

Tacrolimus and corticosteroids can live together.

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Dermatologists tend to apply percutaneously whatever drug is effective on skin disorders when given systemically. This is why, in 1952, a few years after the appearance of systemic corticosteroids, Sulzberger and Witten (17) published the first report on the effectiveness of topically applied hydrocortisone acetate on atopic dermatitis. In the following 25 years two contrasting tendencies were observed. On one hand, in the wake of the initial enthusiasm caused by the revolutionary new treatment, new increasingly powerful molecules were synthesized, through fluorination, acetylation, esterification and double-bond induction. On the other hand, the side-effects of the new molecules were reported. The latter were responsible for a prejudicial fear against corticosteroids till the actual corticophobia.

Starting from the '70ies the drug industries did not invest money anymore in searching for new corticosteroid molecules and for 20 years no new topical corticosteroids appeared on the market. Starting from the '90ies, in spite of a persistent corticophobia, appeared on the market new corticosteroid molecules, such as fluticasone (6), methylprednisolone aceponate and mometasone furoate (11). These corticosteroids can be used once a day, are characterized by a minor systemic absorption and do not induce tachyphylaxis.

Moreover, in the wake of the success of oral cyclosporin on psoriasis and then atopic dermatitis, simultaneously in the '90ies start the studies on topical immunosuppressive drugs inhibiting calcineurin, which will lead to the introduction of tacrolimus and pimecrolimus in the treatment of atopic dermatitis.

Topical immunosuppressive drugs

Immunosuppressive drugs were initially used in the treatment of the transplants. Later on these drugs proved effective in numerous skin disorders, even heterogeneous from the pathogenetic point of view, such as psoriasis and atopic dermatitis, but united by a more or less significant inflammation. Once established their therapeutic effectiveness, started the attempts of their topical application. The first attempt of topical treatment with immunosuppressive drugs regarded cyclosporin and proved ineffective, probably due to its scarce percutaneous absorption, deriving from its high molecular weight. Much more promising appeared the studies regarding pimecrolimus (Elidel®, Novartis) and tacrolimus (Protopic®, Fujisawa), both inhibiting calcineurin and characterized by lower molecular weight and greater lipophilia.

Tacrolimus

Tacrolimus (T) is a macrolide produced by *Streptomyces tsukabaensis* and characterized by a molecular weight of 822.05 Da. By binding to an immunophilin, T competitively inhibits calcineurin. The latter, when bound to calcium and calmodulin, allows dephosphorylation and activation of the nuclear factor of activated T lymphocytes. When entered the nucleus, this factor stimulates the transcription of the gene codifying for IL-2. The transcription and release of IL-3, IL-4, IL-5, IL-13, interferon γ , TNF, and GM colony-stimulating factor are also blocked. Moreover, the release of mediators from

basophils and mastocytes is also inhibited. It is also influenced the number of dendrocytes and Langerhans cells in atopic skin and, finally, the sensitiveness of high affinity receptors for IgE is decreased.

Systemic tacrolimus was for a long time used in subjects undergoing transplants. Topical T is actually on sale as ointment in two different concentrations, namely 0.1%, which cannot be

used under 15 years in Europe, and 0.03%, which cannot be used under 2 years. T is indicated in 2 daily doses in the treatment of moderate to severe atopic dermatitis as monotherapy -non associated to corticosteroids but as an alternative to the latter- in case of resistance to corticosteroid treatment, namely in case of allergic contact dermatitis or relapse of dermatitis immediately after the withdrawal of topical corticosteroids.



Fig. 1



Fig. 2



Fig. 3



Fig. 4

Fig.1, 2, 3, 4: The elective indications of tacrolimus are the lack of response to topical corticosteroids (Fig. 1), alternative to systemic immunosuppressive treatment (Fig. 2), exudating lesions of the eyelids above 2 years of age (Fig. 3) and of the folds in the peripuberal age (Fig. 4).

In most studies, both in children (12) and adults (7), T ointment, after the first 3 weeks of treatment is withdrawn, provided that at least a week passed from the disappearance of the lesions.

Effectiveness. T showed a marked effectiveness in the treatment of atopic dermatitis, both in adults (7) and children (12). Its effectiveness in children was evaluated against both the vehicle (12) and the weakest topical corticosteroid, namely hydrocortisone acetate (14), resulting significantly higher in both cases.

Safety. T showed to be safe both in adults and children in the usage conditions. In the study of Paller et Al. (12) the frequency of side effects was not higher than in the control group with vehicle, except for local paresthesias such as pruritus and burning sensation, mainly at the beginning of the treatment. In the study of Reitamo et Al. (14) 1.6% of patients receiving the 0.3% ointment and 11.3% of patients receiving 0.1% ointment presented plasmatic levels of T higher than 1 ng/mL and nobody showed levels higher than 5 ng, whereas in transplanted patients treated with systemic T side effects arise when the plasma levels of T are higher than 20 ng/mL. An increased systemic absorption of T, with levels superimposable to those ones of transplanted subjects systemically treated with T, were shown in patients with atopic dermatitis and Netherton syndrome (1) and also in patients with severe atopic dermatitis initially treated with large amounts -10-20 g daily- of T (10). In contrast with corticosteroids, T does not inhibit the synthesis of collagen (12). Moreover, the effectiveness of corticosteroids does not increase after a week (14), whereas the effectiveness of T increases continuously, even after the first week (14). However, Sugiura (17) showed a decreased effectiveness of T after prolonged use, suggesting tachyphylaxis.

Elective indications of T. Besides the moderate to severe cases of atopic dermatitis not controlled by topical corticosteroids due to immediate rebound (Fig. 1) or allergic contact dermatitis, T is mainly indicated in the severe cases of atopic dermatitis as an alternative to systemic immunosuppression with cyclosporin (Fig. 2) or other drugs. Moreover, due to the lack of inhibition on the collagen synthesis, T is also indicated

in the moderate to severe cases affecting the eyelids (Fig. 3) above the age of 2 and, in the peripuberal age, the folds, especially the knees (Fig. 4).

Precautions of usage. The fatty excipient of T could be responsible for a scarce compliance, especially in case of intensely exudating lesions, for instance in the inguinal region. The limits of age prevent the usage of T in the very frequent cases of the first two years. Moreover, due to the immunosuppressive activity of the molecule, T cannot be used in pregnancy, breast-feeding, above 65 years of age, during summertime and vaccination, although Stiehm et Al. (15) showed that application of T in children affected by atopic dermatitis does not decrease the production of antibodies against pneumococcal vaccine. The long-term effects of a prolonged immune suppression, although limited to the skin, are not known. This is why it is prudent to limit the period of application to the presence of symptoms and signs of atopic dermatitis and do not apply T for another week after their disappearance, verifying the possible difference of effectiveness between the two modalities of application.

Topical corticosteroids

Corticosteroids act thanks to their vasoconstrictive, anti-inflammatory, immunosuppressive and antimetabolic activity on the cells of the epidermis and dermis and on the leukocytes. The mechanism of their activity has not been fully elucidated. However, corticosteroids probably bind to cytoplasmic receptors, then enter the nucleus, activating the transcription of genes codifying for lipocortines, interleukines and lymphokines (5).

Effectiveness. Topical corticosteroids are the only treatment surely effective in the treatment of atopic dermatitis. This concept was confirmed by Hoare et Al. (9) in their systematic review of treatments for atopic dermatitis, according the evidence-based medicine.

The activity of various topical corticosteroids significantly depends on structural changes, as above mentioned. Their activity is tested with

vasoconstriction studies or measuring their atrophic effect on the skin thickness, namely testing one of their side-effects, confirming the inseparability of their effectiveness from their side effects. The activity of topical corticosteroids is classified in 4 or more classes, ranging from the weakest such as hydrocortisone acetate, to the strongest such as clobetasole propionate. Physicians should be aware that similar molecules can be characterized by different strength, hydrocortisone butyrate or valerate being much stronger than hydrocortisone acetate.

The effectiveness of topical corticosteroids is also related to their percutaneous absorption. Usually, the more fatty the vehicle, the greater the penetration of corticosteroids inside the keratinocytes. Moreover, it is also related to other numerous factors, such as the type of dressing -occlusion and hydration of the skin increase absorption and effectiveness-, the presence of cutaneous disruption and particular sites such as the folds, where there is a natural occlusion.

The effectiveness of topical corticosteroids is maximum during the first applications and does not further increase with time (14). On the other hand, topical corticosteroids exhibit their activity in a shorter time during the first episode of inflammation, whereas the same product, when applied in case of relapsing inflammation, does not reach the same effectiveness or requires a longer time to reach it. In a chronic-relapsing disease such as eczema, this phenomenon is associated to a progressive lengthening of the time of application and shortening of the intervals free of disease and treatment. This process, which is called tachyphylaxis, can be prevented with an intermittent application of topical corticosteroids (3).

Safety. Topical corticosteroids are a heroic drug, to be prescribed and used consciously. In these conditions of use the drug is safe (2, 6, 8, 19). As all the heroic drugs, corticosteroids are not devoid of side-effects. The latter are numerous and should be kept in mind (see table 1).

Side-effects should be remembered because, although today unlikely due to the very frequent corticophobia, in the future they could reappear when corticophobia will stop.

Table 1:

Side effects of topical corticosteroids in children

Local: Whitening, thinning of the skin, persistent vasodilation, rebound effect, striae distensae, granuloma gluteale infantum, possible favoring effect on infection and change of their clinical features, contact allergy.

Systemic: Cushing syndrome, inhibition of hypophysis-adrenal gland axis, inhibition of growth, vaccine problems.

The side-effects can be local or systemic, the latter appearing in case of high systemic absorption. Among the more frequent local side-effects there are whitening of the lesions, occurring immediately after the topical application of corticosteroids, due to their vasoconstriction activity, hypertrichosis, due to a temporary and reversible thickening of the shaft of the hair, and irreversible striae distensae, which mainly occur on the folds of the knees, due to prolonged application of powerful corticosteroids.

The side-effects were due in the past to a scarce knowledge of the molecule and the physiology of the infantile skin or more frequently to a bad relationship between the patient and the physician, which can easily occur in chronic disease and is responsible for autoprescription and multiplication with time of not precociously recognized therapeutical mistakes and side-effects. This can be easily prevented with a conscious administration of the topical corticosteroids and with a meticulous explanation to the patient. A right prescription of the topical corticosteroids does not cause thinning of the skin (19). However, physicians should remember that some side-effects of topical corticosteroids, although prominent such as granuloma gluteale infantum, were unveiled about 20 years after they got available on the market (18).

Indications of topical corticosteroids. Topical corticosteroid treatment is aimed at suppressing the inflammatory spikes. As antipyretics are indicated when the temperature is higher than a conventional level, similarly topical corticosteroids are indicated when the inflammation is so high to be responsible for disruption of the epidermis and exudation, mainly when a limited area of the skin is affected.

When exudating lesions affect less than 10% of the skin surface, topical corticosteroids are the first choice treatment. When topical corticosteroids are consciously applied, they are as effective as systemic corticosteroids but lack their systemic side-effects. Moreover, they act immediately and are more effective than whatever drug. Topical corticosteroids suppress exudation, restore the integrity of the skin, decrease the risk of infection more than systemic and topical antibiotics, decrease pruritus more than antihistamines and make esthetically acceptable the skin. Topical corticosteroids are also indicated on infiltrated and lichenified lesions, even under occlusion.

However, all the positive effects of topical corticosteroids are transitory because they are a symptomatic treatment. This is why they should be stopped when symptoms and signs regress.

Precautions of use. Topical corticosteroids should not be used on a skin surface larger than 20%, especially in children, whose skin surface is relatively larger with regard to the weight. Topical corticosteroids are also contraindicated in the diaper area, until the diaper is used. Contraindications related to the time of application and to the strength of the corticosteroids refer to other sites such as the eyelids, where the skin is thinner and, in peripuberal age, the folds, where more frequently striae distensae occur. With regard to the strength of the corticosteroids, a 18-week study showed that the intermittent application of a powerful drug such as beta-metasone valerate, for instance 3 times a week, is effective as hydrocortisone applied continuously every day (19).

To prescribe topical corticosteroids, physicians should first overcome the prejudicial reluctance of the mother due to corticophobia, emphasizing that they are “natural” and that were never withdrawn from the market.

Later on, physicians should explain to the mother that topical corticosteroids will not definitely cure atopic dermatitis because they are a symptomatic treatment of inflammation. However, given the lack of a causal treatment, they are the best treatment that can help the child to live together with dermatitis waiting for its spontaneous regression.

Finally, the mother should be taught where -localized exudating lesions-, when -once a day when the child is undressed due to other reasons-, how much -1 cm of cream for an area as large as an adult palm-, how -applying the cream in the center of the lesion and massaging for a few seconds till its complete absorption- and finally how long -till exudation stops- topical corticosteroids should be applied.

Conclusions

We are grateful to the drug industries that invested a lot of money in the experimental studies regarding tacrolimus and pimecrolimus, also clarifying the pathogenetic mechanism of atopic dermatitis.

However, we think that the new topical immunosuppressive drugs should not emphasize the side effects of topical corticosteroids, to avoid further diffusion of corticophobia.

On the other hand, we believe that the new drugs, even T, can live together with corticosteroids, substituting them in its elective indications, as we underlined in this editorial.

We also believe that the cost of the new drugs should be reduced to prevent a significant increase of the expenses of the public health system or to avoid that the new drugs are used only by the rich class and societies.

Finally, being aware that some side-effects of topical corticosteroids were unveiled only about 20 years after their introduction on the market, we believe that at least initially the potential risk of a prolonged immune suppression, although only cutaneous, should not be underevaluated.

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