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Cyclical Immunotherapy in Patients with Psoriasis

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Psoriasis, a chronic and unpredictable dermatosis, is a constant therapeutical challenge to dermatologists. However, new knowledge in immunodermatology has stimulated interest in and encourage the use of new molecules, especially cyclosporin A (CyA). Thanks to certain characteristics, this molecule is capable of modulating and blocking the intense network of cytochine that seems to cause this dermatosis. The first clinical experiments have demonstrated that low dosages (3–5/kg die) can achieve rapid and effective remissions. The Italian experience gathered from numerous centres has been assessed to better understand and manage the use of CyA, especially as regards to tolerance and reliability. There is proven remission in 77% of the cases of plaque psoriasis. The duration of remission, as well as the paucity of side effects, has brought to the concept of cyclical therapy with CyA. The advantages of this mode of therapy are: the possibility of determining the most effective dosage; quantification of the dermatosis-free period; opportunity to personalize treatment and decide its duration; early intervention, should the dermatosis recur; exclusion of side effects and better control over those remaining. ***Key words: therapeutical pattern; cyclosporin A; side effects.***

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Cyclosporin A and psoriasis

A number of studies have demonstrated a distinct immunological activity in the etiopathogenesis of psoriasis. Great importance is attached to the associated actions between SALT (Skin Associated Lymphoid Tissue) and the keratinocytes (1–2). These associated actions cause the release of some cytokines from keratinocytes. Fig. 1 outlines graphically what probably happens in psoriasis. It is believed that an initial and not well identified 'noxa' (auto/hetero antigens, trauma, stress, infections, neuropeptides) can stimulate the cells of the APC system that cause an increase of the IL-1. This interleukin stimulates the T lymphocytes to produce other cytokines (in particular, IL-2, IFN-γ) (3) and various growth factors that stimulate the hyperproliferation of keratinocytes. The activated keratinocyte (ICAM-1+, HLA-DR+) produces other cytokines, necrosis factors and inflammation mediators (LTB4) that support the immuno-mediated inflammation.

The outcome of these various activities is psoriasis. Knowledge of this process has allowed us to establish new therapeutical possibilities, in particular through the use of Cyclosporin A (CyA). This particular drug is capable of reducing the activity of the APC cells, thus blocking the secretion of IL-1 (Fig. 1, violet ellipse) (4). In this way, it also blocks the activation of the homing T lymphocyte and of the SALT, thus blocking the production of IL-2 and the cascade of events that follow (Fig. 1, violet ellipse) (3): clonal expansion of the T lymphocytes, endothelial proliferation and hyperproliferation of the keratinocytes (3, 5, 6, 7). The direct action on the keratinocytes is not evident with the low dosage (3–5 mg/kg/die) used in clinical studies (8). However, the hyperproliferation of the keratinocytes is reduced by the inhibitory action on the APC cells and the T lymphocytes (Fig. 1). Briefly, we perceive a direct action that affects the immunological cell-mediated activity responsible for the persistence of the disease. This mechanism of action is quicker and more efficient than that of the standard therapies. It also is more tolerable and easier to manage (9–10). The aim of multicentre Italian studies was to improve the evaluation of the efficiency, tolerability and safety of low-dosage CsA therapy in Erythrodermic Psoriasis and Plaque Psoriasis, by means of an open, multicentre, uncontrolled study lasting 6–12 months. The

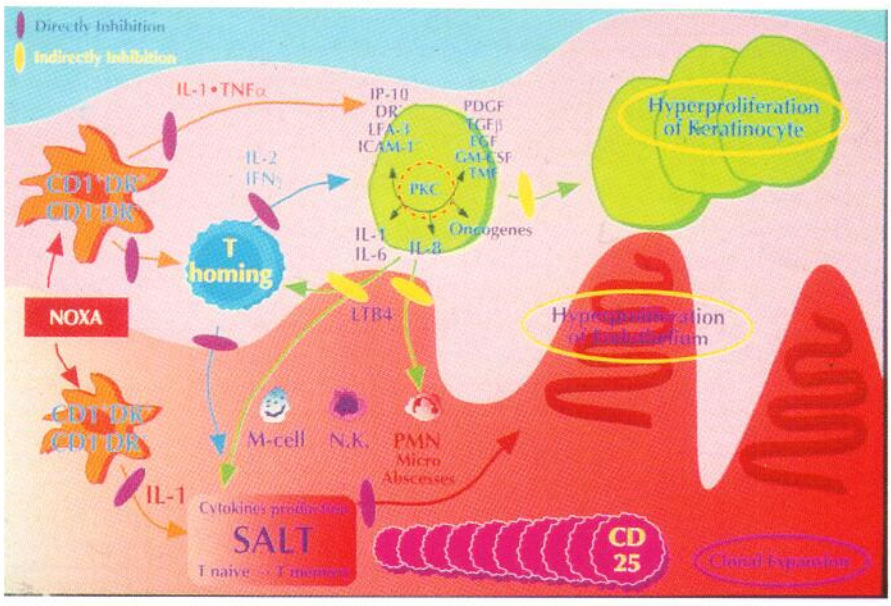

Fig. 1. How Cyclosporin works. For details, see main text.

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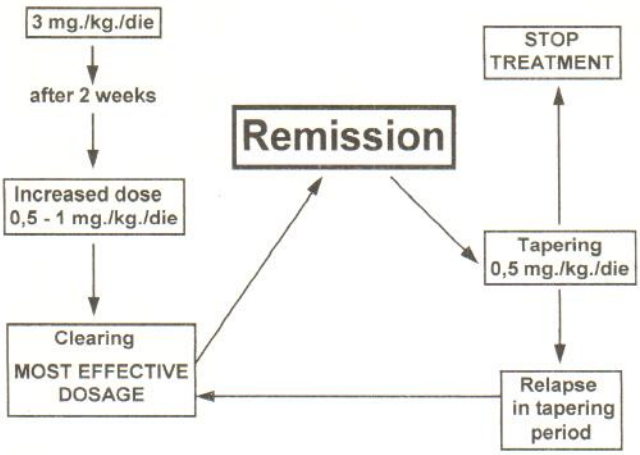

Fig. 2. Schematic illustration of therapy for psoriasis.

therapeutical scheme used was a dose of 3–5 mg/kg/die for the plaque form and 5 mg/kg/die for the erythrodermic form. At remission, a gradual reduction of the drug was practised (0.5 mg/kg/die, every 2 weeks) until suspension.

RESULTS

Plaque psoriasis

314 patients were treated and 293 patients were evaluated. Remission (defined as a reduction in the spreading of the lesions by at least 75%) was present in 225 patients (76.8%). Of these, 73% achieved remission after 2 months (median), on a dosage of CsA of 2.5–3.5 mg/kg/die. On a dosage >3.5 mg or <2.5, remission occurred 3 and 4 months, respectively, after commencing the study.

At remission, 133 pts. who were checked after 8 months, did not manifest relapse. Relapse (defined as a worsening of the clinical aspects of the disease involving more than half of the cutaneous surface) was present in 92/225 patients: 24 patients relapsed at a median time of 6 months, and the remainder 4 months (median) after remission. Side effects were present in 109 of the 293 patients studied (37%) but only 76/293 (26%) were caused by CsA and only 9 pts. (3%) had to suspend therapy because of drug-related side effects. The more frequent side effects were altered renal function, hypertension and an altered lipid profile. All patients could be treated either by reducing the dosage or its suspension (11).

Erythrodermic psoriasis

Remission (total disappearance of erythema and desquamation) was present in 22/33 pts. (67%) at a median time of 2 months in the 12 pts. who took 4–5 mg/kg/die and at a median of 4 months in the 10 pts. who took doses less than 4 mg/kg/die. Relapse occurred in 4 of the 22 patients in remission. Side effects, which were not very serious, were present in 15/33 pts. (45%) of which 8 were caused by the therapy. These side effects disappeared following appropriate reduction of the dosage, and in 6 cases after suspending the drug altogether (12).

DISCUSSION

From the information obtained from the multicentre studies and our own personal experiences, we can see the characteristics of therapy with CsA: *a*) rapid action; *b*) lengthy remission; *c*) a small proportion of side effects (caused by a long and, especially, continuous therapy). In view of this information, it is appropriate to use a cyclical therapy (Fig. 2). This method of therapy offers many advantages which, all things considered, permits a better control of the disease in every single patient, despite its instability. The advantages of cyclical therapy with CsA are as follows. Identifying the most effective dosage: the gradual reducing is the first step towards obtaining optimization of the therapeutic dose. Confronting its therapeutical validity with the dosages of the preceding therapy is the second step. Quantifying the period free from disease: this information is found by confronting the various cycles of therapy instituted, but its identification permits the personalizing and adjusting the duration of therapy: a therapy based on the administration of CsA during the winter months can be established and, at remission, lengthening it with the help of heliotherapy (at the seaside or in the mountains), where possible. Early control of relapse: in fact, in the early stages of this disease, topical therapy with steroids and/or keratolytics can be used. Reducing and better control of the side effects: damage caused by CsA can be manifested by altered renal and liver functions and hypertension. These side effects are all reversible and can be prevented or eliminated (even during therapy) by appropriate reduction of the dosage (reduce by 1 mg/kg/die). In the case of altered renal functions, the use of diuretics is not advised, as it is better to use ionic exchange resins. To conclude, the careful, individual, rational and especically cyclical use of CsA affords good results with only occasional and always reversible side effects.

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