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REVIEW ARTICLE

Topical Corticosteroid-Induced Skin Atrophy: A Comprehensive Review

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Abstract Skin atrophy is an adverse effect of topical corticosteroids (TCs) which, as an established non-life-threatening effect, has been poorly reported by trials involving these drugs. Atopic dermatitis and psoriasis are example of disorders that require repeated therapies with TCs; however, assessing the atrophogenic activity of TCs is still an issue. This study aims to review clinical data on skin atrophy induced by TCs. Searches of the PubMed, EMBASE, and Cochrane (Central) databases from 1965 to May 2013 were undertaken using the keywords 'corticosteroid', 'skin', and 'atrophy'. Skin and epidermal thickness values were retrieved from trials on healthy skin, and studies including skin atrophy as a safety endpoint in trials testing the efficacy of TCs were analyzed. Overall, 60 articles were retrieved. Whole skin and epidermal thickness were relevant parameters to measure early skin atrophy on healthy skin before it becomes clinically obvious. Epidermis thickness also seems to be more sensitive than whole skin thickness in detecting early atrophy; however, measuring skin atrophy still requires standardization. Further clinical trials on the atrophic effects of each TC are required to better evaluate their respective atrophic risks and their risk/benefit ratios. However, measuring epidermal or whole skin thickness will not be relevant in acute phases of inflammatory skin disorders treated with TCs because of the thickening induced by inflammation. In addition, skin atrophy seems to be induced by chronic TC use rather than by acute treatments. Long-term safety studies may be more relevant to evaluate atrophic activity.

Key Points

Epidermal and dermal thicknesses are relevant endpoints for measuring the cutaneous atrophogenic activity of topical corticosteroids (TCs).

Epidermal and dermal thickness measured in healthy volunteers can be used to assess the benefit/risk ratio of TCs but protocols need to be standardized to obtain comparable data.

More follow-up studies and phase IV studies are necessary to assess the long-term safety of TCs in regard to the skin atrophy they induce.

1 Introduction

Topical corticosteroids (TCs) have been used in dermatology for more than 50 years because of their strong anti-inflammatory activity [1, 2]. Even though some alternatives are now available, such as calcineurin inhibitors [3–5], TCs remain the mainstay of treatment for the most common inflammatory cutaneous diseases such as atopic dermatitis and psoriasis. In 2008, clobetasol propionate, a very potent corticosteroid introduced in 1973 [6], was still the most

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used TC for treating psoriasis in the US. Because of their immunosuppressive effects, the anti-inflammatory activity of TCs is still without any equivalent in terms of efficacy for treating acute dermatological inflammatory diseases. Their efficacy when used via the topical route also provides a higher safety threshold than systemic corticosteroids, which induce more severe adverse effects, such as vein thrombosis, diabetes, adrenocortical insufficiency, or osteoporosis [7, 8].

Skin atrophy remains the main adverse effect of TCs [9–11], and their atrophogenic activity has been largely reported [12–14]. Corticosteroids were described as inhibiting the secretion of collagen and hyaluronic acid by fibroblasts in the dermis, and impairing cell proliferation [1, 13, 15–17]. These biological activities explain the TC-induced skin atrophy. Despite an obligation to report the adverse events of the marketed pharmaceutical products, poor specific information has been collected concerning the already marketed TCs and their atrophic activities. One reason for this is that TC-induced skin atrophy is a well-established, non-life-threatening adverse effect, and another reason is that TC-induced skin atrophy probably results from chronic exposure to TCs. If TC-induced skin atrophy has been shown to be rapidly reversed after disruption of TC treatment, no studies have today evaluated the long-term effects of TC use (with long-term being defined as recurrent treatment periods over several years). Better clinical reporting and studies should focus on this TC-induced atrophic effect as some interesting data may ensue to help physicians choose the right corticosteroids for the right disease, with less atrophic activity. The increasing prevalence of skin insufficiency in the population also justifies highlighting this point [18]. If sun exposure is one of the main causes of this increasing prevalence of skin insufficiency, the long-term use of TCs is also potentially involved. Skin insufficiency has also been described under the term of dermatoporosis [14, 19], which consists of progressive atrophy of the skin that can end up with loss of the barrier function. Hallmarks of the first stage consist of a thinning of the skin associated with telangiectasia and small hematomas, and of small skin lacerations in the second stage. The third stage shows more frequent and bigger skin lacerations, together with delayed healing. Finally, hemorrhagic bleeding can occur in the dermis and can be responsible for advanced lesions, also known as dissecting hematomas [19]. This pathology, the first stages of which can appear as early as 60 years of age, is responsible for significant morbidity in the elderly. Therefore, by analogy with osteoporosis, this pathology has been described as a dysfunction of the primary barrier function of the skin and is known as ‘dermatoporosis’ [20].

It is highly suspected that anti-inflammatory therapies with corticosteroids accelerate the occurrence of dermatoporosis [14]. As a result, quality of life in the elderly can worsen significantly because failure of the skin barrier can require heavy medical care, with hospital admittances and sometimes skin grafts. This is why detecting early signs of skin fragility is necessary in order to prevent the incidence of advanced stages of dermatoporosis. A relevant and reliable parameter for evaluating the atrophogenic activity of TCs on the skin has to be defined in order to better appreciate the benefit/risk ratio of TCs already in use.

2 Objective

This study aims to review, with a systematic approach, clinical data on skin atrophy induced by TCs.

3 Methods

Searches of the PubMed, EMBASE and Cochrane (Central) databases from 1965 to May 2013 were undertaken using the keywords ‘corticosteroid’, ‘skin’, and ‘atrophy’, as well as combinations of these. In the EMBASE and Cochrane databases, the filters ‘randomized controlled trials’ and ‘trials’ were applied, respectively, as illustrated in the electronic supplementary material (ESM) 1. References were managed using Endnote X4 software.

4 Results

4.1 Results of the Search

A total of 300 articles were retrieved; 240 were subsequently excluded (see Fig. 1), leaving a total of 60 articles.

Among these 60 articles, 20 evaluated the atrophogenic activity of TCs in healthy volunteers (see ESM 2) and 5 studies tested compounds for their anti-atrophic properties in patients treated with TCs. The remaining articles addressed the use of TCs in patients with atopic dermatitis (15), psoriasis (14), vitiligo (2), mycosis fungoides (1), lichen planus (1), bullous pemphigoid (1), and palmoplantar pustulosis (1).

Among the 20 articles addressing the atrophogenic activity of TCs in healthy skin, thinning values of the skin were extracted from 14 articles (Table 1) [all were randomized, double-blind], and thinning values of the epidermis were extracted from 10 articles (Table 2) [5 were randomized, double-blind]. The tested TCs were applied to healthy volunteers and compared with a placebo cream, with the two products being applied randomly either on the right or left arm of all volunteers. The results were differences between the arm having received the TC and the

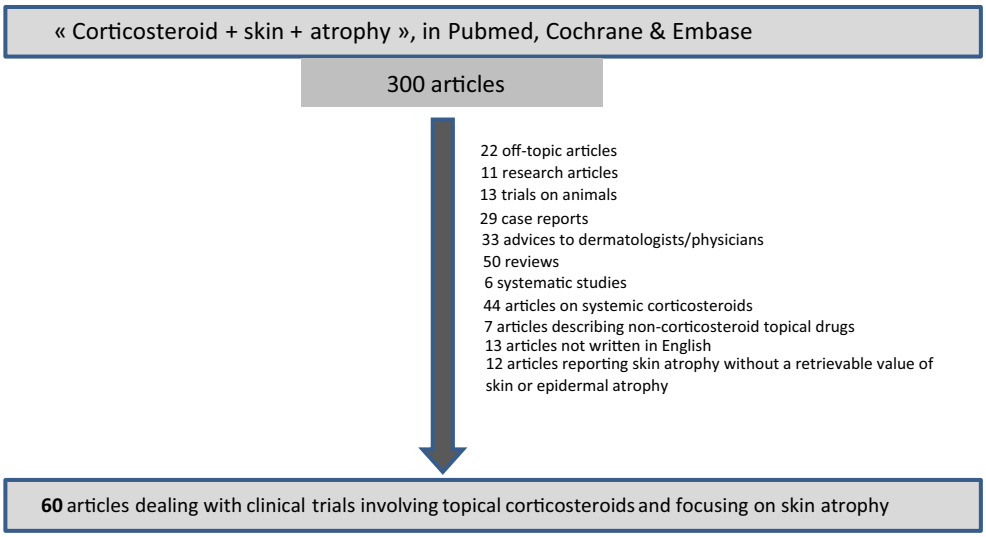

Fig. 1 Retrieved, excluded, and analyzed articles

other arm treated with placebo in the same volunteer. Average thinning values of skin atrophy and epidermis for each TC are listed in Tables 1 and 2.

Fifteen articles focused on TC trials in patients with atopic dermatitis (Table 3). Eight were double-blind randomized studies designed to demonstrate the efficacy of a TC for treating atopic dermatitis, and the remaining studies were open-label or prospective. Two studies measured the epidermal atrophy from skin biopsies [21, 22], and another study measured skin thickness using an ultrasound technique [23]. Other studies assessed skin atrophy clinically.

Fourteen articles focused on TC efficacy to treat psoriasis (Table 4). Nine were randomized, double-blind studies designed to evaluate or compare the efficacy and/or safety of a TC on psoriasis lesions, one was a 3-year follow-up investigating skin atrophy events [24], and another was designed as an open comparative study that compared the efficacy of clobetasol propionate applied under occlusion or as an ointment [25]. One study was reported as an open-label study that assessed the efficacy of a clobetasol propionate spray in addition to standard therapy [26].

Five articles focused on testing anti-atrophic compounds used concomitantly with a TC (Table 5). Four studies reported randomized trials that evaluated the efficacy and safety of a TC treatment with or without an anti-atrophic compound, and the fifth study was an open-label study where the anti-atrophic effect of triiodothyroacetic acid was tested in patients already presenting with skin atrophy [27].

4.2 Standardized Procedures for Measuring Skin Atrophy

Among the 20 articles addressing the atrophogenic activity of TCs in healthy skin, 14 provided data on whole skin thickness and ten provided data on epidermal thickness [28–47] (see Tables 1, 2, respectively). Both tables point out the need to standardize the protocols addressing TC-induced skin atrophy. As protocol settings differ between each study, comparing results is complicated. The duration of treatment, the anatomic area treated, the way of application (occlusive condition or not), and the excipient are parameters that modify the atrophogenic activity of TCs. For example, the frequency of application has been clearly demonstrated to affect the degree of skin atrophy [33, 35] as well as the vehicle used (cream, foam, or ointment) [48, 49]. The most striking results were described in a study performed by Andres et al., where a shampoo and a gel formulation of clobetasol propionate were compared for use in treating psoriasis of the scalp. The mean thickness of the scalp edge was followed with ultrasound sonography. Interestingly, the gel formulation induced a significant decrease of skin thickness, while the shampoo formulation did not [49]. Finally, applying TCs under occlusion is believed to increase the level of skin atrophy as very serious adverse events have been described in cases of long-term therapy with occlusive TCs [11, 50]. However, data presented in Table 1 show that for 4-week treatments skin thinning is not significantly higher under occlusion. The anatomic area treated also seems relatively important since skin thinning (including both dermis and epidermis) differs according to the anatomic location. In very thick skin (back, abdomen), atrophy is usually weak as a small amount of corticosteroids can cross the skin barrier. On the contrary, in locations where the skin is very thin, atrophy can appear rapidly as larger amounts of corticosteroids cross the barrier. For example, the skin of the face, intertriginous areas, and the eyelids are shown to absorb much higher amounts (more than tenfold) of corticosteroids than

Table 1 Effects of TCs on skin thickness, reported in 14 clinical studies

TC class[a]	Drug[b]	Drug mean value (%)[c]	Location[d]	Technique[e]	Percentage of skin atrophy (%)[f]	Time treatment[g]	Occlusion (Y/N)[h]	Posology[i]	Excipient[j]	Conc (%)[k]	n[l]	References
I	HC	−3	Forearm	UTS	0	3 W	Yes	200 mg	Cream	0.100	10	[31]
−2 %			Forearm	UTS	1	4 W	No	1/D	Cream	1.000	20	[41]
			Forearm	RX	0	8 W	No	3/D	Cream	1.000	5	[44]
			Forearm	RX	−7	4 W	No	2/D	Unreported	1.000	7	[45]
			Forearm	RX	−7	4 W	No	3/D	Ointment	1.000	7	[47]
			Forearm	RX	−4	5 W	No	3/D	Ointment	1.000	6	[47]
	HC-V	−1	Forearm	RX	−1	4 W	No	3/D	Cream	0.100	6	[47]
			Forearm	RX	−1	5 W	No	3/D	Cream	0.100	2	[47]
			Forearm	RX	−1	4 W	No	2/D	Unreported	0.200	6	[45]
II	DOP		Forearm	UTS	−21	4 W	Yes	3/W	Ointment	0.100	17*	[36]
−11 %			Forearm	UTS	−16	4 W	Yes	3/W	Ointment	0.030	17*	[36]
			Back	UTS	−11	4 W	Yes	3/W	Ointment	0.100	17*	[36]
			Back	UTS	−2	4 W	Yes	3/W	Ointment	0.030	17*	[36]
	PR	−19	Forearm	UTS	−13	6 W	No	100 mg/2/D	Ointment	0.250	24**	[30]
			Forearm	UTS	−25	6 W	Yes	3/W	Ointment	0.250	12*	[34]
	HC-B	−11	Forearm	UTS	−13	4 W	Yes	3/W	Ointment	0.100	17*	[36]
			Back	UTS	−7	4 W	Yes	3/W	Ointment	0.100	17*	[36]
			Forearm	RX	−13	4 W	No	2/D	Unreported	0.100	4	[45]
			Forearm	RX	−10	4 W	No	3/D	Ointment	0.100	4	[47]
			Forearm	RX	−13	7 W	No	3/D	Ointment	0.100	3	[47]
	MPA	−3	Forearm	UTS	0	3 W	Yes	200 mg	Cream	Unreported	10	[31]
			Forearm	UTS	−6	4 W	No	1/D	Cream	0.100	20	[41]
	TRA	−11	Forearm	RX	−11	8 W	No	3/D	Cream	0.100	5*	[44]
III	BMV	−11	Forearm	UTS	−17	4 W	Yes	3/W	Ointment	0.100	17*	[36]
−9 %			Back	UTS	−7	4 W	Yes	3/W	Ointment	0.100	17*	[36]
			Forearm	RX	−6	4 W	No	2/D	Cream	0.100	8	[45]
			Forearm	UTS	−7	4 W	No	1/D	Cream	0.100	20	[41]
			Forearm	RX	−6	4 W	No	3/D	Ointment	0.100	8	[47]
			Forearm	UTS	−24	6 W	No	100 mg/2/D	Ointment	0.100	24*	[30]
	MF	−8	Forearm	UTS	−16	6 W	No	100 mg/2/D	Ointment	0.100	24*	[30]
			Forearm	UTS	0	3 W	Yes	200 mg	Cream	Unreported	10	[31]
	FluP	0	Forearm	UTS	0	8 W	No	1/D	Ointment	0.050	40	[32]
	FluA	−7	Forearm	Caliper	−7	4 W	No	2/D	Unreported	0.025	8	[45]
			Forearm	RX	−7	4 W	No	2/D	Unreported	0.025	8	[45]

Table 1 continued

TC class[a]	Drug[b]	Drug mean value (%)[c]	Location[d]	Technique[e]	Percentage of skin atrophy (%)[f]	Time treatment[g]	Occlusion (Y/N)[h]	Posology[i]	Excipient[j]	Conc (%)[k]	*n*[l]	References
IV	CP	−15	Forearm	SCT	−13	2 W	Yes	2/D	Ointment	0.050	17*	[33]
−15 %			Forearm	UTS	−22	6 W	Yes	3/W	Ointment	0.050	12*	[34]
			Forearm	UTS	−21	4 W	Yes	3/W	Ointment	0.050	17*	[36]
			Back	UTS	−6	4 W	Yes	3/W	Ointment	0.050	17*	[36]
			Forearm	SCT	−14	2 W	Yes	1/D	Ointment	0.050	13*	[35]
			Forearm	UTS	−12	4 W	No	2/D	Unreported	0.050	13*	[40]
			Forearm	UTS	−10	4 W	No	1/D	Cream	0.050	20	[41]
			Forearm	RX	−17	4 W	No	2/D	Unreported	0.050	9	[45]
			Forearm	UTS	−16	3 W	No	2/D	Cream	0.050	14*	[42]
			Forearm	RX	−17	4 W	No	3/D	Ointment	0.050	9	[46]

Caliper refers to the method derived from a method originally used for measuring human body fat [94] and used to evaluate skin thickness in the study by Dykes and Marks [45]

TCs topical corticosteroids, *Y* yes, *N* no, *HC* hydrocortisone, *HC-V* hydrocortisone valerate, *DOP* domoprednate, *PR* prednicarbate, *HC-B* hydrocortisone butyrate, *MPA* methylprednisolone aceponate, *TRA* triamcinolone acetonide, *BMV* betamethasone valerate, *MF* mometasone furoate, *FluP* fluticasone propionate, *FluA* fluocinonide acetonide, *CP* clobetasol propionate, *UTS* ultrasound sonography, *RX* x-ray radiology, *SCT* skin compression thickness method, *W* weeks, *1/D* one application per day, *1/W* one application per week, * indicates if, in the considered study, the percentage of skin atrophy was reported to be significant compared with placebo, ** indicates that the percentage of skin atrophy was significantly different compared with placebo and other atrophy values for other drugs tested in the same study

[a] Anti-inflammatory strength class of the TC

[b] Evaluated corticosteroid

[c] Mean atrophic value calculated as the mean of the percentage of skin atrophy for the considered corticosteroid

[d] Anatomic part of the body considered in the study

[e] Technique used to measure skin thickness in the study

[f] Extracted significant value of skin thinning in comparison with the control/placebo of the considered study

[g] Time of treatment after which skin thickness was measured

[h] Whether the TC was applied in an occlusive way or not

[i] Frequency of topical application of corticosteroids

[j] Indicates whether the corticosteroid was delivered in a cream or ointment excipient

[k] Used concentration of the considered corticosteroid

[l] Number of subjects included in the study (these trials all included an internal control for each patient)

Table 2 Effects of TCs on epidermal thickness, reported in 10 clinical studies

TC class[a]	Drug[b]	Drug mean value (%)[c]	Location[d]	Epidermis (%)[e]	Technique[f]	Time Treatment[g]	Occlusion (Y/N)[h]	Posology[i]	Excipient[j]	Cone (%)[k]	*n*[l]	References
I	HC	0	Abdomen	0	Histometry	3 W	Yes	3/W	Ointment	0.100	10	[37]
0 %			Forearm	11	OCT	4 W	No	1/D	Cream	1.000	20	[41]
			Forearm	−10	Histometry	4 W	No	2/D	Cream	1.000	9	[45
II	MPA		Forearm	4	OCT	4 W	No	1/D	Cream	0.100	20	[41]
−8 %	HC-B		Forearm	−20	Histometry	4 W	No	2/D	Cream	1.000	9	[45]
III	BMV	−17	Abdomen	−7	Histometry	3 W	Yes	3/W	Ointment	0.100	10	[37]
−18 %			Forearm	−15	OCT	4 W	No	1/D	Cream	0.100	20	[41]
			Forearm	−29	Histometry	4 W	No	2/D	Cream	0.100	9*	[45]
	DDE		Abdomen	−27	Histometry	3 W	Yes	3/W	Ointment	0.100	10	[37]
	FluA		Abdomen	−27	Histometry	3 W	Yes	3/W	Ointment	0.100	10	[37]
			Sacrolumbar	−28	Histometry	6 W	Yes	1/D	Ointment	0.025	22*	[38]
	FluP		Sacrolumbar	−21	Histometry	6 W	Yes	1/D	Ointment	0.020	22*	[38]
	Flu	−5	Forearm	−3	Histometrv	2 W	No	2/D	Cream	0.100	20	[28]
			Forearm	−7	OCT	3 W	No	2/D	Cream	0.100	10*	[29]
IV	CP	−26	Forearm	−18	Histometry	2 W	No	2/D	Cream	0.050	20*	[28]
−26 %			Forearm	−15	OCT	3 W	No	2/D	Cream	0.050	10**	[29]
			Forearm	−7.84	OCT	3 W	No	2/D	Foam	0.050	10*	[29]
			Abdominal	−33	Histometry	3 W	Yes	3/W	Ointment	0.100	10	[37]
			Forearm	−23	MultiPhotonMicr	2 W	Yes	Unreported	Cream	0.050	4*	[39
			Forearm	−28	OCT	4 W	No	2/D	Unreported	0.050	13*	[40]
			Forearm	−13	OCT	4 W	No	1/D	Cream	0.050	20	[41]
			Forearm	−22	LOriTOCdl	4 W	No	2/D	Cream	0.050	14	[42]
			Forearm	−42	Histometry	3 W	Yes	3/W	Cream	0.050	3	[43]
			Forearm	−59	Histometrv	6 W	Yes	3/W	Cream	0.050	4	[43]

TCs topical corticosteroids, *HC* hydrocortisone, *HC-B* hydrocortisone butyrate, *DDE* dudesonide, *MPA* methylprednisolone aceponate, *BMV* betamethasone valerate, *FluP* fluticasone propionate, *FluA* fluocinonide acetonide, *Flu* fluocinonide, *CP* clobetasol propionate, *Histometry* histological analysis on biopsy, *OCT* optical coherence tomography, *MultiPhotonMicr* multiphoton microscopy, *Confocal* confocal microscopy, *W* weeks, *1/D* one application per day, *1/W* one application per week, * indicates if, in the considered study, the percentage of epidermal atrophy was reported to be significant compared with placebo, ** indicates that the percentage of epidermal atrophy was significantly different compared with placebo, and also with regard to other atrophy values for other drugs tested in the same study

[a] Anti-inflammatory strength class of the TC

[b] Evaluated corticosteroid

[c] Mean epidermal atrophy value calculated as the mean of epidermal atrophy for the considered corticosteroid

[d] Anatomic part of the body considered in the study

[e] Percentage value of epidermal thinning, extracted from the considered study as a comparison with the placebo

[f] Technique used to measure epidermal thickness in the study

[g] Time of treatment after which the epidermal thickness was measured

[h] Whether the TC was applied in an occlusive way or not

[i] Frequency of topical application of corticosteroids

[j] Indicates whether the corticosteroid was delivered in a cream or ointment form

[k] Concentration in corticosteroid of the cream or ointment used

[l] Number of subjects included in the study (these trials all included an internal control for each patient)

Table 3 Clinical studies focusing on skin atrophy induced during AD treatment with TCs

References	Study duration[a]	Type of AD[b]	Design[c]	Results[d]	Atrophy reported[e]	n[f]
[21]	3 W	All	Miltefosine vs HC1 %	HCl > Miltefosine	No	16*
[60]	2 W	All	Flu vs Vehicle	Flu > Vehicle	5.6 vs 4.3 % (NS)	109 vs 50
[22]	3 W	Mild and moderate	Pimecrolimus vs BMV	BMV > Pimecrolimus	BMV < Pimecrolimus	14*
[66]	3 W	Mild and moderate	Tacrolimus vs BMV	Tacrolimus = BMV	No	89 vs 92
[62]	6 M	Trunk and extremities Moderate and severe	Tacrolimus vs HCB	Tacrolimus > HCB	0 vs 2 cases	487 vs 485
[67]	3 W	Seborrhoeic Dermatitis	Pimecrolimus vs BMV	Pimecrolimus = BMV	No	11 vs 9
[23]	12 M	Moderate to severe	Tacrolimus vs Corticosteroids	Tacrolimus > Corticosteroids	Tacrolimus > Corticosteroids	56 vs 36
[64]	3 M	Pediatric AD	FluP versus HCB and HC	FluP > HCB and HC	No	67 and 59 vs 67 and 54
[65]	10 W	Facial and intertriginous versus Non-facial and non-intertriginous	FluP	FluP = effective	No	21
[59]	4 W	Moderate and severe	CP vs Vehicle	CP effective	No	41 vs 40
[61]	2 W	All	CP	CP effective	l Case	59
[63]	2 W	All	CP	CP effective	No	124
[58]	3 W	All	CP vs Other corticosteroids	CP > others	No	330 vs 330
[57]	1 M	Pediatric AD	CP	CP effective	No	50
[56]	Unreported	All	CP versus HC and fluocortolone	CP > HC and fluocortolone	No (no HPA axis depression)	409*

AD atopic dermatitis, *TCs* topical corticosteroids, *HC* hydrocortisone, *Flu* fluocinonide, *BMV* betamethasone valerate, *HCB* hydrocortisone butyrate, *FluP* fluticasone propionate, *CP* clobetasol propionate, *HPA* hypothalamic-pituitary-adrenal, *NS* non-significant, *W* weeks, *M* months, * indicates that both drugs were applied on different lesions or locations of a same patient, thus including an internal control

[a] Duration of the protocol

[b] Type of AD treated in the study

[c] Tested drugs

[d] Whether the drug tested was effective, superior, or equal to another study drug

[e] Number of atrophies detected or which drug was shown to be superior (less atrophic) to another study drug

[f] Number of patients included in each arm of the study

Table 4 Clinical studies on skin atrophy induced during psoriasis treatment with TCs

References	Study duration[a]	Type of psoriasis[b]	Design[c]	Results[d]	Atrophy reported[e]	n[f]
[68]	8 W	Scalp	Calcipotriol + BMD vs Calcipotriol	Calcipotriol + BMD > Calcipotriol	No	207 vs 105
[26]	4 W	All	CP spray safety when added to a biologial treatment	Open label	2	159
[69]	52 W	All	Calcipotriol vs Calcipotriol + BMD vs Calcipotriol and BMD	Safety study	2 vs 4 vs 1	209 vs 213 vs 212
[70]	4 W	All	CP vs Vehicle	CP > Vehicle	No	60 vs 60
[49]	4 W	Scalp	CP shampoo vs CP gel	CP shampoo = CP gel	CP shampoo > CP gel	14 vs 12
[71]	4 W	Scalp	CP vs Calcipotriol	CP > Calcipotriol	No	76 vs 75
[72]	3 W	Scalp	FluA vs Vehicle	FluA > Vehicle	No	43 vs 46
[73]	2 W	I&F	FluP on I&F versus FluP on non I&F	Comparative, I&F lesions heal faster than non I&F lesions	No	20
[25]	6 W	All	CP vs CP/occlusion	CP = CP/occlusion	No	6 vs 10
[74]	12 W	All	Taratozen vs Taratozen + low TC vs Taratozen + mild TC vs Taratozen + potent TC	Taratozen + potent TC and Taratozen + mild TC > Taratozen vs Taratozen + low TC	No	70 vs 73 vs 71 vs 70
[75]	3 W	Scalp	BMD vs Flu	BMD > Flu	1 vs 0	49 vs 25
[76]	2 W	All	CP vs Vehicle	CP > Vehicle	No	108*
[77]	2 W	All	DMT vs PR	DMT = PR	No	28 vs 29
[24]	3 Y	All	TRA(topical) + Etretinate (oral)	Follow-up	11 cases of atrophy (38 %)	29

BMD betamethasone dipropionate, *CP* clobetasol propionate, *DMT* desoximethasone, *FluA* fluocinonide acetonide, *Flu* fluocinonide, *FluP* fluticasone propionate, *I&F* intertriginous and face, *PR* prednicarbate, *TCs* topical corticosteroids, *TRA* triamcinolone acetonide, *W* weeks, *Y* years, * indicates that both drugs were applied on different lesions or locations of the same patient, thus including an internal control

[a] Duration of the protocol

[b] Type of psoriasis treated in the study

[c] Drugs compared or evaluated in the study

[d] Whether the drug tested was effective, superior or equal to another study drug

[e] Number of atrophies detected or which drug was shown to be superior (less atrophic) to another study drug

[f] Number of patients included in each arm of the study

the forearm skin [13]. This was also well illustrated by Serup and Holm [36], who showed that, in 4 weeks, atrophy induced by clobetasol propionate on the forearm is more than threefold greater than atrophy induced on the back skin of the same patient.

4.3 Whole Skin Thickness as an Endpoint to Measure Early Topical Corticosteroid (TC)-Induced Skin Atrophy

Dermal or whole skin thickness is probably the most interesting parameter, besides epidermal thickness. While the average epidermal thickness is approximately 100 μm, dermal thickness fluctuates between 0.5 and 3 mm according to anatomic location. The high skin fragility characterizing skin treated with TCs is also believed to be due to the corticosteroid inhibitory effects on collagen and aminoglycan secretion by fibroblasts, leading to a strong loss of dermal extracellular matrix [1, 12, 15, 16]. Skin consistency and elasticity rely on this extracellular matrix and its ability to retain water [51–53]. Intuitively, the atrophogenic activity of a given TC is thought to be proportional to its anti-inflammatory strength. However, a correlation between the anti-inflammatory strength of TCs and their proven atrophogenic activity has not been established (Tables 1, 2). TCs can be classified into four classes according to their anti-inflammatory strength. Class I corresponds to weak TCs, class II corresponds to mild TCs, class III corresponds to strong TCs, and class IV corresponds to very strong TCs [1, 13]. If class I TCs are the significantly lesser atrophic compounds, when compared with classes II, III and IV, no significant differences are shown between the three other classes (see Table 1). This indicates that TCs have different benefit/risk ratios, and that more accurate clinical trials should be conducted to investigate the atrophogenic properties of TCs and to compare this with their anti-inflammatory strength. Most of the trials reported in Table 1 measured values of skin atrophy, using either x-ray or ultrasound sonography techniques. However, because of a lack of statistical power, only one study reported significant differences of atrophy between two corticosteroids [30]; Korting et al. reported that prednicarbate was significantly more atrophic than betamethasone valerate or mometasone furoate. This trial was also one of the larger ($n = 24$) and longest (6 weeks), showing that longer trials with larger cohorts help to assess differences between two TCs.

A ranking of the benefit/risk ratio of TCs can be established according to their reported atrophogenic activity and their respective TC class (see Table 1) [1]. Mometasone furoate appears to have an optimal benefit/risk ratio as it shows relatively low atrophic activity while belonging to the class III of potent TCs (see Table 1). This is in agreement with the report by Schoepe et al. [1], who also reported mometasone furoate as the TC presenting the higher benefit/risk ratio. However, the limited atrophogenic activity of mometasone furoate has been shown in only two studies. One study showed no atrophic effect of mometasone furoate in 10 patients after 3 weeks of application under occlusion [31], but this study only describes a limited duration trial in a small cohort of ten subjects. The other study found an atrophy of approximately −16 % for mometasone furoate, a surprisingly high value close to the average atrophy found for betamethasone valerate, the most atrophic class III TC [30]. However, in this same study, mometasone furoate was still found to be significantly less atrophic than betamethasone valerate after 6 weeks of application, i.e. −16 % for mometasone furoate as opposed to −24 % for betamethasone valerate. The long duration of this protocol probably explains these high atrophic values. Other molecules such as fluticasone propionate and fluocinonide acetonide may be close to mometasone furoate in terms of benefit/risk ratio as they are poorly atrophic [32, 45]. Table 1 shows clobetasol propionate as being the most atrophic compound [33–36, 40–42, 45, 47]; however, as clobetasol propionate (class IV) is also considered as the most powerful anti-inflammatory, its risk/benefit ratio can still be considered as good [54]. Betamethasone valerate, a class III TC that also has high atrophogenic power, has a weaker benefit/risk ratio [30, 36, 41, 45, 47]. Within class II, the most interesting TC may be methylprednisolone aceponate [31, 41]. Prednicarbate, domoprednate, hydrocortisone butyrate, and triamcinolone acetonide show a worse benefit/risk ratio because of their higher atrophogenic power [30, 31, 34, 36, 41, 44–46]. Finally, the less powerful TCs, hydrocortisone and hydrocortisone valerate, are the less atrophogenic [31, 41, 44, 45, 47]; however, because of their low anti-inflammatory activity, their risk/benefit ratio may be considered as low.

4.4 Epidermal Atrophy, a New Parameter to Follow Skin Atrophy

Available data from trials that used epidermal thickness as an endpoint are in line with conclusions obtained by measuring whole skin thickness (Table 2). According to epidermal atrophy, clobetasol propionate is the most atrophogenic TC (−26 %). Betamethasone valerate (class III) presents a relatively high atrophogenic value (−18 %) on the epidermis, positioning it again as a mild TC in terms of benefit/risk ratio. The low atrophogenicity activity of hydrocortisone on the epidermis is also in agreement with what has been observed in hydrocortisone-induced skin atrophy. The interesting point regarding epidermal atrophy is that it looks proportionally greater than whole skin

Table 5 Clinical studies retrieved that tested anti-atrophic compounds

References	Tested compound[a]	*n*[b]	Time[c]	Design[d]	TC efficacy[e]	Epidermis[f]	Dermis[g]	Present disease[h]
[27]	Triiodothyroacetic acid	39	8 W	On already-installed atrophy	Non-applicable	+24 %	+28 %	Hand eczema
[85]	Tazaroten	24*	4 W	Tazarotene vs Tazarotene + DFA vs DFA	Non-applicable	Tazaroten reduces by 37 % the DFA-induced epidermal atrophy	Unreported	Healthy
[86]	Tretinoin	20*	8 W	BMD vs BMD + tretinoin	BMD = BMD + tetrinoin	BMD = −20 %, BMD + tretinoin = +1 %	Unreported	Psoriasis
[87]	Retinoic Acid	18*	2/3 W	TRA vs TRA + retinoic acid	TRA = TRA + Retinoic acid (irritation = adverse event observed with RA)	Unreported	Unreported	Atopic Dermatitis
[88]	12 % amonium lactate (AL)	5*	4 W	AL vs CP + AL vs CP	CP + AL = CP	Al =+18 %, CP = −52 %, CP + AL = −36 % (S)	Improved**	Induced inflammation on health skin

TC topical corticosteroid, *DFA* diflorasone diacetate, *AL* ammonium lactate, *BMD* betamethasone dipropionate, *TRA* triamcinolone acetonide, *CP* clobetasol propionate, *W* weeks, * indicates studies including an internal control for each patient, ** indicates that dermis aspect with regard to collagen and hyaluronic acid content was improved in patients treated with AL + CP compared with CP alone, on behalf of histological analysis [88]

[a] Evaluated anti-atrophic compound

[b] Number of patients included in the study

[c] Duration of the study

[d] Summarizes the two arms of the study, generally a corticosteroid versus corticosteroid + tested anti-atrophic compound

[e] Whether the TC anti-inflammatory activity was as effective or not with or without the anti-atrophic compound

[f] Epidermal thickness changes after treatment

[g] Indicates either an increase of its thickness [27] or an improved histological aspect

[h] Disease which affected the patients included in the study

atrophy. The average epidermal atrophy induced by clobetasol propionate is indeed approximately −26 % (Table 2), while the average clobetasol propionate-induced skin atrophy is approximately −15 % (Table 1). Similarly, in class III, the average epidermal atrophy is −18 %, while the average skin atrophy is −9 %. Epidermal atrophy may be more likely to assess differences of atrophogenicity between two distinct TCs. For example, in a study where both epidermal and whole skin thickness were measured, Josse et al. [40] found a skin atrophy value of −11 %, while epidermal atrophy was −28 %. Similarly Kolbe et al. [42] found an epidermal atrophy of −22 % and a skin atrophy of −16 %. Gans et al. [29] also measured significant values of epidermal atrophy between two formulations of clobetasol propionate (foam vs. cream). The clobetasol propionate cream induced an atrophy of −15 %, while the foam induced an atrophy of −8 %. Epidermal atrophy may also appear earlier than dermal atrophy, allowing an analysis of the atrophic activity of corticosteroids via shorter clinical trials. Uliasz et al. observed an atrophy of −18 % of the epidermis, and El Madani et al. observed an atrophy of −16 %, both at 2 weeks of treatment, and two values higher than the average atrophy usually observed after 4 weeks of treatment [28, 39]. However, more studies are necessary to consider epidermal atrophy as a relevant parameter. The last techniques available, multiphoton microscopy, confocal microscopy, and optical coherence tomography, seem precise and reliable. Moreover, these techniques are non-invasive, making them relevant for performing studies in large cohorts of volunteers.

4.5 Reversibility of TC-Induced Atrophy

Whether skin atrophy is reversible or not has been less investigated. Studies including a follow-up after stopping TC treatment indicate that skin thickness returns to normal values in approximately 2 weeks [33, 35, 41, 42]. Lubach et al. [35] established a dose relationship between the amount of TC applied and the degree of atrophy, with skin atrophy being proportional to the weekly frequency of TC application. Interestingly, skin thickness almost returned to normal values independently of the frequency of TC application, a very interesting point in terms of TC safety. Moreover, this also means that the posology of TCs is crucial and can be adapted in order to reduce the undesired atrophic effects. The epidermis also seems able to rapidly return to a normal thickness after stopping TC treatment [41, 42].

4.6 Skin Atrophy Induced in Pathological Skin

The most relevant skin disorders where corticosteroids constitute a main part of the available therapeutic tools are atopic dermatitis and psoriasis, both of which require repeated rounds of TC therapy because of their recurrence during the patient's life. The therapeutic approach against these autoimmune inflammatory disorders mainly resides in symptomatic relief by using the immunosuppressive activity of corticosteroids. The topical route is usually preferred as a much safer option than systemic corticosteroids [55].

4.6.1 TC-Induced Skin Atrophy in Atopic Dermatitis

In the 15 retrieved articles dealing with TC efficacy in atopic dermatitis (Table 3), epidermal thickness was measured in three trials, while skin thickness was considered an endpoint in one study [21–23]. Other studies reported skin atrophy from clinical observations made by clinicians. Therefore, skin atrophy induced by TCs during atopic dermatitis treatment is probably underestimated as the smooth reduction of skin thickness (as reported in Tables 1, 2) is not likely to be macroscopically detectable. For example, Munro and Wilson [56], Herz et al. [57], Yawalkar et al. [58], Maloney et al. [59], and Guzzo et al. [63] reported no sign of atrophy when using clobetasol propionate 0.05 %, the most atrophogenic corticosteroid, even though the cohorts analyzed in these studies were large enough to allow a significant detection of skin atrophy. Additionally, the corticosteroid was applied during a period of 2 weeks, while studies measuring skin atrophy on healthy skin were performed over 2 or 4 weeks (see Tables 1, 2). However, some studies have reported skin atrophy but their incidence was not significant when compared with the control group [60–62].

Dölle et al. and Jensen et al. followed epidermal thickness as an endpoint [21, 22], but this parameter is not relevant for assessing skin atrophy when considering an atopic dermatitis lesion. The epidermis is indeed hyperplasic and largely thickened in atopic dermatitis lesions. Therefore, following a decrease of epidermal thickness in this case is equivalent to assess the clearance of the inflammation, as epidermal thickness is just returning to normal. However, Jensen et al. [22] interestingly explored the epidermal barrier and its differentiation markers in atopic dermatitis lesions treated with either betamethasone valerate or pimecrolimus, a non-corticosteroid drug. If both reversed the inflammation, betamethasone valerate reduced the epidermal cell proliferation markers below what is usually observed in normal skin, and the superficial differentiation markers (loricrin) appeared thinner with betamethasone valerate than with pimecrolimus. These signs are probably early molecular markers of an epidermal atrophy. Additionally, the fact that the loricrin layer within the epidermis becomes thinner in skin treated with betamethasone valerate can impair the epidermal barrier,

making the skin more permeable to allergens, which can facilitate a subsequent new round of inflammation after the end of treatment. This is a probable cause of atopic dermatitis rebounds usually observed when TC treatments are stopped.

Regarding the potential skin atrophy induced by long-course TC treatments, the study by Kyllonen et al. [23] brings interesting answers. These authors measured the average thickness of the skin after 12 months of TC treatment in 30 patients. Skin thickness was assessed by ultrasound sonography technology and determined as the mean of eight anatomic locations independently of their atopic dermatitis-presenting status in order to assess skin atrophy generalized to the entire body. A significant 8 % decrease in skin thickness was observed, while an increase was observed in another group treated with tacrolimus, a non-corticosteroid drug. This observation suggests that long-term TC treatments may induce generalized skin atrophy. A systemic effect of small amounts of TCs chronically reaching the systemic fluids by crossing the skin barrier is a logical explanation to such an observation. The permeability of the skin barrier to TCs can additionally be expected to be higher as the integrity of the skin on the atopic dermatitis lesion is altered. A transcutaneous passage of TCs with systemic-like adverse events was demonstrated in 1975 by Munro and Wilson [56], who demonstrated that the hypothalamic-pituitary-adrenal (HPA) axis response was affected in patients presenting with extended atopic dermatitis lesions and treated with TCs.

With regard to TC efficacy for clearing atopic dermatitis lesions and their benefit/risk ratio, the results summarized in Table 3 tend to confirm the benefit/risk ratio determined from Tables 1 and 2. Clobetasol propionate is a very effective anti-inflammatory that is superior to other types of corticosteroids [56–59, 61, 63]. Fluticasone is also a very effective anti-inflammatory, and is superior to hydrocortisone butyrate (class II) and hydrocortisone (class I). As it is also poorly atrophic (Tables 1, 2), it may be considered a high benefit/risk drug [64, 65]. Finally, in addition to their efficacy, atopic dermatitis remission is an important issue when TC treatments are stopped. Non-corticosteroid molecules, namely pimecrolimus and tacrolimus, were shown not to induce skin atrophy, but with poor or reduced anti-inflammatory efficacy [22, 23, 62, 66, 67]; however, they may be relevant between acute atopic dermatitis stages in order to reduce TC rebounds [67].

4.6.2 Skin Atrophy Induced by TCs in Psoriasis

As observed with atopic dermatitis studies, few studies have detected significant skin atrophy during the treatment of psoriasis lesions with TCs (Table 4) [24–26, 49, 68–77]. Skin atrophy can hardly be detected clinically within a treatment time of 2–4 weeks; however, because of the higher recurrence rate of psoriatic rashes during the patient's life, epidermal atrophy has been investigated more accurately in psoriasis. The earliest and most interesting study followed 87 patients treated with TCs for psoriasis during a 3-year period. This is the longest follow-up study performed with a cohort of patients using TCs [24]. In this study, Polano et al. reported that 87 patients were followed initially but 29 patients could still be analyzed after 3 years. Eleven patients presented signs of skin atrophy detected clinically. Eight showed bruises and two showed marked atrophy. Therefore, after 3 years of repeated use of TCs, approximately 38 % of patients showed clinical signs of skin atrophy. This study confirms that short protocols for assessing skin atrophy may not be suitable, at least if the skin atrophy is only assessed clinically. The study by van der Vleuten [25] focused on the epidermis in psoriasis lesions treated with TCs; however, the epidermal thinning reduction reported a clearance of psoriasis, as psoriatic epidermis is very hyperplasic. Nevertheless, epidermal differentiation markers, assessed histologically, showed early signs of atrophy in the most differentiated layers of the epidermis. Finally, Andres et al. [49] confirmed that some discrete signs of epidermal atrophy can be detected, even after only 4 weeks of a treatment with clobetasol propionate for psoriasis of the scalp. First, by using ultrasound sonography, Andres et al. detected a significant thinning (−0.25 mm) of the skin at the edge of the treated area (the scalp). Subsequently, they also measured depression of the HPA axis, meaning that the corticosteroid reached significant systemic levels. This is a main point in terms of safety as adverse events usually associated with systemic corticosteroids may then be expected. Treating psoriasis with TCs often implies a large body area is to be treated. This may then be a concern as treating a large body area with TCs will favor a higher transcutaneous passage of significant amounts of corticosteroid. This study also points out that treatment of psoriasis with TCs should be adapted according to the anatomic area affected. The head appears to be a location where a transcutaneous passage of corticosteroids is more likely to occur, as demonstrated by the HPA axis depression. Eye, eyelid, and face skin were shown to absorb larger amounts of TCs [13]. At the same time, this study also highlights the crucial role of the excipient as the shampoo had no atrophic effect on the skin, or systemic effect on the HPA axis, compared with the gel formulation.

Finally, in terms of efficacy and benefit/risk ratio, psoriasis usually requires potent or very potent TCs. In addition to their strong atrophic activity, clobetasol propionate and betamethasone dipropionate still nowadays remain the most used TC for psoriasis treatment, and were shown to be superior to less-potent TCs for clearing psoriatic lesions

[75] or to calcipotriol, a new non-corticosteroid compound [68, 69, 71]. However, less potent and poorly atrophic TCs may still be an option for treatment of the face and intertriginous areas, both very sensitive to TC-induced atrophy. Lebwohl et al. [73] showed that fluticasone propionate, a poorly atrophic TC (Table 1), is an effective and well-tolerated topical therapy for clearing psoriatic lesions of the face and intertriginous skin.

4.6.3 Other Pathologies Requiring TCs and Exposing Patients to the Risk of TC-Induced Atrophy

Even if on a much less frequent basis than atopic dermatitis or psoriasis, other autoimmune inflammatory disorders require TCs. A recent study explored the efficacy of TCs against bullous pemphigoid [78]. This study evaluated the safety of TCs against systemic corticosteroids in bullous pemphigoid, which mainly affects elderly patients and can cause a high degree of morbidity because of the large bullous lesions that compromise the barrier function of the skin. To date, systemic corticosteroids are still used as a primary intention treatment but remain quite challenging to handle in old patients because of the strong adverse events associated with systemic corticosteroids (e.g. HPA depression, adrenocortical insufficiency, diabetes, cardiovascular and neurovascular disorders, osteoporosis). A whole-body topical treatment with clobetasol propionate was considered in this study and, interestingly, was shown to be significantly efficient for controlling bullous pemphigoid while causing less adverse events than systemic therapy, which was in agreement with another study [79]. Because large areas of skin with a compromised barrier function were treated, significant amounts of corticosteroids were detected in the blood of these bullous pemphigoid patients; however, the overall amount and severity of adverse events was still lower than in patients treated with systemic corticosteroids.

Another study evaluated the efficacy of TCs in patients affected by vitiligo [80]. This autoimmune disease that specifically targets melanocytes, usually generates white non-pigmented marks on the body, affecting the patient's appearance. TCs were shown to be the most effective therapy [80]. In this 6-month study, 76 % ($n = 28$) and 81 % (23) of two groups of patients treated with betamethasone dipropionate plus an ultraviolet therapy, and with betamethasone dipropionate alone, respectively, showed signs of clinically detected skin atrophy. Thus, the authors recommended TCs for vitiligo affecting less than 10 % of the body surface. Another more recent study also investigated the efficacy of corticosteroids plus tretinoin for treating vitiligo against corticosteroids alone over a 6-month period [81]. They observed no atrophy of the skin in 49 patients, in contradiction to the study of Lotti et al. [80]. Nevertheless, they did not specify which class of corticosteroid was used, while Lotti et al. used betamethasone dipropionate, a very potent and atrophogenic corticosteroid.

Other skin inflammatory disorders may involve TCs, such as palmo-plantar pustulosis, lichen planus, and mycosis fungoides [82–84]. In the lichen planus trial, some withdrawals from the study were reported to be due to skin atrophy, indicating that this may also be a concern for this type of pathology [84]. However, as lichen planus is a less recurrent pathology, the atrophic risk can be considered low. Nevertheless, special attention may be necessary, i.e in the event of mouth or genital lichen planus, as their higher permeability to corticosteroids increases the risk of atrophy in these areas. Regarding palmo-plantar pustulosis, no skin atrophy was reported in one study [83]; however, this disorder affects an anatomic surface relatively resistant to skin atrophy as skin is very thick in the palms and soles. With regard to mycosis fungoides, cases of skin atrophy were also reported as adverse events [82].

4.7 Complementary Treatments for Limiting TC-Induced Atrophy

Five articles tested the activity of compounds to counteract skin atrophy induced by corticosteroids (Table 5) [27, 85–88]. Ammonium lactate was shown to reduce skin atrophy induced by clobetasol propionate, the strongest atrophic corticosteroid [88]. However, this observation was only based on the investigator's appreciation of histologic slides from five patients. Additionally, a change in clobetasol propionate bioavailability due to ammonium lactate cannot be ruled out. Ammonium lactate is indeed known as a moisturizer that increases hydration of epidermis. Nevertheless, this article points out that accurate skin care, such as emollients, may help reduce skin atrophy induced by TCs. Retinoids were also investigated by Schmied et al. [87]; however, the authors reported an improvement of the epidermal atrophy only. As retinoic acid causes skin irritation, less active precursors of retinoic acid were further introduced [89–91]. Some were tested by Kaidbey et al. [85] and Yazdanparast et al. [27, 86]. Tretinoin, tazaroten, and triiodothyroacetic acid appeared to be able to at least partially reduce skin atrophy induced by TCs.

As a result of these findings, it seems that at least emollient creams may limit the severity of atrophy induced by corticosteroids. Retinoids seem to at least partially counteract epidermal atrophy induced by TCs. Whether they can counteract TC-induced whole skin atrophy, the most important parameter associated with skin fragility, needs further investigation. Available data were also collected from short-duration protocols, while skin atrophy induced by TCs is due to long and repeated therapy.

Longer duration protocols may then be considered. Nevertheless, the hyperplastic activity of retinoids on the epidermis, with their large, broad range of biological activities on epidermal cells, might be a limitation for associating this class of drugs with long-course TC therapies [92, 93].

5 Discussion

This review confirms the already suspected benefit/risk ratios of available TC drugs. Thus, mometasone furoate, fluticasone propionate, and fluocinonide acetonide may be good TCs in terms of benefit/risk ratio as it was shown they were the less atrophic while still belonging to the class 3 of strong TCs in terms of anti-inflammatory activity. Mometasone furoate may be recommended for the treatment of less severe disorders or anatomic areas sensitive to TC-induced atrophy, such as the face or intertriginous areas. With regard to clobetasol propionate, if this drug remains the most atrophic drug, its high efficacy for clearing acute inflammatory skin disorders such as psoriasis or bullous pemphigoid makes it the mainstay treatment for severe diseases.

In the past, the atrophic effects of TCs have been assessed with several techniques, but reliable and non-invasive techniques have only appeared recently. Nowadays, ultrasound sonography is reliable for measuring skin thinning accurately. This technique is far more convenient than previous techniques which required a biopsy. This review also shows that epidermis thickness can now be assessed very accurately and correlates with TC-induced skin atrophy. Confocal microscopy and multi-photon microscopy can accurately measure the epidermal thickness. In addition, epidermal atrophy seems to appear sooner and to be proportionally greater than whole skin atrophy. Epidermal atrophy may then be considered as an early endpoint of TC-induced skin atrophy; however, considering epidermal or skin atrophy as good markers of corticosteroid-induced atrophy (Tables 1, 2) remains hazardous because of unstandardized trials. Skin atrophy can differ according to the treated anatomic location, treatment duration, and also the excipient and frequency of application. Another issue is that skin and epidermal thinning were mainly measured on healthy volunteers, while aged or chronically sun-exposed patients are probably much more sensitive to TC-induced skin atrophy.

Another point is that very little is known about skin atrophy in pathological skin. Measuring skin thinning in trials designed to demonstrate the anti-inflammatory efficacy of TCs is indeed irrelevant. These trials are usually performed over 2 weeks, which is too short a period to measure significant skin thinning. Nowadays, measuring epidermal or skin thickness is more reliable but still remains irrelevant in pathological skin as the epidermis and dermis are thickened in inflammatory lesions. Thus, measuring epidermal thickness during an acute inflammatory phase treated with a TC will finally follow the clearance of the inflammation and not a TC-induced atrophy. This is a main point that future studies should take into account. Specific attention to skin disorders affecting important areas of the body should also be planned as there is a significant chance that TCs can cross the skin barrier and induce a significant plasmatic concentration of corticosteroids. In such cases, skin/epidermis thinning may then be measured in body areas relatively distant from the lesions to eventually assess generalized skin atrophy. This is less likely to occur in less extended lesions. Measuring skin/epidermis thinning may then be considered to be done on the edge of the lesions. Nevertheless, in both cases long-term follow-up and phase IV studies considering skin/epidermis thickness as endpoints should be performed as chronic exposure to TCs is the most important issue to analyse. Following the skin/epidermis thickness between the acute phases of patients affected by disorders requiring recurrent TC therapies may be an interesting approach. This type of follow-up should also bring answers on the reversibility of the skin atrophy according to the patient's history, sex, and age. All in all, in addition to confirming the known atrophogenic effects of the different TC drugs and their ranking with respect to their ability to reduce whole skin and epidermal thickness, this review highlights that TC-induced atrophy has not been accurately investigated in pathological skin; however, it only focused on TCs, and comparing adverse events of TCs with systemic corticosteroid therapies may bring other information. Finally, a lack of follow-up is obvious with regard to skin atrophy induced by TCs. Non-invasive methods to measure skin and epidermal thickness are now available and should be investigated in future trials in pathological skin, healthy skin, and phase IV follow-up trials in order to assess the atrophic risk in chronic diseases such as atopic dermatitis or psoriasis.

6 Conclusions

Large trauma and skin lacerations described in patients intensively using TCs over long periods clearly pointed to high skin fragility as the cause of this TC adverse event; therefore, the investigators focused on skin thickness as an early marker of skin insufficiency. Ultrasound sonography, as a non-invasive technique, has become the method of choice for measuring skin thickness [36]. The newest techniques, based on photonic technologies, are now available and allow the measurement of epidermal thickness, therefore becoming an easy measurable parameter. In

addition, because of its barrier function, the epidermis is directly exposed to TCs, making epidermal thinning a very precocious marker of skin atrophy induced by TCs. The studies retrieved in this review give a picture of TC-induced skin atrophy that is still poorly investigated. More studies using the most recent tools available to reliably measure skin and epidermis thickness are now needed to investigate the kinetics of skin thinning induced by TCs. This may also bring interesting answers to the specific atrophic activity of each corticosteroid.

Another concern is the lack of long-duration follow-up studies in patients intensively using TCs, as most of the studies evaluate the atrophic risk over 2–4 weeks, while clinically relevant skin insufficiency (dermatoporosis) takes years to appear. Studies are needed in healthy patients to understand the kinetics of atrophy, its reversibility, and to compare the atrophic effects of each TC more accurately. Short studies of 4 weeks, or maybe less if only focusing on epidermal thickness, may be sufficient for this purpose, but including the assessment of skin/epidermis thickness in trials that evaluate TC efficacy on inflammatory lesions is more challenging. As skin and the epidermis are thickened during acute inflammatory phases, the choice of where and when to measure skin/epidermis thickness is crucial. It may be relevant to measure it on the edge of the inflammatory lesion, or close to it, and in diseases affecting large areas of the body in several parts of the body. This would allow investigators to look for generalized skin atrophy, which could be due to systemic-like effects because of transcutaneous passage of the drug. Follow-up studies should then be adapted accordingly. In order to analyse local atrophic adverse events, skin/epidermis thickness should be measured on the edge of the lesion during the acute phase, and on the lesion only between acute phases. Measures on several locations of the whole body may be carried out in patients treated for extended lesions in order to evaluate whole-body skin atrophy.

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