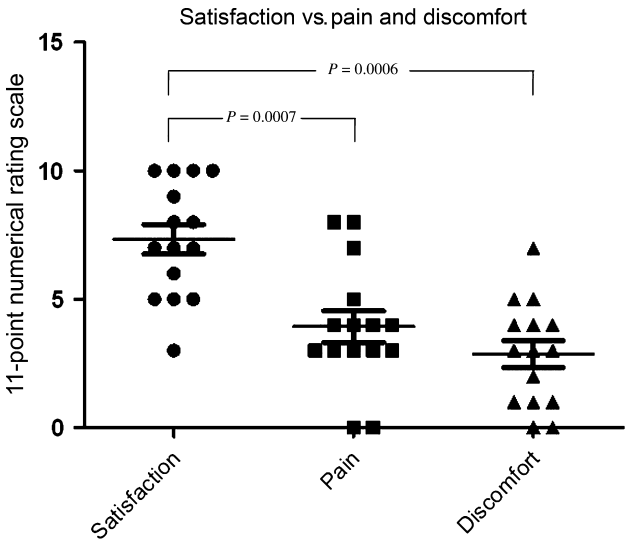

Figure 4 Comparison of satisfaction level vs. pain and discomfort perceived by OPV patients via a 11-point numerical rating scale ($P < 0.001$, Wilcoxon signed-rank test).

To shorten the time of complete clinical remission and permit more rapid reduction of the total amount of CS, our study suggests that the use of PITA injections might successfully join the CIST and their compliance is highly acceptable comparing the overall satisfaction perceived by OPV patients with pain and discomfort.

Despite the encouraging outcomes achieved from this study, it has demonstrated several limitations, mostly related: (i) to its retrospective nature, which allowed us to make suggestions and not to draw definitive conclusions; (ii) to the small sample size, due the rarity of this disorder; and (iii) to non-homogeneous systemic and topical treatments, due to the unpredictability of the clinical course of PV.

Therefore, despite our positive results, we do strongly believe that further long-term and multicentric double-blind clinical trials should be performed to better confirm our results, which will be a course we intend to follow in the near future.

Funding sources

No funding sources for this work were provided.

Acknowledgements

No sources of funding were used to assist in the preparation of this study. The authors have no conflicts of interest that are directly relevant to the content of this study.

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