CONVENTIONAL THERAPIES FOR PSORIASIS

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SUMMARY

Conventional treatments of psoriasis include topical and systemic drugs. For sake of brevity, the presentation will deal only with systemic therapy. Three drugs are presently available in Italy: methotrexate, acitretin and cyclosporin A. Their efficacy is almost identical, all of them achieving PASI 75 in about 60% of cases in 12 weeks The indications (which, in Italy, do not include psoriasis for methotrexate), the contraindications, the interactions, the adverse effects and the precautions in their use will be discussed. Methotrexate side effects account for more than 10% of cases and include nausea and vomiting and chiefly increase of blood levels of liver enzymes. Acitretin side effects are numerous and varied, the most severe being increase of liver enzymes and blood lipids, renal impairment, and teratogenicity. Cyclosporin side effects are chiefly hypertension and renal failure. The Author concludes that cylosporin is the drug with the best efficacy/side effect ratio, though it should be used in selected cases.

Key words: Psoriasis, methotrexate, cyclosporine A, acitretin

Psoriasis can be treated with a host of topical remedies and a handful of systemic drugs. In this essay, I will discuss only the systemic drugs available on the Italian market.

According to Naldi and Griffiths (1), in an excellent paper that should be read by all involved in treating psoriatic patients, only three drugs can be formally used in Italy: acitretin, cyclosporine and methotrexate. They should be restricted to patients with PASI over 10. Psoralens, fumarates, azathioprine and hydroxyurea are for different reasons off-label drugs. The efficacy of acitretin, cyclosporin and methotrexate has been reported to be very similar, PASI 75 being achieved in 12 weeks by about 60% of patients by all of them (2).

METHOTREXATE

In Italy, methotrexate is marketed for several indications: choriocarcinoma and other trophoblastic tumors, chorioadenoma destruens and hydatidiform mole, acute lymphatic leukemia (lymphoblastic) in children and young adolescents, meningeal leukaemia, lymphoma, breast cancer, osteogenic sarcoma, bronchogenic carcinoma, tumors of head and neck and bladder carcinoma. Psoriasis is not included. In the USA, instead, methotrexate is indicated in the symptomatic control of *severe, recalcitrant, disabling psoriasis* that is *not adequately responsive* to other forms of therapy, but only when the diagnosis has been established as by biopsy and/or after dermatologic consultation. It is important to ensure that a psoriasis "flare" is not due to an undiagnosed concomitant disease affecting immune response (3).

In fact, no prospective, randomized, placebo controlled trials have ever been published, but an active controlled study which compares methotrexate with cyclosporine (4). In this study, methotrexate proved to be poorly tolerated in that about $^{1}/_{4}$ of patients had to discontinue it because of elevation of transaminases.

Usually, methotrexate is given IM at 7.5-10 mg/week. The clinical pharmacology of methotrexate has not been well studied in older individuals and doses should be reduced to 2.5-5 mg/week.

Methotrexate can cause fetal death or teratogenic effects and, therefore, it is contraindicated in pregnant patients and in nursing patients. Pregnancy should be avoided if either partner is receiving methotrexate during and for a minimum of 3 months after therapy for males, and during and for a minimum of 1 ovulatory cycle after therapy for

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females. Because of its hepatotoxicity, methotrexate is contraindicated in alcoholics and in patients with chronic liver disorders. A screening for HBV and HCV infection should be carried out before initiating methotrexate

Toxic effects may be related in frequency and severity to dose or frequency of administration, but they have been observed at all doses and at any time during therapy. Transaminases become elevated in more than 15% of cases, nausea and vomiting in 10%. Incidence of stomatitis and thrombocytopenia (<100.000 ml) is in between 3 and 10%.

Rarer (between 1 and 3%) are rash, diarrhea, alopecia, leucopenia (<3000 ml), pancytopenia and dizziness. Abdominal discomfort, chest pain, chills, mouth sores, painful urination, sore throat, unusual tiredness or weakness are occasionally observed. Very rare are leucoenkefalopathy, paresis, convulsions, a transitory cognitive dysfunction with mood alteration and a pulmonary syndrome with fever, cough, dyspnea and pulmonary infiltrate. Curiously, psoriasis may get worse after UV therapy.

Patients should be informed of the early signs and symptoms of toxicity and the need for close follow-up. In the USA, it is recommended that the risk of effects on reproduction should be discussed with *both partners*.

Blood tests should be performed at the beginning and differential white cell and platelet count at least monthly. Liver and renal function are usually performed every 1 to 3 months, but in my experience, transaminases may become suddenly elevated without any warning symptom. X-ray and pulmonary function tests may also be useful.

Methotrexate may interact with other drugs. NSAIDs and aspirin enhance toxicity while tetracyclines and nonabsorbable antibiotics may decrease intestinal absorption or suppress bacterial metabolism of the drug. Folic acid decreases responses to methotrexate (3), giving the false impression of improve tolerability. Folate deficiency, instead, may increase its toxicity. Bactrim increases bone marrow suppression.

ACITRETIN

The sole indication of acitretin is severe psoriasis including forms with arthropathy, but pustular psoriasis, erythroderma and palmo-plantar psoriasis are the best indications.

Acitretin is given at the dose of 10-75 mg/day. In my experience, the dose, contrary to etretinate, is extremely individual and efficacy and tolerance should be monitored very closely.

A randomized, placebo-controlled study compared the efficacy of acitretin versus etretinate in 168 patients with "long-standing, severe psoriasis" (median PASI 12.5) at the median dose of 40 mg/day. After 4 months, the acitretin group revealed a PASI reduction of 76% versus 71% of the etretinate group (5). Four daily doses of acitretin (10, 25, 50 and 75 mg/day) were studied in another controlled study of 38 patients. Efficacy was observed only in the 50-75 mg/day groups, but the improvement (modest in fact, 17.4%) was statistically significant only in the 75 mg/day group (6).

Tolerance was poor in the 40 mg/day group and, naturally, in the patients treated with higher doses. The commonest mucocutaneous side effects of the 40 mg/day group were cheilitis (99%), dry nose (84%), peeling palms and soles (83%), xerosis (70%), dry mouth (66%), conjunctivitis (49%) and alopecia (48%). Transaminases increased in 12% of cases, cholesterol in 10% and triglycerides in 12% (6).

Acitretin is teratogenic. Pregnancy or its planning should be avoided before 3 years after stopping the drug. Two negative tests must be done before starting: the first one when the decision is taken, the second during the first 5 days of the next cycle. Two reliable forms of contraception must be followed for one month before, during and for 3 years after stopping the drug. Other contraindications are breastfeeding and any alcohol intake during and for two months after stopping the drug. In fact, the half life of acitretin is 49 hours, but alcohol transforms it into etretinate which may take more than 3 years to be cleared at 98%.

Severe liver and renal impairment has been observed as well as blood lipids constantly elevated. The simultaneous use of methotrexate should be avoided. Blood donation must be interrupted for at least one year. As cases of decreased night vision has been observed, caution is recommended when driving any vehicle at night on in tunnels.

Acitretin may interact with Vitamin A or other retinoids, with phenytoin and tetracyclines. Importantly, it reduces the contraceptive capacity of the minipills.

The adverse effects of acitretin are the same as etretinate, and too many to mention, but the patient should be monitored for ECG, lipid blood level and coagulation before and during the treatment. There have been cases of renal failure and reports

of malignancies. In addition, reports of generalized edema have been published.

CYCLOSPORINE

Cyclosporine has psoriasis as indication. Doses vary from 2.5 mg/kg/day to 5mg/kg/day. Higher doses are usually discouraged. Continuous treatment should not exceed 6 months.
A placebo-controlled study concerned 85 adults with moderate to severe psoriasis. The analysis of intention-to-treat showed that the disease improved in a dose-dependent manner. Clearing was achieved by 36% of patients treated with 3 mg/kg/day, 65% in the 5 mg/kg/day group and 80% in the 7.5 mg/kg/day group. No patients improved with placebo (7).
When compared with methotrexate (15 mg/week) in a prospective randomized trial, cyclosporine (3 mg/kg/day) reduced the PASI score by 72% after 16 weeks statistically comparable (p=.14) to the 64% achieved by methotrexate (4).
Adverse effects of cyclosporine are the renal impairment with creatinine clearance less than 60 mL/min, the uncontrolled hypertension and infections, and possible malignancies. Serum creatinine has been observed to increase in 9% of cases (8) and the glomerular filtration rate to decrease by 16% (7). For this reason, pregnancy and breastfeeding should be avoided.
Precautions include blood pressure and renal function monitoring at least twice before starting treatment. Creatinine blood level should be controlled at least twice a month for the first 3 months, then once a month until the doses are not tapered below 2.5 mg/kg/day. If the level is over 30%, the doses should be decreased by 25-50% and the drug withdrawn if the increase continues. In addition, malignancies (including those of the skin and uterus) should be ruled out before initiating therapy, even by biopsy if necessary. Treatment should be interrupted if lymphoproliferative disorders develop.
Cyclosporine interacts with grapefruit juice and a host of drugs that increase cyclosporinemia, like ursodeoxycholic acid, allopurinol, NSAIDS, amiodarone, macrolides, doxycycline, quinolones, trimetoprin, chloroquine, flu- and itra-conazole, Ca^{++}-channel blockers, melphalan, methotrexate, colchicine, prednisolone and methylprednisolone, estrogens and progestins, metoclopramide, cimetidine and fenofibrate.
Beside hypertension and the increase of blood levels of creatininemia, side effects include headache (12%), abdominal pain (12%), nausea /12%), hyperlipidemia (9%). Contrary to hypertension, hypertrichosis and gingival hypertrophy are dose-dependent. Hypertrichosis occur in a little more than 15% of cases treated with 2.5 mg/kg/day and in about 27% in those treated with 5 mg/kg/day (9).
The increase of creatininemia depends on the dose, the duration of the treatment (more than 1-2 years without interruption) and some characteristics of the patient ("sensitive kidneys", more than 50 years of age, diastolic pressure over 75 mm Hg).
During pregnancy, cyclosporine produced hypertension in 64% of cases, preeclampsia in 37%, proteinuria in 12% and a modest renal failure in 5% (10). Psoriasis cleared, however, in 65% of cases. The therapy withdrawal induced relapse after 113 days if the dose was tapered down and in 103 when interrupted abruptly.

ONCOLOGIC RISKS

All conventional systemic treatments have an oncologic risk. According to Paul (11), the risk to develop a general malignancy is statistically significant only for PUVA. The risk of developing a cutaneous malignancy is significantly higher for cyclosporine (RR 2.7 CI 1.1-6.4), retinoids (RR 4.5 CI 1.5-19.5) and especially for PUVA (RR 5.8 CI 2.0-25.0). Methotrexate have a risk at the limits of the statistical significance (RR 2.1 CI 0.9-5.3).

CONCLUSIONS

Conventional systemic treatments for psoriasis include non negligible risks. They should be prescribed, therefore, only to patients with severe psoriasis who failed to respond to the usual topical medications and never to pregnant or breastfeeding women.
Those patients must be thoroughly monitored according to the mentioned procedures. Acitretin should be limited to palmo-plantar and pustular psoriasis in which it appears really useful. Cyclosporine is recommendable to quench inflamed forms like erythroderma or sub-erythroderma, and should be alternated, especially in summertime, with sunexposure or topical treatments. In my experience, initiating with 5 mg/kg/day and not less than 300 mg/day is recommendable as this sched-

ule reduces the cumulative doses. Methotrexate is particularly indicated in inflamed forms associated with arthritis. Extreme caution should be paid in all cases.

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