Traditional Systemic Treatment of Psoriasis

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ABSTRACT. Psoriasis is an inflammatory skin disease with a chronic relapsing course. In about 20%–30% of psoriatic patients, disease severity requires systemic treatment, which carries a huge economic and management burden for the healthcare system. The decision to employ systemic treatment, reserved for severe or extensive forms, needs to be weighed carefully and is influenced by factors from the host. Each form of treatment, i.e., photochemotherapy, cyclosporin A, methotrexate, acitretin – considered the traditional psoriatic treatments – should be evaluated for each specific clinical condition. (J Rheumatol 2009;36 Suppl 83:46-48; doi:10.3899/jrheum.090223)

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PSORIASIS

Psoriasis is an inflammatory skin disease with a chronic relapsing course that is associated with often severe physical and psychological comorbidities[1]. The most common form is chronic plaque-type psoriasis characterized by a symmetrical distribution of erythrosquamous plaques on typical body areas (elbows, knees, lower back, scalp). In 30% of patients there is concomitant joint disease, with potential progression to a profoundly destructive form. Studies on the quality of life of psoriatic patients have found that the effect of the illness is comparable to that in patients with cancer, arthritis, or heart diseases[2,3].

In Western countries, psoriasis is fairly frequent, affecting 2%–3% of the population equally between males and females, with a slightly higher prevalence among males. In about 20%–30% of psoriatics, disease severity requires systemic treatment, which carries a huge economic and management burden for the healthcare system.

The decision to employ systemic treatment, reserved for severe or extensive forms, needs to be weighed carefully and is influenced by a host of factors. The final choice may be further determined by other circumstances, such as the presence of comorbidities, the possibility of hospitalization or treatment with appropriate topical therapy, treatment cost, patient compliance, and patient's occupation. An additional factor is the physician's experience with available therapeutic means: drug pharmacokinetic and pharmacodynamic profiles, possible drug interactions, optimal dosing, and risk-benefit and cost-benefit ratio[4]. The use of potentially toxic drugs requires collaboration by the patient, who will need to be informed about the potential risks of treatment and expected clinical results, the time needed for clinical response, and generally prolonged or repeated duration of treatment. The active principles of the compounds in systemic treatment exert their effect by modulating basic pathogenetic processes such as keratinocyte overproduction and/or abnormal T lymphocyte response[5].

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PHOTOCHEMOTHERAPY

Photochemotherapy refers to the use of ultraviolet irradiation (UVA) in combination with oral psoralens (PUVA therapy). Although its effectiveness is well documented, the major drawback to prolonged administration of PUVA is its carcinogenic risk. This is why PUVA, as administered according to various treatment regimens, cannot be used in the long term or combined with immunodepressants, so as not to increase the risk of skin cancer. Combination with retinoids (RePUVA) may offer the advantage of enhancing the therapeutic effect of PUVA, reducing cumulative radiation doses, and protecting against the risk of neoplasia. PUVA therapy is inconvenient for patients, however, as it involves returning to a specialized medical center for repeated treatments[6,7].

CYCLOSPORIN A

Cyclosporin A (CsA) is an immunosuppressant initially developed for the prevention of organ rejection after transplant[8]. Following the incidental discovery in 1979 that CsA improves psoriasis treatment, the drug's potent antipsoriatic effect has been confirmed in over 25 years of clinical use. Its principal indications are psoriatic erythroderma, generalized pustular psoriasis, psoriatic arthropathy, and persistent generalized psoriasis. Pustulosis palmaris et plantaris (PPP), psoriasis of the scalp, and ungual dystrophy also respond to CsA treatment. At dosages of 3–5 mg/kg/day CsA is highly active, with rapid onset of action. Preferably, a starting dose of 2.5 kg/day may be augmented by 0.5 mg/kg every 2 weeks in case of lack of response. Given that the higher the dose, the faster the clinical response, it is advisable not to go beyond a dose of 5 mg/kg/day as the risk-benefit ratio increases considerably after this limit. When clinical

clearing is achieved (within 2 months of therapy on average at a mean dose of 4 mg/kg/day), the next step is to decide whether to discontinue treatment or switch to a maintenance dose. In the latter case, the dose is tapered to the lowest effective dose in the attempt to keep the illness within acceptable limits. CsA may be given in an intermittent regimen, particularly in less severe forms of psoriasis. Therapy cycles lasting up to 6 months are recommended, and may be repeated in case of relapse, using the previous dosage that was found to be effective and tolerated[9].

The side effects of CsA are time- and dose-dependent. The most frequently encountered are those affecting the kidneys. Increased serum creatinine and potassium levels signal kidney damage (reversible) and should therefore be monitored. If serum creatinine rises above 30% of individual baseline values, the CsA dose should be reduced by 0.5–1 mg/kg/day until the values return to within normal range, or treatment discontinued. Kidney damage does not progress after drug withdrawal. However, structural kidney alterations have been found after at least 2 years of continuous treatment at doses of 2.5–6 mg/kg/day, and the severity of damage was correlated with treatment duration. For this reason extensively prolonged treatment cycles should be avoided, or kidney function scrupulously monitored. A common side effect of CsA is elevated blood pressure. If diastolic pressure remains around 95 mm Hg, the CsA dose should be decreased; if pressure levels do not return to within normal range, antihypertensive treatment may be initiated, preferably with nifedipine. Although CsA is classified as an immunosuppressant, the risk of infection or neoplasia does not appear high, at least according to available data. Malignant cutaneous neoplasms have been described only in subjects who had undergone phototherapy or PUVA cycles. In patients with prior UVA or PUVA exposure, concurrent administration of CsA is not recommended[10]. The occurrence of neoplasms in transplant recipients receiving CsA is no higher than the rate observed for other types of treatment. In transplant recipients, the risk of developing neoplasia may be influenced by the elevated CsA doses administered and their combination with other immunosuppressants[11].

CsA toxicity is often related to the concurrent use of other treatments that may reduce its metabolism and increase its plasma levels, whereas other compounds that promote hepatic CsA synthesis may reduce the drug's active concentration, thus diminishing its effectiveness.

The new microemulsion formulation (Sandimmun Neoral®, Sandoz, Basel, Switzerland) permits better absorption of CsA and increases its bioavailability. Thanks to the new formulation's improved pharmacokinetic profile, determination of cyclosporinemia should be reserved for selected cases, e.g., suspected interaction with other drugs. CsA treatment is well tolerated and accepted. Although the agent is neither myelotoxic nor teratogenic, administration is not recommended in pregnant women[12].

METHOTREXATE

Methotrexate (MTX), a folic acid antagonist indicated in the treatment of generalized and pustular psoriasis, psoriatic erythroderma, and psoriatic arthropathy, is both myelotoxic and hepatotoxic, particularly at elevated doses[13]. Normally administered by mouth at weekly intervals to reduce toxicity, it can also be given by the intramuscular or intravenous (iv) route. Most adults respond to a dosage between 7.5 and 15 mg/week. Treatment monitoring should be performed every 2 to 4 months. Liver biopsy is usually undertaken after a cumulative dose of 1.5 g has been reached. As a preliminary step, serum assay of aminoterminal peptide of type III procollagen can be done, which appears to be a fairly reliable index of liver damage. MTX toxicity may be potentiated by several compounds that reduce its excretion via the kidneys or at lower folate levels. In the liver, alcohol abuse may increase the drug's toxicity[10,14-16]. Elderly patients are at greater risk of accumulation due to decreased renal function.

Nausea and megaloblastic anemia can be managed with folinic acid (5 mg/day) supplementation. Folinic acid given intravenously may be necessary in case of overdosage. Good hydration is essential for promoting renal excretion of MTX; urine alkalinization with sodium bicarbonate may prevent precipitation in the renal tubules. MTX is also teratogenic, increases the risk of abortion, and decreases spermatogenesis[17].

ACITRETIN

Acitretin is indicated in plaque-type psoriasis, PPP, and generalized psoriasis[18]. Diffuse patchy psoriasis may be treated with acitretin, but clearing is less satisfactory and so may require therapy in combination with other agents (corticosteroids, ditranol, tar, phototherapy, or PUVA). The best therapeutic response is achieved with doses between 0.50 and 1 g/kg/day per os. Preferably, the starting dose is 0.5 mg/kg/day to better check for side effects before increasing the dose, depending on clinical improvement. During the initial treatment period triglyceride and cholesterol levels may rise; to curb this effect, the acitretin dose should be increased gradually or given with ethyl esters of polyunsaturated fatty acids. As radiographic spinal alterations (asymptomatic) after prolonged treatment have been noted, radiologic assessment after 1 year of treatment is recommended. Intermittent acitretin treatment may avert the risk of osteoarticular damage; since acitretin may interfere with bone growth, its use in children is limited.

Other frequent side effects are mucocutaneous manifestations (dry skin, mouth and lips, dry eyes, epitaxis),

which are dose-correlated. Most acitretin-induced side effects remit after lowering the dose and do not always require suspension of treatment. Acitretin is teratogenic and accumulates in fatty tissues, where it is slowly released into the bloodstream for up to 1 year after final administration. Therefore, strict contraception during this period is recommended in women of childbearing age. Moreover, women of childbearing age must not take alcohol while under acitretin treatment and during the 2 months after the end of therapy because part of the compound is reesterified *in vivo*, with increased lipophilia and slower metabolism. Contraception should be continued for an additional 2 years after drug withdrawal. Patients also need to be advised not to donate blood while under acitretin therapy and up to 1 year after the end of treatment[19].

THERAPEUTIC REGIMENS WITH CONVENTIONAL DRUGS

Although all are effective in monotherapy, these compounds are widely used according to standard regimens to reduce dosage and to improve tolerability. The regimens are often employed in instances where a certain drug's effectiveness is lost, adverse events occur, or psoriatic lesions do not respond to therapy. Various therapeutic strategies have been devised in which the compound is administered intermittently, in combination with another conventional drug, in rotation or sequential fashion. This is done to enhance therapy effectiveness, manage the illness over the long term, and reduce toxicity.

Rotational therapy. Rotational therapy refers to changing from one compound to another before significant toxicity occurs. The frequency of rotation may depend on response to a specific drug, tolerability, or suspected onset of side effects. Rotation also allows for attenuation of potential toxic effects of a drug before it is administered again.

Sequential therapy. Sequential therapy refers to administration of the most effective drug (e.g., CsA) to rapidly improve the patient's condition, followed by another compound that may be better tolerated (e.g., acitretin) to maintain therapeutic response. The synergy between the 2 drugs permits not only maintenance of initially achieved improvement but also reduces longterm toxicity. This regimen may be summarized in 3 phases: a clearing phase, a transition phase to a maintenance drug in combination with the first at scaled dosage, and a maintenance phase. The second phase should be long enough to allow switching from a more effective to a less effective but safer and better tolerated drug while maintaining initial clinical improvement. The switch from one drug to another is the most challenging aspect of the regimen and requires considerable expertise on the part of the clinician. Finally, whichever treatment is indicated in monotherapy or in one of the above regimens, the clinician would be well advised to remember the Hippocratic oath (430 BC; modern version by Louis Lasagna, 1964), "I will apply, for the benefit of the sick, all measures which are required, avoiding those twin traps of overtreatment and therapeutic nihilism."

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