

ESTABLISHED TREATMENTS FOR PSORIASIS. A CRITICAL REVIEW

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Psoriasis is a chronic, genetically-determined disease, characterized by an immuno-mediated pathogenesis. Treatment is based on symptomatic therapy that is able to induce remission of the disease and therefore make such a condition more acceptable for the patients. However, no therapy is yet able to induce a permanent remission of psoriasis. A large number of treatment options are now a days available, and the choice depends on the extension and severity of the disease. We will review the most safe and effective treatments for this debilitating disease, trying to highlight the most common side effects associated with each treatment, which should help in determining options for therapy.

Psoriasis is a genetically-determined disease, characterized by immuno-mediated pathogenesis and unpredictable, often chronic course. Waiting for future genetic interventions, treatment is based on symptomatic therapy that induces temporary remission of lesions and makes the disease more acceptable to the patients.

Treatments vary according to the patient's age, the location on the body and the extension of the lesions and to various clinical patterns. In the mild forms topical therapy is generally preferred to systemic because it is sufficient to obtain reduction of the symptoms and has less adverse effects.

Undoubtedly, systemic treatment is addressed to severe forms or particularly extended ones. In the final choice other factors may play an important role, including the presence of other diseases, the possibility for the patient to be hospitalized or to follow correctly a topical therapy, treatment costs, patient compliance and job.

The principal agents, active in systemic-treated psoriasis, modulate some important pathogenetic processes such as keratinocytes hyperproliferation and/or T-lymphocytes response.

The main contraindications of these drugs, the parameters for patients selection and monitoring of the treatment are listed in table I, while all possible side effects are reported in table II.

The principal contraindications of the above mentioned drugs cause the patients to give up effective systemic treatments because therapeutic effects tend only to induce temporary remission of the lesions.

A wide range of different approaches characterized by absolute lack of side effects (for example occlusion and more recently phototherapy with excimer light) or by less important adverse effects have been introduced.

OCCLUSION IN THE ABSENCE OF DRUGS

Hydrocolloid occlusion can cause regression of psoriatic lesions. Such a phenomenon raises questions about the role of the physical agents (entity of the pressure applied on the psoriatic plaques and clinical remission of the plaques, for example) in cutaneous physiopathology and in the pathogenesis of psoriasis in particular. Apart from interesting pathogenetic considerations (why should cutaneous lesions characterized by specific biochemical and immunologic derailments achieve clearance using occlusion, in other words only applying a constant pressure, without using drugs?), psoriasis clinical remission obtained without drugs prescription represents a therapeutic and ethical chal-

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Tab. I. Systemic agents for the treatment of psoriasis: possible contraindications and useful parameters for patients selection and monitoring of the therapy.

Drug	Contraindications	Parameters that need to be evaluated before and/or during therapy
Cyclosporine A	Renal function anomalies Uncontrolled arterial hypertension Past or present neoplasias Active infections Hepatitis B or C Severe hepatopathy Concomitant use of immunosuppressive, nephrotoxic agents, or agents that modify CsA metabolism Concomitant or past exposure to radiations Drugs and alcohol abuse Malabsorption History of epilepsy Hyperlipidemia Altered glucose tolerance CsA hypersensitivity Pregnancy, wish for procreation, breast feeding	Physical examination Arterial pressure (frequent control) Papanicolau test Pregnancy test* <i>To be done every one or two weeks regularly during the first two months, then every 6-8 weeks in the absence of problems</i> Creatinemia (frequent control) Uricemia Urinalysis Serum electrolytes Glycemia Serum lipids Renal function test Glomerular filtration index (optional)
Methotrexate	Anemia, leukopenia, platelet disorder Renal function relevant alterations Relevant hepatic alterations Active infections present or past hepatitis B or C Active peptic ulcer Present or past ulcerative colitis Alcohol abuse Concomitant use of drugs that increases MTX toxicity Immunologic deficit Pregnancy and breast feeding Wish for procreation (also in males) Diabetes and relevant obesity	Pregnancy test* Physical examination** <i>To be done first every week, then a little delayed (max. every 2-4 months)</i> Complete blood count, white blood cell count, platelets Azotemia, creatinemia, serum electrolytes Liver function test, serum albumin Glomerular filtration index (optional) <i>To be done every 3 months</i> Serum PIIINP dosage Hepatic biopsy (recommended for cumulative dosage of 1,5 mg)
Ethretinate	Pregnancy and breast feeding Wish for procreation (until 2 years after suspension) Relevant hyperlipidemia Severe hepatopathy and nephropathy	Complete blood count with leukocytic formula Pregnancy test* <i>After the first month of therapy, then every 3-6 months</i> Cholesteremia, triglyceridemia Liver function test <i>After a year of treatment</i> Rachis radiography
Hydroxyurea	Anemia, leukopenia, platelet disorder Renal insufficiency Pregnancy, wish for procreation, breast feeding Drug known hypersensitivity	Pregnancy test* Azotemia, creatinemia, serum electrolytes Papanicolau test Physical examination** <i>To be done every week for the first six weeks, then at longer intervals (no longer than 3 months)</i> Complete blood count, white blood cell count, platelets Liver function test
Azathioprine	Anemia, leukopenia, platelet disorder Renal insufficiency Hepatic insufficiency Pregnancy, wish for procreation, breast feeding Azathioprine and 6-mercaptopurine hypersensitivity	Pregnancy test* Azotemia, creatinemia, serum electrolytes Papanicolau test Physical examination** <i>To be done every week for the first six weeks, then at longer intervals (no longer than 3 months)</i> Complete blood count, white blood cell count, platelets Liver function test
PUVA therapy	Pregnancy, wish for procreation, breast feeding Cataract Past cutaneous neoplasias Past exposure to ionising and arsenical radiations Past PUVA with a cumulative total dose > 1500 J/cm ² Concomitant use of CsA and MTX Psoralen hypersensitivity	Liver function test Ocular examination Pregnancy test* Cutaneous physical examination***
* Combine contraception to treatment; **Exclude clinically evident neoplasias, infections or lymphadenopathy; ***Consider the presence of neoplasias or cutaneous precancerous lesions From: Vena G.A., Cassano N. Terapia sistemica nella psoriasi. In Lotti T.M. (ed). La psoriasi verso il terzo millennio. Milano, UTET, 1999; 169-170.		

Tab. II. Possible side-effects of the principal drugs used in the systemic treatment of psoriasis.

Drugs	Side effects
Cyclosporine A	<p>Nephrotoxicity: hypercreatinemia, <glomerular filtration, possible structural injuries in case of prolonged therapies</p> <p>Hyperkalemia, low magnesium plasma level</p> <p>Arterial hypertension</p> <p>Hyperbilirubinemia</p> <p>Hepatic function alterations</p> <p>Hyperuricemia</p> <p>Hyperlipidemia</p> <p>Glucose tolerance alterations</p> <p>Normochromic anemia, mild normocytic anemia</p> <p>Arthralgias</p> <p>Gastrointestinal disorders: nausea, diarrhea, abdominal pains</p> <p>Gingival hyperplasia</p> <p>Cephalalgia Hypertrichosis</p> <p>Paresthesias/Hyperesthesias, tremor</p> <p>Infections (?) Neoplasias(?)</p>
Methotrexate	<p>Myelotoxicity: megablatic anemia, leukopenia, platelet disorder</p> <p>Hepatotoxicity: liver function alterations, liver fibrosis, liver cirrhosis, > alcohol hepatotoxicity</p> <p>Abortus, teratogenicity, oligospermia, menstrual alterations</p> <p>Gastrointestinal disorders: nausea, diarrhea, vomit, anorexia, dispepsia, enteritis, hematemesis</p> <p>Hyperazotemia, nephropathy, cystitis, microhematuria</p> <p>Cephalalgia, fever, shivers, vertigo, drowsiness, blurred vision, ataxia</p> <p>Depression, other psychic disorders</p> <p>Sepsis, Tbc reactivation</p> <p>ung diseases</p> <p>Osteopathy (pain, osteoporosis, distal tibia fracture)</p> <p>Muco-cutaneous: keratoconjunctivitis, ulcerations and erosions, cutaneous burning, pruritus, pain, urticaria, ecchymosis, folliculitis, candidiasis, toxic epidermal necrolysis, cutaneous neoplasias, alopecia</p>
Ethretinate	<p>Teratogenicity</p> <p>Hyperlipidemia</p> <p>Hypertransaminase, hepatitis</p> <p>Muco-cutaneous: dryiness and mucous ragades, epistaxis, corneal ulcerations, burning, pruritus, xerosis, erythema, palmo-plantar desquamation, cutaneous/ungual thinning and fragility, paronychia, alopecia, frizzy hair</p> <p>Skeletal muscle: myalgias, arthralgias, arthritis, hyperostosis, entheses, rachis alterations (disk anomalies, ligaments calcification, osteophytes, bony, bridge), epiphysis anticipated knitting, growth retardation</p> <p>Cephalalgia</p> <p>Nyctalopia</p> <p>Taste and smell loss</p> <p>Profuse sweating</p> <p>Lethargy</p> <p>Generalized edema</p>
Hydroxyurea	<p>Myelotoxicity: leukopenia, anemia, macrocytosis, thrombocytopenia (sometimes preceded by thrombocytosis)</p> <p>Teratogenicity</p> <p>Fever</p> <p>Psychic disorders</p> <p>Cutaneous disorders: Diffuse hyperpigmentation, atrophy, desquamation, actinic psoriasis, erythema on the face and hands, vasculitis, lichenoid eruptions, unguial dystrophies, alopecia</p>
Azathioprine	<p>Myelotoxicity: Macrocytic anemia, leukopenia, platelet disorder</p> <p>Gastrointestinal disorders: nausea, diarrhea, abdominal pains</p> <p>Myopathy</p> <p>Pyrexia with atrial fibrillation</p> <p>Hepatitis, cholestasis</p> <p>Interstitial pneumonia</p> <p>Pancreatitis</p> <p>Opportunistic infections</p> <p>Neoplasias (mostly lymphoreticular)</p> <p>Cutaneous rash</p> <p>Nephritis</p> <p>Shock</p>
PUVA	<p>Cutaneous disorders: erythema, burn, cutaneous and unguial hyperpigmentation, photo-onycholysis, vesicles hypertrichosis, pruritus, pain, lichenoids, psoriasis worsening (Koebner's phenomenon), actinic keratosis, cutaneous neoplasias, similar lupus erythematosus syndrome</p> <p>Cataract</p> <p>Nausea</p> <p>Liver function test anomalies (rarely hepatotoxicity)</p> <p>Immunologic anomalies (< total circulating T-lymphocytes and T helper, <Langerhan's cells, delayed hypersensitivity low response)</p>

From: Vena G.A., Cassano N. Terapia sistemica nella psoriasi. In Lotti T.M. (ed). La psoriasi verso il terzo millennio. Milano, UTET, 1999; 169-170.

lenge to the dermatologist: why should we use locally- or generally-active drugs not devoid of side effects and expensive for patients and community, if psoriasis clears simply applying an occlusion/cutaneous pressure? After a week of treatment thickening and desquamation are significantly reduced and three weeks later also erythema improves with a simple occlusion with hydrocolloid bandage (1). Ten weeks later lesions obtain complete clearance (2).

Occlusive therapy mechanism is not completely known. Fry L. et al. (3) demonstrated that occlusive therapy decreases after four days mitotic index of psoriatic epidermis and causes after two weeks reappearance of the granular layer. Humidity and hydration of the horny layer may play a fundamental role in increasing desquamation. The rise of temperature due to hydrocolloid occlusion provides a benign effect.

Recently, Lotti T.M. et al. (4) have demonstrated that occlusive therapy (like other topical and systemic treatments for psoriasis, such as anthralin, betamethasone, and PUVA) is characterized by the antagonist activity of plasminogen activator.

Plasminogen activators (PAs) are plasmatic proteinases that transform seric plasminogen in plasmin, named also fibrinolysin since it is a fibrinolytic enzyme.

After a week of exclusive occlusive treatment, PA activity of the epidermis decreases significantly. This explains, at least in part, the therapeutic effect of hydrocolloid occlusion and focuses attention on modulation of physiopathologic cutaneous events, mostly ignored or underestimated by researchers and dermatologists.

In the last twenty years patients addressed to "less common" therapies, sometimes "alternative" to classic topical and systemic treatments. Often the patient himself informs the doctor about the new discoveries in homeopathy, musicotherapy, Chinese medicine, acupuncture, all treatment strategies that a prepared, open-minded dermatologist, sensible to patients problems should not diminish often because of the lack of specific knowledge. The title of a recent work should make us reflect: "Chinese medicine stopped me feeling like an outcast" (5); perhaps patients interest for alternative medicine may be justified by the deep necessity to know and accept the disease.

Less common treatments for psoriasis, that are considered future strategies for particularly severe forms, include the following ones.

POLYUNSATURATED FATTY ACIDS VIA INTRAVENOUS INFUSION

Numerous studies have considered the therapeutic efficacy of α -3 polyunsaturated fatty acids present in fish oil, using either fish oil or ethyl-esterified and highly purified mixture administered orally, topically or via intravenous infusion.

In a recent work (6) Austrian-German authors and from Eastern Europe have considered the efficacy of a combination of α -3 polyunsaturated fatty acids (omegavenous 200 ml/die with eicosapentaenoic acid - EPA - 4,2 mg and docosahexaenoic acid - DHA) administered intravenously for the treatment of psoriasis vulgaris.

No side effects are referred and the efficacy seems to be correlated to their ability to modulate the arachidonic acid cascade, thus inhibiting E2 inflammatory prostaglandin production and B4 leukotriene and moving production in favour of the less inflammatory B5 leukotriene.

FUMARIC ACID

Interest in therapy with fumaric acid arises recently with the introduction of the so called FACT – fumaric acid compound therapy – that uses dimethylester (DMFAI) and monoethylester (MEFAE) and their salts administered orally in enteric-coated pills of 30-120 mg. Galenic formulations and therapic strategy have been studied by Schafer and then confirmed in controlled double-blind trials that evidenced significant improvement in psoriasis and psoriatic arthritis. Side effects consist of intense cutaneous flush that arises soon after drug assumption, nausea, vomit, gastralgia and diarrhea; the last one often being considered the cause of therapy suspension.

MYCHOPHENOLIC ACID

Mychophenolic acid (MPA) is an organic acid isolated in the products derived from *Penicillium stoloniferum* fermentation, that, being liposoluble, is orally well absorbed. MPA inhibits the biosynthesis of purines, thus presenting well documented antifungal, antiviral, antibacterial and immunosuppressive activity. Because of its properties and in particular for the last one, its oral use in the therapy of psoriasis has been investigated since the '70 (7).

Approval in 1995 by the Food and Drug Administration of mycophenolate mofetil (MMF-MYCO- M), a MPA ester, that is characterized by high bioavailability, stimulated interest in the antiprosoriatic properties of the drug. Nowadays, MMF is used, combined with cyclosporine and steroids, for preventing organ rejection in transplantations.

TACROLIMUS

Renewed enthusiasm in recent reviews is turned to an other effective immunosuppressive agent, the tacrolimus (FK506).

It is also used in organ transplantations. It has been employed with success in systemic treatments of severe psoriasis recalcitrant to conventional therapies (8). Its use has been limited because of demonstrated nephrotoxicity.

DRUGS THAT INTERFERE WITH THE IMMUNE SYSTEM OCCASIONALLY USED IN PSORIASIS

Peptide T. Synthetically formulated, peptide T – so called for the high content of threonine – is able to compete with HIV-1 gp 120 glycoprotein on the CD4 receptor. Because of this activity it has been used in AIDS treatment and has improved psoriatic lesions in one patient. The results of therapeutic trials in HIV patients affected by psoriasis have been encouraging, obtaining good results in 50% of patients and minor adverse effects (9).

Zidovudine. Many authors suggest that drug efficacy in psoriasis lays in its immuno-modulated and cytostatic activity (10).

CD4 monoclonal antibodies. They are employed as immunosuppressors in numerous diseases characterized by a massive infiltration of CD4+ cells. Therefore, the use of CD4 antibodies in psoriasis seems suggestive. Administration of CD4 monoclonal antibodies (20 mg every 5-8 days) reduces significantly psoriasis in few days (11).

Tumour necrosis factor β

This cytokine causes complete clearance of psoriatic lesions when administered in patients affected contemporaneously by neoplasias and psoriasis (12).

PHOTOCHEMOTHERAPY

Photochemotherapy consists in the combined use of ultraviolet radiations (UVA) and oral psoralens (PUVA therapy). Although the effectiveness of such treatment is well documented, the most important restriction on its long-term use is represented by the risk of carcinogenesis (13). For this reason PUVA therapy (14) can not be utilized long term and should not be associated with immunosuppressive drugs that can intensify its carcinogenic potential. The concomitant use of retinoids (RePUVA) enhances therapeutic effect of PUVA therapy, helping to reduce the dose of radiations and to protect from the risk of neoplasias (15). PUVA treatment is expensive and uncomfortable, for patients need necessarily to reach specialized centres for their therapeutic sessions.

PHOTOTHERAPY WITH UVB

For a long time the idea was to practise phototherapy with devices that intended to reproduce artificially the sun light. Voltaic arc and xenon lamp deserve to be cited but only for historical interest.

Progress in phototherapy has been achieved with the introduction of mercury vapour lamps, a hollow fused quartz lamp filled with small quantities of mercury vapour.

After bringing electrodes into incandescence, mercury evaporates rapidly producing intense radiations within a wide but scarcely homogeneous spectrum.

The addition of heavy metallo-halogenes to mercury has improved the spectral emission from mercury vapour lamps; spectrum becomes more homogeneous and UVC radiation is completely eliminated.

Recently a new fluorescent lamp has been developed (Philips TL-01). Although maintaining high intensity it is capable of emitting narrow-band light comprised between 311 and 312 nm. This new lamp is characterized by a therapeutic activity that is superior to the one offered by traditional UVB sources and minimizes contemporaneously irritating effects.

COMBINED THERAPIES

In order to reduce UVB total dose and limit

the toxicity of the drugs that are active in the treatment of psoriasis, UVB phototherapy has been utilized in combination with the other conventional therapies (16,17). Associations with ultraviolet radiations characterized by a different spectrum and combined or not with psoralen administration deserve to be cited. Combination of UVA with UVB or PUVA reduces UVB total dose, while combination with topic methoxalene, useful with UVB, has given no advantages with UVB (18-20).

Concomitant use with drugs, in particular with methotrexate, enhances a better therapeutic effect than that obtained using the two treatments in monotherapy. The addition of retinoids, both etretinate or acitretin (50 mg/day) reduces the number of treatments and UVB total dose. In fact retinoids enhance the thinning of psoriatic plaques, a phenomenon that influences presumably penetration and UVB response.

Cyclosporine can be administered subsequently to phototherapy especially in forms characterized by an intense flogistic component and by the presence of pruritus. In these cases therapy with cyclosporine (3-5 mg/kg/day for 1-2 months) can minimize acute symptomatology and can favour phototherapy avoiding problems of the initiation of therapy.

THE NEW TREATMENT WITH 308 nm EXCIMER LIGHT @

Recently, it has been demonstrated that the light produced by xenon-chloride excimers (generated by sophisticated devices with a peak of 308 nm) induces clearance of psoriatic spots although through not completely defined mechanisms and in the absence of adverse side effects. Repetitive treatments with excimer light cause the stabilization of the results with prolonged time of relapses.

Groups of investigators working in Belgium, Czech Republic and Italy have verified results on a large population and identified the principal immunologic modifications produced by the effect of 308 nm excimer light on psoriatic cutis.

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