Current Problems in Dermatology

Vol. 38

Series Editor

P. Itin Basel

Management of Psoriasis

Volume Editor

Nikhil Yawalkar Bern

30 figures, 30 in color, and 11 tables, 2009

KARGER

Basel · Freiburg · Paris · London · New York · Bangalore · Bangkok · Shanghai · Singapore · Tokyo · Sydney

Yawalkar N (ed): Management of Psoriasis.
Curr Probl Dermatol. Basel, Karger, 2009, vol 38, pp 79–94

Retinoids, Methotrexate and Cyclosporine

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Abstract

Acitretin alone is efficient (PASI 90: 40%). In responders, it is the best long-term maintenance treatment (up to 29 years of continuous treatment). The main side effect is its teratogenicity in females. It is necessary to begin retinoid treatment at low doses (10 mg/day), increasing the dose step by step, looking for the maximum well-tolerated dose (usually defined as a mild cheilitis). Doses higher than the highest well-tolerated dose are frequently responsible for the Köbner phenomenon. In children, retinoids are very efficient and nearly always well tolerated, but it seems important to never give more than 0.5 mg/kg/day. Methotrexate is the best treatment for severe psoriasis. Given at low doses once a week, it is a safe, cheap, convenient and efficient treatment, if carefully monitored. The main problem is the possible long-term liver toxicity of methotrexate. The risk is very low in patients not at risk (no liver disease). In these cases, liver biopsies are dangerous and useless. In the other cases, the need for liver biopsy is very rare, decided only by the hepatologist, and should be replaced by FibroTest and FibroScan. The old American guidelines should not be followed, and new guidelines are needed. Cyclosporine at low doses is an outstanding emergency treatment. It was first used as the last possible systemic treatment, but long-term continuous treatments are seldom possible due to alterations in kidney functions. A careful follow-up of kidney functions, with measurement of the glomerular filtration rate after each year of cumulative treatment, is necessary. The cyclosporine dose must be calculated according to the theoretical body weight in obese patients to avoid overdosage. Cyclosporine is mainly used now as a short-term treatment that is very efficient for young people, who find this illness particularly difficult. Cyclosporine is not contraindicated during pregnancy.

Acitretin, methotrexate and cyclosporine remain as the first-line systemic treatments of psoriasis, and their indications must be carefully evaluated for each patient before using biologicals for legal and safety reasons.

Retinoids

The antipsoriatic activity of aromatic retinoids (etretinate and its principal metabolite acitretin) was discovered by chance when these substances were being developed with

the aim of producing anticancer agents. With varying affinity from one substance to another, retinoids bind to nuclear receptors (α-, β- and γ-RAR), though there is no way of currently establishing a correlation between the receptors involved and their antipsoriatic activity. It is known, however, that retinoids are capable of modifying the terminal differentiation of the epidermis. High doses are able to severely impair the skin barrier function of normal skin [1], but to improve terminal differentiation in psoriasis plaques [2]. They are also known to have strong anti-inflammatory activity, and more specifically are able to inhibit migration of the neutrophilic polynuclears from the capillaries of the superficial dermis towards the epidermis [3]. Finally, retinoids are capable of inhibiting antigen presentation by acting quite simultaneously on the Langerhans cells and T lymphocytes, though this immunosuppressive activity is far less than that of cyclosporine [4].

Aromatic retinoids are hydrophobic molecules (etretinate far more so than acitretin) that accumulate progressively in the adipose tissue. Their elimination is slow, the half-life being 120 days for etretinate and 2 days for acitretin. These 2 substances, like all retinoids, are powerfully teratogenic. In the presence of alcohol, it is possible to induce inverse metabolism and thus transform acitretin into etretinate, hence the need for 2 years' contraception after stopping treatment with acitretin as well as etretinate; 2 weeks are sufficient for ladies who have never drunk alcohol [5].

When psoriasis requires systemic treatment, acitretin and etretinate are the best long-term treatment, when efficient and well tolerated. Unfortunately, they are contraindicated in any woman contemplating motherhood, due to the need for contraception throughout the duration of the treatment and the 2 years following withdrawal.

The available retinoids are etretinate (Tigason®) and acitretin (Neotigason®/ Soriatane®). Acitretin is the principal metabolite of etretinate. Etretinate and acitretin have the same therapeutic profile during the first months of treatment, but do not have the same side effects in the long term. Furthermore, some patients are more sensitive to one substance or the other. It is particularly detrimental, therefore, that these 2 substances are no longer available to patients in all countries.

The therapeutic effectiveness of retinoids shows up slowly, whereas their side effects for any given dosage appear within the first fortnight of the treatment. When the dose is reduced due to the side effects, they disappear within a fortnight of adjusting the dose. Therapeutic studies have shown that the maximum dose well tolerated by a patient is the most effective dose for that patient. In fact, with a high dose (0.5–1 mg/kg/day), the percentage of patients showing clearance (PASI 90%) was only 25%, whereas, when starting at a low dose (10 mg/day) and progressively increasing up to the maximum well-tolerated dose, the percentage of clear patients was 40% [Roche, unpublished report of a 1-year double-blind study].

Retinoids are thus the only family of drugs in the pharmacopoeia whose dosage is chosen not on the strength of their efficacy but on their tolerability, and hence the patient's quality of life. Effectively, the side effects are basically harmless, albeit highly

uncomfortable at times due to the weakening of the epithelium and integumentary system brought about by these agents.

Prescription Strategy

The rules for prescription are particularly simple. Usually, start off on 10 mg/day with meals, then increase the doses by increments of 5 mg of the daily dose, either fortnightly or monthly, until the maximum tolerated dose is found, i.e. most commonly, the dose entailing tolerable cheilitis. If this dose is exceeded, have the patient reduce the dose until the maximum well-tolerated dose is again found [6–8]. Efficacy is judged by the improvement in the skin observed 3 months after reaching the maximum dose that is perfectly well tolerated.

It needs to be stressed that for each patient retinoid activity goes through 3 phases, according to dosage. At very weak doses, there is no therapeutic effect. Then, if it exists, the therapeutic efficacy dose is reached. If this dose is exceeded, the retinoids may weaken the skin to the point where aggravation of the psoriasis is caused by Köbner's phenomenon. The dose variation between inefficacy and intolerability may be as low as 5 mg. Given their long half-life, it is always possible to adjust treatment with retinoids in increments of 5 mg, varying the number of 10-mg tablets taken on even and uneven days, for example.

Side Effects

The side effects of retinoids are dose dependent [7]. However, the maximum well-tolerated dose is extremely variable from one patient to another, potentially ranging from less than 10 mg/day up to more than 75 mg/day. The reasons for these variations are not well understood, and are likely to couple sizable variations in retinoid absorption capacity with highly variable individual sensitivity to these drugs. This great variability explains why it is preferable to start off with very small doses, given that the drug is not prescribed for emergency situations. If this individual sensitivity cannot be predicted, it must be stressed that the weakening of the skin by the retinoids will increase with age and is often severe in atopic subjects.

The clinical side effects essentially result from a weakening of the epithelia and their products, nails and hair, by the retinoids. The earliest side effect is generally cheilitis. Dryness of the eyes is frequent and contact lenses are contraindicated. Rhinitis sicca, sometimes with epistaxis, is not uncommon. Fragility of the skin can be accompanied by pruritus, particularly in all rubbing or friction zones. Retinoids can frequently trigger (sometimes fierce) senile pruritus. At strong doses, retinoids generate hair cycle synchronization, with hair loss of sometimes spectacular proportions. Regrowth is usual on discontinuing the treatment, but may be incomplete. Conversely, retinoids may modify the texture of the hair, making it look more or

less curly and sometimes unmanageable. Nail growth may be disturbed, sometimes producing Köbner's phenomenon at this level, entailing the development of ungual psoriasis, sometimes severe. The periungual skin may be weakened, promoting the development of granulation tissue, particularly on the feet.

Apart from such epithelial fragility, numerous other side effects may be observed: a reduction in night vision that may be dangerous in the case of long-distance lorry drivers, mood swings capable of leading up to depression and libido decrease, as well as a faster appearance of muscle aches contraindicating the use of retinoids in elite sportsmen and sportswomen. Headaches can be debilitating.

Numerous other side effects may be observed, which may be unpleasant but are quite harmless. The patient must be informed that in the event of any disturbing side effect ascribed to retinoids, the most simple solution is to stop the treatment for a fortnight; actually, there is no rebound phenomenon from discontinuing retinoids. If the trouble disappears and then reappears when the treatment is resumed, it is because it is connected with retinoids. On the basis of his/her quality of life and the therapeutic results, it is then up to the patient to choose whether or not to continue with retinoids.

The main side effect of retinoids is their teratogenicity. Provisions must be made for totally effective contraception throughout treatment and for the 2 years after halting treatment. In practice, this restriction prevents retinoids being prescribed to fertile women. What should be done in the event of an onset of pregnancy during the 2 years following discontinuation of the treatment? For virtually all patients, acitretin is completely eliminated 1 month after treatment stops, and is therefore no longer any teratogenic risk. To verify this, it is possible to determine the quantity of retinoids in the blood (e.g. by Roche Laboratories).

Biomonitoring

Biological monitoring (biomonitoring) is quite simple, as it will suffice to make a quantitative determination of transaminases, cholesterol and triglycerides before treatment, at the end of 1 month's treatment and then every 3 months. Acitretin more often increases triglycerides, whereas etretinate more often increases cholesterol. Lipid problems will be more frequent if the patient is obese, diabetic or abuses alcohol, and all of these situations are associated with hepatic steatosis. Only a large increase in triglycerides is a contraindication to starting treatment: in fact, acitretin may provoke a sudden increase in triglycerides in this case, with a risk of acute pancreatitis. There again, a moderate increase in triglycerides or cholesterol will simply provide an incentive to monitor the lipid balance every month and implement a diet. In the event of a progressive increase in cholesterol, the decision will be relative to the therapeutic improvement obtained: diet only, a lipid-lowering drug or discontinuation of retinoids.

Acitretin is only hepatotoxic in exceptional cases [9, 10], but may quite often bring about an increase in transaminases of 2 or 3 times the norm, particularly in patients

with hepatic steatosis. In these situations, it is important to intensify biomonitoring (monthly monitoring), and to ask patients to cut out alcohol and excess sugar and fat. Prescribing polyunsaturated omega-3 fatty acids (MaxEPA®) seems to be able to improve this situation and reduce the cutaneous side effects of the retinoids. However, this has still to be demonstrated, and does not eliminate the need for dieting anyway. Cirrhosis or hepatitis C and B are not contraindications to retinoids, but an indication for monthly monitoring and a proper joint effort with the hepatologist.

Bone Monitoring

Bone monitoring is useful in 2 different contexts: in the child and in the adult. In the child, retinoids are remarkably effective, but must always be monitored in liaison with the general practitioner (GP) or pediatrician to make certain that there is no deterioration in the growth curve. In adults, the risk is calcification of the tendon insertions. The presence of hyperostosis is more common in psoriatics than in normal subjects, but in some subjects it is clear that retinoids may favor the development of (sometimes spectacular) hyperostosis. Given the rarity of this side effect, systematic monitoring would seem to offer a very poor cost/benefit ratio. Conversely, if painful areas appear (a calcaneal spur, for example), it seems fair to perform bone scintigraphy and X-rays targeting any areas of hyperfixation. In the event of hyperostosis, it is then possible to monitor its development every 2 or 3 years. The indication for subsequently stopping retinoids is highly controversial, and each case must be considered on its own according to the therapeutic benefits observed by the patient. Some patients presenting pain-free hyperostosis that is clearly linked to the treatment refuse to stop taking retinoids due to the therapeutic benefits observed.

A few patients have been on retinoids for more than 30 years now, raising the problem of potential side effects over a very long period. Vigilance remains the keyword for these patients. Some of them present atrophy of the dermis, although this is difficult to interpret as these patients also make occasional use of a little topical corticotherapy. These observations have led to a study conducted for over 5 years to investigate the occurrence of osteoporosis in subjects on retinoid therapy. During this time, no significant variation was observed [11]. For treatments over a very long time, it seems reasonable to perform bone densitometry every 5 years to verify that the latter falls within the norm relative to the patient's age.

Strong Doses

Retinoids can be given in strong doses of almost 1 mg/kg/day in 2 circumstances:
Pustular psoriasis. High doses are given over 7–10 days, and thereafter reduced to tolerated doses. In this indication, acitretin or etretinate may be replaced with 13-cis-

retinoic acid (Roaccutane) in fertile women wishing to contemplate pregnancy. In fact, the anti-inflammatory effect sought – inhibition of neutrophilic polynuclear migration – is the same with 13-cis retinoic acid as with acitretin, and contraception can be stopped 1 month after discontinuing the treatment.

Psoriatic rheumatism. High-dose retinoids, approaching 1 mg/kg/day, bring about a clear improvement in some two thirds of cases, the downside being substantial cutaneous or mucous side effects. Methotrexate's efficacy/side effect ratio is generally more favorable in this indication, where retinoids are rarely used [12].

Retinoids for Children

Retinoids are the best first-line systemic treatment for children.

Children must not be given retinoids at a dose higher than 0.5 mg/kg/day. More often than adults, children will sustain discreet cerebral edema with cephalalgia and irritability of a nature that should bring treatment to a halt, and be resumed at much weaker doses or even contraindicated.

Retinoids and Psoriasis Erythroderma

In psoriatic erythroderma, retinoids may be a good treatment, but only in very low doses (10 or a maximum of 20 mg/day). At higher doses, there is a risk of causing Köbner's with oozing erythroderma, which is capable of rapidly jeopardizing a good prognosis.

Retinoids and Psoriasis in HIV

Retinoids are usually quite effective for psoriasis occurring in HIV patients [13].

Combination Therapies

Retinoids combine successfully with all topical treatments, but do heighten the irritant nature of some (vitamin D derivatives and, of course, topical retinoids). They potentiate the effectiveness of phototherapy and are increasingly being used in tandem with broad-spectrum UVB, TL01 UVB and PUVA. They provide faster and more frequent (+15% excellent results) clearance of lesions. They can even be useful in patients resistant to retinoids alone, as they potentiate phototherapy by countering the photoprotective thickening of the stratum corneum caused by the latter [14]. They can be combined with methotrexate provided that weekly or bimonthly monitoring

of liver enzymes is carried out [15]. The potential interest of combining them with cyclosporine has never been clearly assessed.

The combination acitretin/TNFα inhibitors is quite interesting [16].

Finally, the combination of retinoids and tetracyclines is contraindicated, as it entails a risk of cerebral edema.

Retinoids are the best maintenance therapy over a very long time for psoriasis of patients in whom they are efficacious [17]. Their efficacy peaks after 1 year of treatment, so it will often be necessary to combine them with some quick clearing therapy from the outset, thereby allowing the patient's state to improve more quickly.

Methotrexate

Methotrexate remains the benchmark therapy for severe psoriasis and/or psoriasis associated with peripheral articular involvement. It is the treatment that offers the best efficacy/tolerability/convenience/cost ratio for psoriasis.

Despite having been used in psoriasis for more than 40 years, the reasons for its effectiveness remain poorly understood. In fact, its antifolic effect (it is a structural analogue of folic acid, a powerful inhibitor of dihydrofolate reductase) is undoubtedly insufficient to explain its effectiveness at weak doses used just once a week. Methotrexate has many pharmacological properties, each of which may contribute to its antipsoriatic activity: cytokine inhibition (IL-1, IL-6, TNFα), inhibition of LTB_4, PGE_2, PAF and histamine production; inhibition of adhesion and of intratissular migration of macrophages and neutrophilic polynuclears; induction of apoptosis (programmed cell death) in phase-S cells; inactivation of activated T lymphocytes at weak doses. The main constraint on its use is its hepatic toxicity, which is clearly overestimated. It is a teratogenic drug that persists in the tissues for several weeks after stopping treatment. It is partly linked to plasma proteins, and its free form is the active one. It is eliminated through the kidneys.

Pretreatment Testing

The pretreatment testing is strictly structured: to start with, a general clinical examination and a biological checkup must be performed. This has to include a blood count, in order to ensure the absence of any hematological anomaly, and above all the absence of macrocytosis. A quantitative creatininemia analysis will be needed to ensure that there is no renal insufficiency, and liver enzymes must be checked for the absence of hepatopathy. A systematic investigation for hepatitis B and C seems useful. HIV testing could be proposed. Effective contraception must be prescribed before treatment that will last throughout the treatment and for the 3 months following its discontinuation, in men as well as in women.

Chest X-rays are frequently proposed, but the rational is poor [18].

Strategy for Use

Strategies for use are different in the north and in the south of European Union.

The first dose of methotrexate should be 5 mg, in order to detect any intolerability or idiosyncrasy, and then it should then be raised to a dose somewhere between 20 and 25 mg once a week on a precise day chosen along with the patient and noted on the prescription. In order to improve methotrexate tolerance, 5 mg of folic acid should be taken every evening, except the day on which methotrexate is taken [19]. Many strategies for the prescription of folic acid are used without comparative studies, but even with 5 mg folic acid the day after injection the tolerance seems improved. In order to avoid therapeutic error wherever possible and to start treatment under the best conditions for bioavailability and digestive tolerance, it is preferable to start treatment by intramuscular or subcutaneous injection for the first 6 months. Once sure that the patient is properly trained and treatment is effective, it will of course be far more convenient to switch from injections to tablets (Novatrex®/Rheumatrex®). The tablets are often taken in 3 parts over a week: that is, for example, on Friday evenings at 8 p.m., Saturday mornings at 8 a.m. and Saturday evenings at 8 p.m. It is quite possible to administer the weekly dose in 2 parts. Taking the weekly dose in 1 part decreases the absorption, increases the risk of digestive disturbances and of turning the treatment into a boring routine, thereby making compliance less strict. It is not uncommon to observe a relapse during the changeover from subcutaneous administration to taking tablets, the oral method often being less effective, certainly due to an initial hepatic passage and less favorable bioavailability.

With methotrexate, a number of drugs need to be avoided, and these must be listed on the prescription. These are antifolics such as Bactrim, sulfamides, sulfones, drugs that reduce renal elimination (like probenecid) or drugs that displace methotrexate from its plasma bonds (like strong doses of aspirin or non-steroidal anti-inflammatories). It is, of course, quite possible to start methotrexate treatment while patients are taking small doses of aspirin or non-steroidal anti-inflammatories for psoriatic arthritis, for instance.

Side Effects and Monitoring

The side effects are the occurrence of digestive disturbances during the 2 or 3 days following injection, and a feeling of a (sometimes incapacitating) fatigue during the same period. The occurrence of (sometimes severe) mucitis is particularly observable in the elderly or in patients with folate or vitamin B_{12} deficiencies. Taking folic acid (5 mg/day), except on the injection day, greatly reduces these side effects without decreasing therapeutic efficacy. The appearance of macrocytosis and its progressive aggravation should alert the medical professional to check for a folate deficiency or alcohol abuse, and to lower the doses. Pancytopenia mainly occurs during the first weeks of treatment [20]. Erosion of psoriatic plaques is also an early sign of toxicity [21]. In case of

the appearance of hepatic cytolysis 3 times above the highest normal values, the treatment must be stopped and the advice of a hepatologist must be requested.

The immunosuppression caused by methotrexate is weak at the doses used in psoriasis treatment in the absence any other immunosuppressants, but vigilance is still called for.

Contraception is essential, of course, in fertile women during treatment and for 3 months following its discontinuation, due to this drug's teratogenic properties and its prolonged presence in tissues. The same duration of contraception is also advisable in men, as methotrexate reduces spermatogenesis. On the other hand, contrary to what used to be suggested, there seems to be no point in storing and preserving sperm before undergoing treatment because inhibition of spermatogenesis is reversible at antipsoriatic doses.

Methotrexate is not demonstrated as mutagenic, and is not considered contraindicated in a patient who has had cancer. However, this drug does contribute to reducing immune defenses, and rare cases of Epstein-Barr virus lymphomas have been described in psoriatics on methotrexate.

Biomonitoring is simple. A blood count every week for 2 months and then every month will suffice, along with a dose of transaminases every month. This biomonitoring must be conducted during the 2 days prior to taking methotrexate, as there is often a transient cytolysis, of no significance, during the days immediately following treatment.

The major problem is monitoring the liver. Cirrhosis may develop with biological liver tests showing normal results for a long time, and the liver biopsy puncture is an examination entailing non-negligible morbidity and mortality. The old guidelines were to perform a liver biopsy puncture every time a cumulative dose of 1.50 g of methotrexate had been exceeded. French hepatologists consider this strategy to be quite excessive and to cause patients to take needless risks. They also consider that there is no evidence to believe that methotrexate entails hepatic risks in patients who have no progressive hepatopathy and consume little alcohol. Finally, the scales used by anatomical pathologists (liver specialists) to measure hepatic fibrosis do not seem suitable for monitoring hepatic fibrosis on methotrexate, which explains without doubt the disparities observed in the literature concerning the rate of cirrhosis that ranges from 0 to 7.4%. It is important then to work with a team of hepatologists trained to monitor this drug. Finally, it should not be forgotten that the existence of hepatic fibrosis is more common in psoriatics than in non-psoriatics, without knowing with any certainty if such thing as a 'psoriatic liver disease' exists or if psoriatics tend to be consumers of alcohol more than non-psoriatics.

A series of follow-up studies extending up to 10 years have suggested that the risk of hepatic fibrosis occurring while on methotrexate is extremely faint, if not none, in patients whose serum type III procollagen rate (increased when there is collagen synthesis) is normal and remains normal when monitored systematically every 3 months [22]. It seems useful, therefore, to dose type III procollagen in patients on

methotrexate every 3 months. A liver biopsy is useless in patients whose type III procollagen rate stays within normal limits.

Conversely, it must be remembered that the increase in type III procollagen is absolutely not specific to any hepatic involvement whatsoever, and that the only consequence of its increase is to eliminate an item of information that would have given the green light for abstaining from liver biopsy. There remains a need to carry out a wide-ranging study comparing patients on methotrexate who drink no alcohol whatsoever with others who drink occasionally, in order to find out whether or not total abstention from alcohol might help avoid hepatic biopsy puncture.

Fortunately, the association of a biological test (FibroTest) with a new non-invasive technique (FibroScan) allows a very sensitive evaluation of hepatic fibrosis and reduces the need for liver biopsies [23]. Using these tests every 3 years, we stopped performing liver biopsies 6 years ago.

The pulmonary toxicity of methotrexate crops up in 2 different contexts:

- The first is a hypersensitivity syndrome with 39–40°C fever, coughing, dyspnea, the appearance of major eosinophilia and of a non-systematized pulmonary infiltrate. Needless to say, treatment must be stopped urgently and never resumed. Systemic corticosteroid treatment can be necessary. This illness is exceptional.
- The second problem is that of pulmonary fibrosis while on methotrexate. Although being used for over 40 years in dermatology without this side effect ever being noted [18], our colleagues from rheumatology have remarked on the appearance of pulmonary fibrosis in some patients 2 or 3 years after starting methotrexate treatment of rheumatoid polyarthritis; in contrast, they never utilize liver biopsy punctures. This illustrates that the side effects of a drug are not the same according to the pathology treated. It should also prompt dermatologists to be heedful of dyspnea occurring in psoriatics, because even if this side effect is exceptional in the treatment of psoriasis, it nevertheless needs to be borne in mind.

Methotrexate osteopathy is very rare [24], and another piece of good news is that methotrexate reduces the incidence of death due to vascular diseases in patients suffering from psoriasis or rheumatoid arthritis [25].

Combination Therapies

Methotrexate may be combined with all topical treatments. If combined with phototherapy, methotrexate needs to be injected on the Friday evening following the last session in order to avoid photoactivation. Methotrexate is not a photosensitizer but is phototransformed into a highly photosensitizing photoproduct, [2,4-diamino-6-pteridinyl] carboxaldehyde [26]. Methotrexate may be combined with retinoids, provided there is tighter hepatic monitoring, and with cyclosporine in exceptional cases. It is commonly combined with infliximab in order to decrease the production of anti-infliximab antibodies.

Cyclosporine

The history of treating psoriasis with cyclosporine is particularly interesting. Cyclosporine was isolated from a fungus found in a sample of soil on a high plateau in southern Norway in 1969. At the time, the Sandoz laboratories were looking for new antibiotic substances. Cyclosporine proved to be a second-rate antibiotic; however, its weak toxicity provided an incentive to pursue pharmacological studies, and in 1972 the laboratory of J.F. Borel discovered its immunosuppressive properties. In 1978, the first organ transplant succeeded, thanks to cyclosporine, and in 1979 the substance's antipsoriatic powers were fortuitously recorded in patients suffering from psoriasis arthritis.

The use of cyclosporine in psoriasis developed in 2 stages, 12 years apart. First, cyclosporine was used in patients resistant to all other treatments. Under these conditions, it was a last-resort treatment administered over a long period of time; in particular, beyond the first year of treatment, it was usual to observe a reduction in glomerular filtration often signaled, though not always, by an increase in creatininemia. This renal insufficiency, the upshot of irreversible renal fibrosis, left no choice but to stop the treatment once and for all. A second side effect, not always reversible after stopping treatment, was the appearance of hypertension, a frequent cause of halting the treatment. These 2 side effects, potentially serious and not completely reversible once the treatment stopped, initially prompted dermatologists to cut down on the indications for this drug, as it could only resolve particularly difficult situations for a limited time [27].

Twelve years after cyclosporine had started to be used in psoriasis, it was suggested using cyclosporine as a systemic treatment of first intention, but during short interventions so as to try avoiding renal toxicity and hypertension. It was then ascertained that these short interventions, nearly always very well tolerated, could bring about prolonged remissions in some 30% of patients. Today, cyclosporine has thus become a treatment of first intention, usually reserved for short interventions. This 3- or 4-month prescription is designed to cope with urgent situations or seasonal psychological intolerance to the illness. Though particularly appealing to sufferers, it remains to be proved that this new strategy will help avoid cumulative kidney toxicity [28].

Pretreatment Checkup

The pre-cyclosporine therapy checkup is quite standardized. It calls for:

- a complete clinical examination to make sure that there is no progressive disease;
- a complete blood count and an inflammation test to check that there is no major biological anomaly;
- creatininemia determination 3 days in a row to calculate the average creatininemia that will enable treatment dosage to be adjusted in relation to renal tolerability;

- monitoring of lipid levels, as cyclosporine can induce hypertriglyceridemia during the initial months of treatment [29];
- a gynecological checkup in women to ensure the absence of any papilloma virus lesion of the cervix; HPV proliferation might be aggravated by the immunosuppression produced by the cyclosporine;
- a dental examination to verify the absence of parodontopathy, which must be treated prior to treatment in order to reduce the risk of gingival hypertrophy triggered by the cyclosporine;
- finally, one must check for the absence of chronic viral diseases, hepatitis C and B or HIV, and also that the patient has not had strong doses of PUVA, which would contraindicate cyclosporine.

Tolerance to the treatment may be partly predicted beforehand, given that treatment cessation due to side effects is more frequent with advancing age, patient obesity, diastolic pressure bordering on the norm and average creatininemia close to the upper limits of the norm. One major advantage of cyclosporine is that it requires no contraception for women and all pregnancies on cyclosporine have completed without fetal problems. The ideal profile for benefiting from cyclosporine is therefore that of a young slim hypotensive woman.

Monitoring

Monitoring is simple:

- Creatininemia has to be determined every month (mornings, on an empty stomach and with no previous muscular exertion). If the creatininemia increases by more than 30% by comparison with the patient's base value and is not within the norm, we must then check the dosage – which is highly variable – and, if the increase is confirmed, lower the cyclosporine dosage.
- Arterial pressure must be measured every month.
- Triglycerides must be monitored every month for the first 3 months of treatment.
- The gynecological examination must be repeated every year for women.
- Whenever the cumulative duration of cyclosporine treatment has reached 1 year, a measurement of the glomerular filtration rate must be performed. This will provide a complete sense of security when it comes to renal tolerability. This is an inexpensive and non-invasive examination.

Side Effects

The main side effects, around which all clinical and biological monitoring are arranged, are nephrotoxicity and hypertension [27]. Moreover, these are the 2 prime causes of discontinuing cyclosporine. It must be remembered here that renal insufficiency

brought about by cyclosporine may appear eventhough creatininemia remains in normal range. That is why regular renal functional explorations are necessary when monitoring this treatment. Hypertension brought about by cyclosporine is more frequent when diastolic pressure is high before treatment. It is not always reversible. In the event of hypertension appearing while on cyclosporine, a salt-free diet must be started; if that is not sufficient, one must then resort to calcium inhibitors. Of these, it is necessary to avoid Nifedipine (Adalat®), which promotes gingival hyperplasia, and give preference to the family of dihydropyrimidines, like nicardipine (Loxen®). If the latter are not effective, cyclosporine will have to be stopped. Side effects leading to the discontinuation of treatment increase with the duration of treatment, with the age of the patients, with base creatininemia, with increased pretreatment diastolic pressure and, undoubtedly, with the presence of obesity.

Other less severe side effects are observed with cyclosporine: an increase in facial hairiness (reversible on discontinuation of treatment) and a slight increase in skin infections (folliculitis, verrucas, herpes and shingles). The only cancers to increase in incidence under cyclosporine are the cutaneous squamous cells carcinomas, especially in patients who have had many PUVA sessions and more than 2 years of cyclosporine treatment [30]. No increase has been noted in the incidence of lymphomas, but this eventuality remains possible. Epstein-Barr virus lymphomas have been caused by the combination of cyclosporine and systemic corticotherapy.

Other side effects are gastrointestinal disturbances, gingival hyperplasia, the appearance of paresthesia at the beginning of treatment, fatigue, headaches and, exceptionally, convulsions. Finally, cyclosporine reduces the absorption of calcium and vitamin D_3.

Strategy for Use

Cyclosporine treatment is started at a dose somewhere between 2 and 3 mg/kg/day [for an overview, see 31]. The maximum dose prescribed in psoriasis is 5 mg/kg/day. At the very outset of cyclosporine use in psoriasis treatment, it has been suggested starting therapy at high doses (5 mg/kg/day), clearing the patient rapidly, then progressively reducing doses until a relapse is observed, in order to find the effective minimum dose. This strategy was very soon dropped, as it was more aggressive to the kidneys and, above all, less well received by the patient. In fact, the patient experiences a rapid alleviation combined with a psychological questioning associated to the sudden disappearance of a chronic illness, and then he witnesses the disease relapse with equivalent unrest. The strategy that has won acceptance is to start off with small doses in order to obtain progressive improvement in the illness, while keeping as a fallback (should this improvement be insufficient) the possibility of progressively increasing the cyclosporine doses without ever exceeding 5 mg/kg/day. The patient then benefits from a progressive improvement in his quality of life until the dose is found that will

restore to him a satisfying quality of life, even if it does not achieve complete clearance. Even with this strategy, however, the number of patients who have to break off cyclosporine treatment due to its side effects increases with time, and after 5 years of treatment there are only about 5% of patients who are able to continue without complications.

The association of magnesium (100 mg/day) to cyclosporine seems able to protect the kidneys, but this remains to be proved.

In order to avoid overdosage in obese patients, the daily dose of cyclosporine must be calculated using to the theoretical weight (according to the body size) [32].

Due to its renal toxicity in prolonged therapy, it was suggested to use cyclosporine for a short intervention of 3–5 months, either as an emergency treatment or 'to turn a corner', or as a short-term clearing treatment prescribed in conjunction with a long-term slow-acting maintenance treatment (e.g. acitretin); thus, giving this last one time to act. Some patients use cyclosporine for 4–5 months every year, for example, in order to spend the summer enjoying normal social life.

This new therapeutic approach has led to cyclosporine being put forward as a systemic treatment of first intention. In these conditions, it has been observed that 30% of patients remained clear for 6 months after breaking off a short course of cyclosporine [28]. In order to increase the chances of obtaining prolonged remission, it is important not to stop cyclosporine suddenly, but to decrease doses gradually over 2 months. These observations have profoundly changed the way this drug is used. It is now suggested as a systemic treatment of first intention for young subjects in order to perform short interventions not exceeding 4 months, followed by 2 months of dose reductions.

The change in the pharmacokinetics of cyclosporine brought about by other drugs is so frequent that it is important for psoriatics being treated with it to report always this treatment to their GP, so that if a prescription is needed for some other disorder, the GP can bear the drug interactions in mind.

Combination Therapies

In order to potentiate the effects of cyclosporine, topical treatments (especially vitamin D derivatives) seem particularly interesting. Combining with phototherapy is contraindicated, due to the immunosuppressant role of cyclosporine, which may favor the development of squamous cells carcinomas. The sudden appearance of multiple squamous cells carcinomas has been observed in some patients on cyclosporine who had had high cumulative doses of PUVA therapy, sometimes a great number of years before the cyclosporine treatment. Intensive and prolonged PUVA therapy therefore contraindicates the use of cyclosporine. Cyclosporine may be combined with retinoids, though the potential interest of this combination has not yet been validated. The most interesting strategy is, without doubt, the use of retinoids as a relay of

cyclosporine to reduce the speed and intensity of a relapse on cessation of this potent therapy. At weak doses, the cyclosporine/methotrexate combination is effective, but used exceptionally as no test is available to measure the importance of the immunosuppression produced by combining these 2 treatments.

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