Management of systemic treatment of moderate-to-severe psoriasis: brief literature review with reference to the most relevant Italian experiences

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Summary

The treatment of moderate-to-severe psoriasis usually requires phototherapy with short wave length UVB and psoralenes plus UVA (PUVA) and systemic drugs (methotrexate, acitretin, cyclosporin A). In the last few years, biological agents have become available which can be used if systemic traditional drugs are ineffective or contraindicated. Biological agents are divided into different groups according to their mechanism of action. Some of them are TNF-α antagonists (etanercept, infliximab, adalimumab) and others are interleukin 12 e 23 inhibitors (ustekinumab). When a therapy is chosen, the patient’s overall health status – especially hepatic and renal functions – age, fertility status, cardiometabolic comorbidities and presence of psoriatic arthritis should be considered. The current guidelines, including the European ones, recommend a first-line treatment with conventional systemic agents and/or phototherapy and photochemotherapy. In case of poor response or contraindications to these treatments, it is possible to switch to biological agents.

KEY WORDS: psoriasis; topical therapy; phototherapy; conventional systemic drugs; biological drugs.

Introduction

The pharmacological approach to psoriatic patients should always include a thorough internist evaluation aimed at the early diagnosis of possible comorbidities, as well as at choosing the most appropriate drug for each patient. Some recent Italian cases showed that different comorbidities are frequently observed in psoriatic patients; therefore, when choosing a treatment option, any possible undesired effects that may occur during therapy should be considered (1-13). Since psoriasis is a chronic disease, treatment is often adapted to other patient specific conditions, including age, psychological conditions and pregnancy (14). Therefore, before starting any systemic treatment, it is necessary to assess the severity of the cutaneous disease keeping all the above into due consideration (15). Over the years, several assessment scales have been proposed to evaluate disease severity; a recent study selected 44 of them, of which only 6 are validated (16). The simplest and most used scales include: Psoriasis Area and Severity Index (PASI), Body Surface Area (BSA), Dermatology Life Quality Index (DLQI) (17, 18). PASI and BSA are used to measure psoriasis severity by assessing clinical parameters including erythema, desquamation, affected body surface. DLQI is used to measure disease impact on patient quality of life (QoL). In most clinical studies, PASI is the main tool to calculate response to drug treatment or to therapeutic treatments in general, although its objectivity and repeatability are significantly related to the experience of each dermatologist in calculating this score. For PASI scores up to 10, psoriasis is considered to be mild-to-moderate, from 10 to 20 moderate and over 20 severe (15). Recently, an Italian research group has proposed a new assessment method called Psodisk to measure psoriasis which is capable of evaluating and simultaneously monitoring in a single questionnaire both clinical and QoL features in psoriatic patients (19).

A critical issue when choosing a therapeutic intervention concerns a group of patients with forms classified as moderate, because although the definition may suggest a limited clinical relevance, they often involve particularly body areas which are critical from an emotional and social point of view, i.e. face, scalp, hands or genital areas; in these cases, it is possible to choose a therapeutic option based on systemic drugs, although they are usually limited to the treatment of moderate-to-severe forms (20, 21).

Methods

The search was carried out in PubMed (MEDLINE) and EMBASE databases by using the following terms: ‘psoriasis’, ‘cyclosporin(e)’, ‘methotrexate’, ‘acitretin’, ‘phototherapy’, ‘therapy’, ‘etanercept’, ‘infliximab’, ‘adalimumab’, ‘ustekinumab’, ‘comorbidities’. The search was limited to clinical studies published in English; additional information on Italian guidelines published on reference websites were also included.
Data

As topical therapy, usually the first-line treatment, physicians currently prefer to use Vitamin D analog preparations. Among these, calcitriol and tacsalcitol are usually less irritating than calcipotriol, that should be used with caution on flexor surfaces, folds and areas frequently exposed to sunlight. Calcipotriol in combination with a topical steroid is a currently very much used option. The combination of a topical steroid and 3% salicylic acid can be useful in hyperkeratotic forms, especially if palms of the hands or soles of the feet are affected (22-24).

Traditional Systemic Treatments (Table 1)

The switch to systemic drugs is agreed between dermatologists and patients and occurs only after other alternatives have been explored, including topic treatment failure, disease extension or worsening or involvement of particularly critical areas for patients social life, i.e. face, hands, scalp or genital areas. Also the appearance of signs and symptoms suggesting psoriatic arthritis (PsA) leads to switching to or initiating systemic treatments (25). The therapeutic armamentarium available to dermatologists includes the

Table 1 - Traditional systemic drugs: main general features.

<table>
<thead>
<tr>
<th>Screening tests</th>
<th>METHOTREXATE</th>
<th>CYCLOSPORIN A</th>
<th>ACITRETIN</th>
<th>PHOTOTHERAPY and PHOTOCHIMOTHERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage</td>
<td>7.5-25 mg/week.</td>
<td>2.5-5 mg/kg/day</td>
<td>0.3-1 mg/kg/day</td>
<td>Individualized dose according to phototype and minimum erythemogenic dose (MED).</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Pregnancy and lactation, alcoholism, pulmonary disease, severe liver disease, serious infections, immunodepression, hematologic dyscrasias, severe renal disease.</td>
<td>Liver and renal insufficiency, uncontrolled hypertension, severe infections, history of or presence of malignancies.</td>
<td>Pregnancy and lactation, women in childbearing age, liver and renal insufficiency, severe dyslipidemia.</td>
<td>Photodermatosis, history of or presence of skin malignancies PUVA only: pregnancy and lactation, cyclosporin treatment, severe liver or renal insufficiency.</td>
</tr>
<tr>
<td>Drug-to-drug interactions</td>
<td>Trimethoprim, probenecid, retinoids, NSAIDs.</td>
<td>Barbiturics, rifampicin, ticlopidine, bosentan, macrolides, antifungal drugs, diltiazem, nicardipine, verapamil, metoclopramide, oral contraceptives, metiprednisolone, allopurinol, amiodarone, colchicine.</td>
<td>Phenytoin, tetracyclines, methotrexate, alcohol, imidazolac drugs, vitamin A.</td>
<td></td>
</tr>
<tr>
<td>Main undesired effects</td>
<td>Nausea, altered liver function, bone marrow suppression, pulmonary fibrosis, pneumonia, photosensitivity.</td>
<td>Hypertricosis/hirsutism, gengival hyperplasia, increased bilirubin, renal insufficiency, blood hypertension, gastroenteric disorders, headache, hyperkalemia, hypomagnesemia.</td>
<td>Skin and lip xerosis, xeroftalmia, epistasis, hyperlipidemia, altered liver function, teratogenicity, altered bone and nondesnse soft tissue X rays.</td>
<td>Erythema, pruritus, bullous eruption, increased risk of skin malignancies PUVA only: nausea, photoaging, freckles, cataract, increased risk of onset of non-melanoma tumors.</td>
</tr>
</tbody>
</table>
so-called traditional systemic therapies, i.e. phototherapy (UVBTL01, PUVA), acitretin, methotrexate (MTX) and cyclosporin A (CsA) and the more recent biological agents. The choice of a systemic drug is currently regulated by indications from a number of therapeutic guidelines on the use of systemic drugs to dermatologists who can comply with international suggestions or to guidelines agreed upon with national or regional authorities (26-28).

The outcome measure of efficacy for a systemic drug usually used and recommended is the so-called PASI75 achievement, i.e. a reduction of 75% in baseline PASI score after an initial period of treatment up to 16 weeks (26).

**Phototherapy**

Type B or Type A ultraviolet radiation (UVB-UVA) with different wave lengths is used in the treatment of psoriasis. UVA rays are only used in association with topical or systemic administration of photosensitizing drugs (psoralens) which should precede the exposure, since the use of UVA alone does not allow for a significant PASI improvement (29).

Since the 1980s, UVB with different wave lengths (ranging from 280 to 320 nm) have been increasingly used, until phototherapy equipment with UVB emission reaching a peak of 311 nm were developed (UVBTL01). A recent literature review including 2416 patients from 41 RCTs showed phototherapy efficacy in terms of PASI 75 achievement in 73% and 62% of cases treated with PUVA e UVBTL01, respectively, with treatment discontinuation due to undesired effects in 2-5% of cases (30).

The main adverse event associated with phototherapy long-term use is the risk of cancer, in particular basal-cell and spindle-cell carcinomas (26).

Besides being associated with available topical therapies, phototherapy can be associated with systemic treatments, including acitretin in order to increase its efficacy (31).

Absolute contraindications to the use of phototherapy is the presence of genetic diseases causing increased photosensitivity and skin carcinogenicity, as well as autoimmune diseases, including Lupus erythematosus, photosensitivity, personal history or the presence of previously ascertained skin cancer (26, 32).

**Retinoids**

Systemic retinoids have been used in the treatment of psoriasis for the last 40 years. Acitretin is the only systemic retinoid indicated for the treatment of psoriasis available in most European countries.

A relatively low dose of 0.3-0.5 mg/kg/day is recommended as initial dose. After 3 to 4 weeks, the dose is increased or decreased according to the efficacy obtained and to patient’s tolerability until a maintenance dose of 1 mg/kg/day is usually achieved (26, 33-35).

As regards efficacy, in an open clinical study published by Murray, the long-term, 1-year, efficacy and safety of acitretin were evaluated in 63 patients with psoriasis who were initially treated with a daily dose of 25-50 mg. A total of 37 patients completed the study of whom 76% achieved a significant reduction in PASI score; the most common adverse events were chelitis (78%), defluvium capillorum (52%) and pruritus (51%) (36).

The drug showed the greatest efficacy in specific forms of psoriasis, i.e. pustular and erythrodermic psoriasis, and onycopathy (33, 35, 37, 38).

Moreover, during acitretin treatment, an increased photosensitivity has been observed, and therefore avoidance of excessive exposure to sun rays and use of sunscreens are recommended. In case of hyperlipidemia (in particular of hypertriglyceridemia), close monitoring of serum lipids is recommended, as well as treatment discontinuation, if needed. Concomitant use of lipid-lowering agents (i.e. gemfibrozil or statins) can be associated with an increased risk of muscular toxicity. This treatment is absolutely contraindicated in women of child-bearing age during pregnancy (or if they intend to become pregnant), breast-feeding, or in case of insufficient use of contraceptive measures until 2 years from treatment discontinuation. Other contraindications include serious liver and renal insufficiency and ethylism. Bone growth of children treated with acitretin should be monitored at regular intervals (26, 34, 35, 39).

**Methotrexate**

Methotrexate (MTX) has been used in the treatment of psoriasis for more than 60 years (40).

In the dermatological setting, methotrexate is frequently used in the treatment of moderate-to-severe psoriasis, especially in case of articular involvement or in pustular and erythrodermic forms.

MTX is a folic acid analog and exerts its action by competitively inhibiting the dihydrofolate reductase enzyme and a number of other folate-dependant enzymes. MTX main effect is the inhibition of thymidylate and purine synthesis, consequently reducing DNA and RNA synthesis (41). This determines its capability to inhibit the synthesis of nucleic acid in activated T cells and in keratinocytes which seems to be at the basis of the antiproliferative and immunomodulating effects which are considered to be the main mechanisms of methotrexate therapeutic effects in psoriasis (42).

MTX is administered once weekly via oral, intramuscular or subcutaneous route at initial doses usually ranging from 7.5 to 25 mg; the dose should be reduced in elderly patients (26, 43).

A number of studies has evaluated MTX efficacy and safety in psoriatic patients. If administered in monotherapy, a PASI 50 is observed in 70-80% of cases after one month of treatment (44). In a clinical study published in 2000, a total of 157 patients with erythrodermic, pustular and arthropathic psoriasis were enrolled and treated with weekly MTX doses ranging from 15 to 20 mg for a mean duration of 237 weeks.
The clinical results were considered good in 76% of cases; during the treatment, all patients underwent regular monitoring of bone marrow and hepatic function (45). With regard to this, the possible adverse events that may occur during treatment include: among the most common, nausea (usually avoidable with intramuscular or subcutaneous administration), less common were increased risk of infections, altered hepatic function, bone marrow suppression (periodical monitoring of hepatic and bone marrow function is recommended), peptic ulcer, and more rarely hepatic fibrosis and interstitial pneumonia were reported (46). Moreover, it has been highlighted that in order to improve drug tolerability simultaneously reducing the risk of adverse events, oral administration of folic acid is recommended usually on the day following MTX administration (26, 46).

MTX is contraindicated in pregnant and lactating women, and it seems to induce negative effects on spermatogenesis (47). MTX can be used in association with other treatments, especially with other anti TNF-α drugs in order to reduce anti-drug antibody formation and to improve clinical efficacy (48-50).

Cyclosporin A

Cyclosporin A (CsA) is a cyclic polypeptide consisting of 11 amino acids with a non specific capability of inhibiting calcineurin. It is a potent immunosuppressant capable of inhibiting the production and release of lymphokines in the cell, including interleukin 2-3-4-5, GM-CSF and TNF-alpha. Cyclosporin A also exerts an inhibitory action on keratinocyte replication (51). It can be used in the short-medium-term treatment of moderate-to-severe psoriasis at an initial dose usually of 2.5 mg/kg daily with progressive increase up to 5 mg/kg daily, usually with treatment cycles of 12-24 weeks on average; in case of continuate treatments, recommendations on treatment duration vary among the available guidelines: in Europe, it is recommended not to exceed 2 years (26). CsA can usually ensure a mean response of over 60% of patients achieving PASI 75 (52-54). Some Italian papers have suggested low-dose treatment schedules, including the week-end therapy in order to reduce the risk of drug toxicity in cases in which long-term treatments are required (55).

A recent literature review evaluated the therapeutic association of CsA and biological drugs; although efficacy and safety data is reassuring, it is appropriate to limit this schedule to in selected clinical cases (56). Clinical and laboratory monitoring at initiation and during therapy should always be closely performed (particularly of renal function and blood pressure parameters); however, treatment is contraindicated in case of unstable severe hypertension uncontrolled by drug treatment, uncontrolled infections, previous or ongoing cancer; concomitant use of other drugs should be carefully assessed (26).

Systemic Treatments: Biological Agents (Table 2)

In case of failure or contraindication to traditional systemic treatments, European guidelines recommend the use of biological drugs (26, 27). Biological agents available for the treatment of psoriasis belong to two pharmacological classes: TNF-alpha antagonists or inhibitors and interleukin (IL) 12/23 antagonists. The agents which have received approval for the treatment of psoriasis are etanercept, infliximab, adalimumab belonging to anti-TNF-alpha class, and ustekinumab belonging to IL 12/23 inhibitor class. Main contraindications of these treatments include the risk of activating hidden infections, i.e. hepatitis and tuberculosis viruses, the presence of active infections, demyelinating diseases and previous cancer (26). Therefore, it is necessary that patients candidate to these treatments undergo accurate screening examinations before starting the treatment and monitoring follow-ups after treatment initiation (26).

Etanercept

Etanercept is a fusion protein and competitive inhibitor of TNF binding to its cell surface receptors, and thereby inhibits the biological activity of TNF. TNF and lymphotxin exist predominantly as homotrimer, with their biological activity dependent on cross-linking of cell surface TNFRs. The use of an immunoglobulin Fc region as a fusion element in the construction of a dimeric receptor imparts a longer serum half-life. The mechanism of action of etanercept is thought to be its competitive inhibition of TNF binding to cell surface TNFR, preventing TNF-mediated cellular responses by rendering TNF biologically inactive. Etanercept may also modulate biologic responses controlled by additional downstream molecules (e.g., cytokines, adhesion molecules, or proteinases) that are induced or regulated by TNF (57).

Etanercept efficacy and safety have been evaluated in a number of clinical studies. In a study carried out in 672 patients treated with etanercept, Leonardi et al. reported PASI 75 response in 49% (50 mg twice a week) of cases after 12 weeks; after 24 weeks, the percentage of patients who achieved PASI 75 increased to 59% (58). Similar results were reported in the studies carried out by Papp et al. and by Tyring et al. (59, 60).

With regard to long-term results, in a study on 618 patients evaluating the efficacy up to week 132, etanercept clinical efficacy was maintained over time achieving PASI 75 efficacy also in the arm initially treated with placebo (61). Etanercept can be used also in intermittent therapeutic regimen, maintaining great efficacy with therapeutic response recovery following retreatment (62, 63).

Etanercept efficacy and safety have also been evaluated in pediatric patients, initially in Italian preliminary studies and then in a clinical trial on 211 patients aged 4 to 17 years with disease duration of at...
least 6 months, previously treated with systemic drugs or considered as poor responders to topical treatment (64, 65). In this study, etanercept was used at a dosage of 0.8 mg/kg or up to 50 mg week^{-1} (> 60 kg). Twelve-week efficacy data showed that PASI 75 was achieved in 57% of cases (65). As of today, etanercept is the only biological drug which is indicated in the treatment of moderate-to-severe psoriasis in children and adolescents starting from 6 years who have not achieved a good control of the disease or are intolerant to other systemic treatments or phototherapy (57).

With regard to Italian studies on etanercept, a number of reports are available, with 810 patients treated. Overall, PASI 75 was achieved at week 12 in 31.7-54% of cases treated with etanercept at a 50 mg dose bi-weekly; at week 24, independently from the dosage used during the induction phase, PASI 75 response was observed in 66-80% of patients initially treated with 50 mg bi-weekly (66). In the study by Cassano et al., 54% of patients treated with etanercept 50 mg twice a week achieved PASI 75 by week 12; the dose increase to 100 mg twice a week has not shown any additional benefit (67).

In the rheumatological setting, good quantity of data is available on the association of etanercept, or other anti TNF-α agents, especially with MTX (68). Conversely, literature data is scarce on the combination of biological drugs and conventional treatments in psoriasis. With regard to etanercept, a number of Italian relevant studies have been published (66).

A study by Gisondi has shown that the addition of acitretin 0.4 mg/kg/d to etanercept 25 mg weekly has an efficacy and safety profile at week 24 equal to etanercept monotherapy 50 mg weekly (69). Also the association with UVBTL01 has shown etanercept improved efficacy without any important undesired effects (70).

**Infliximab**

Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNF-alpha but not to lymphotoxin α (TNFβ). The efficacy of infliximab was assessed in two multicenter, randomized, double-blind studies: EXPRESS and EXPRESS II, which were carried out in 378 and 835 psoriatic patients, respectively (71, 72). Patients in both studies had plaque psoriasis (BSA ≥10% and PASI score ≥ 12). The primary endpoints in both studies included the proportion of patients who achieved PASI 75 at the end of the induction phase and efficacy maintenance at week 50. Results have shown a PASI 75 response in 80% and 75.5% of cases at week 10 and 14, and in 61% and 54.5% of cas-

### Table 2 - Biological drugs: main general characteristics, screening and monitoring tests.

<table>
<thead>
<tr>
<th></th>
<th>ETANERCEPT</th>
<th>ADA LIMAB</th>
<th>INF LIMAB</th>
<th>USTE KINUMAB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening tests</strong></td>
<td>Blood count, hepatic enzymes, CRP, ESR, creatinine, urinalysis, pregnancy test, HBV/HCV serology, HIV test, TBC screening (Mantoux intradermoreaction and/or QuantiFERON-TB Gold test), chest X-ray, ECG</td>
<td>Blood count, liver and renal function tests and urinalysis should be repeated at the first and then at three-month intervals. For TBC, HIV, HBV/HCV risk monitoring, see note*</td>
<td>Blood count, liver and renal function tests and urinalysis at weeks 2 and 6 and before every infusion. For TBC, HIV, HBV/HCV risk monitoring, see note*</td>
<td>Blood count, liver and renal function tests and urinalysis should be repeated at the first and then at three-month intervals. For TBC, HIV, HBV/HCV risk monitoring, see note*</td>
</tr>
<tr>
<td><strong>Follow-up tests and timing</strong></td>
<td>50 mg x 2/week subcutaneously</td>
<td>80 mg subcutaneously</td>
<td>5 mg/kg endovenously</td>
<td>45-90 mg subcutaneously, for body weight &lt; or &gt; 100 kg, respectively</td>
</tr>
<tr>
<td><strong>Recommended maintenance dose</strong></td>
<td>50 mg/week subcutaneously</td>
<td>40 mg subcutaneously every other week</td>
<td>5 mg/kg endovenously at week 2, 6 and then every 8 weeks</td>
<td>45-90 mg subcutaneously after 4 weeks, and then every 12 weeks</td>
</tr>
<tr>
<td><strong>Main undesired effects</strong></td>
<td>Reactions at the injection or infusion (infliximab only) site, infections, including TBC and opportunistic infections, autoantibody onset, bone marrow suppression, demyelinating disease (except for ustekinumab), possible increased risk of malignancies</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*It is appropriate to repeat QuantiFERON-TB Gold test, viral hepatitis markers and anti-HIV antibodies (in subjects at risk). In HCV+ subjects, it is recommended to periodically carry out an assessment of HCV-RNA and HBV-DNA in patients with history of hepatitis B.*
es at week 50 for EXPRESS I and EXPRESS II, respectively, thus confirming a trend towards a mild loss of efficacy in the course of therapy. Infliximab also showed to be effective in nail psoriasis, with a clinical improvement of the affected nails seen by as early as week 24 (71). Recent studies have shown that intermittent therapy with infliximab seems to cause a loss of efficacy in terms of maintained PASI75 response, with an increased incidence of infusion-related reactions during the re-induction phase (73). Such loss of efficacy is likely to be due to the formation of anti-drug antibodies that are mainly directed against the murine component of the drug. To prevent this, it is a common practice – especially in rheumatology – to use infliximab in association with MTX, in order to reduce infusion-related reactions and improve efficacy (74).

In this case, too, the Italian experience in the long-term use of the drug (3 years) have shown varying results on PASI 75 response, ranging from 41 to 75% according to the data analysis methodology used (75).

**Adalimumab**

Adalimumab is a recombinant human monoclonal antibody selectively binding to TNF and neutralizing its biological function by blocking its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (76). The safety and efficacy of adalimumab were evaluated clinical trials in adult patients with chronic plaque psoriasis (BSA ≥10% and PASI ≥12 or ≥10). Among these studies, the REVEAL trial evaluated 1,212 patients treated with adalimumab following the approved dosing regimen vs placebo. After 16 weeks of therapy, 70.9% of patients treated with adalimumab achieved PASI 75 response with a PGA of recovery/marked improvement in 62% of patients (77). Treatment responders were then enrolled in an open-label extension study to collect efficacy data for up to 160 weeks of treatment, showing a maintained PASI75 response in 76 and 88% of cases, according to the method used for statistical analysis (78). An Italian study has shown the efficacy of adalimumab in patients with psoriasis and psoriatic arthritis who had previously received biological agents and had then discontinued them for lack of efficacy or adverse events (79). About 8.4% of treated patients develop anti-adalimumab antibodies, with a subsequent reduction in therapeutic efficacy (74).

**Ustekinumab**

Ustekinumab is a fully human IgG1κ monoclonal antibody that binds with high affinity and specificity to the p40 protein subunit of the human cytokines IL-12 and IL-23, thus inhibiting its activity and preventing the activation and differentiation of T cells. The recommended dosage of ustekinumab is an initial dose of 45 mg or 90 mg (in patients with body weight >100 kg) administered subcutaneously, followed by a 45 mg (or 90 mg) dose 4 weeks later, and every 12 weeks thereafter (80). The main Phase III clinical trials on this drug, PHOENIX 1 and PHOENIX 2, include a population of 1996 patients with moderate to severe psoriasis (81, 82).

At week 12, PASI75 response was achieved by 66-67% of treated patients, and at week 28 – for PHOENIX 1 and PHOENIX 2, respectively – by 79 and 76% of subjects with a body weight of less than 100 kg, and by 74% of subject regardless of body weight (81, 82).

The 5-year extension study conducted in the PHOENIX I population showed that PASI75 response was maintained in 72% of cases treated with the 90 mg dose every 12 weeks, and in 63.4% of those treated with the 45 mg dose every 12 weeks (83).

A recent Italian study conducted in 51 patients has shown a predisposition to optimal response to ustekinumab in subjects with psoriasis who are positive to HLA-Cw6 (84).

**Clinical considerations during treatment with biological agents**

**Vascular and dysmetabolic comorbidities**

In the last few years, many studies have investigated on the association between psoriasis and metabolic conditions such as obesity, diabetes, dyslipidemias, cardiovascular diseases and liver diseases. The data collected from Italian studies show a prevalence of metabolic syndrome (MS) in about 30% of patients with psoriasis, with a relationship with disease duration, but not with disease severity (4).

Obesity is defined as a Body Mass Index (BMI) > 30 Kg/m² (when the BMI is between 20 and 25, the subject is considered to be “overweight”); the available epidemiological data show a relationship between BMI and psoriasis. In fact, in subjects with psoriasis, BMI values are higher than in the general population; it has also been observed that a BMI increase is a risk factor for the development of psoriasis (1). Obese psoriatic patients often have a more severe disease presentation and show reduced response to systemic therapies, with both traditional and biological agents, thus demonstrating a pro-inflammatory role of fat tissue (5, 10, 11).

To further support this theory, some reports from the literature have described an increased efficacy of CsA therapy in psoriatic subjects following a diet-induced weight loss (85). On the contrary, anti TNF-α drugs induce weight increase in treated subjects, unlike what has been observed with ustekinumab (86-88).

This should be considered especially in subjects who are already overweight and for whom a diet would be advisable during therapy.

One of the main consequences of obesity is insulin-resistance, that is strictly associated to type 2 diabetes mellitus; in psoriatic subjects, this form of diabetes shows a two-fold prevalence compared to the general population (3).
A relationship between psoriasis and some gastrointestinal disorders such as non-alcoholic fatty liver disease (NAFLD), Crohn’s disease, ulcerative rectocolitis and coeliac disease has been observed. NAFLD is definitely an expression of the metabolic; it can potentially evolve into cirrhosis and liver carcinoma. In psoriatic patients, its prevalence is 48-59%, twice that observed in the general population (8). NAFLD is thought to induce a worsening of psoriasis due to the production of phlogosis mediators, including PCR and IL-6, by the inflamed liver (9).

The assessment of NAFLD in psoriatic patients is particularly important, especially if drugs which are potentially toxic for the liver (i.e. MTX) are needed (9). MS presence increases the risk of possibly severe cardiovascular disorders in psoriatic patients, especially in the youngest age ranges, with consequent increased risk of mortality (2, 6, 7).

The link between cardiovascular risk and psoriasis can be explained by some common pathogenic mechanisms (12). A recent study Italian study showed that some psoriatic subjects, who are asymptomatic from the cardiovascular point of view, have reduced coronary reserve capacity of as compared to healthy subjects (89).

This led to the hypothesis that some comorbidities may be modified by the treatment of psoriasis especially with biological drugs, resulting into a potential cardioprotective effect (90).

With regard to this, data available are conflicting. Some studies reported that systemic treatment administered continuously improves a number of biomarkers of cardiovascular risk, while other data from the Psocare registry showed an increase in cholesterol, tryglicerides, glycaemia, hepatic enzyme levels, in subjects treated with systemic conventional and biological drugs (13, 91).

**Patients with latent tuberculosis infection (LTBI)**

One of the most crucial issues concerning the safety profile of treatments based on biological drugs is the diagnosis and management of infectious diseases, in particular of tuberculosis infection (TBC). The main guidelines suggest TBC screening and management methods, focusing on LTBI forms detected before starting treatment with biological drugs (26, 92, 93).

An Italian retrospective study evaluated the long-term safety of biological agents (anti TNF-alpha and anti IL 12-23) in the treatment of moderate-to-severe psoriasis in 33 patients with LTBI undergoing specific prophylaxis treatment oral isoniazid 300 mg/day, continuative for 9 months and started 3 weeks on average before starting treatment with biological agents. Patients enrolled remained on biological treatment up to 82 weeks. One patient discontinued the prophylactic treatment with isoniazid due to hepatotoxicity, while another patient who had been diagnosed erythrodermic psoriasis, with negative QuantiFERON TB Gold test and chest X rays at screening, developed tuberculous pleuritis; after being successfully treated with a specific antibiotic multi-therapy the patients started etanercept treatment again with no further problem (94).

**Hepatitis B and C**

Before starting a treatment with anti TNF-α or IL 12-23 inhibitors, all patients should undergo a complete screening in order to assess the possible concomitance of HBV or HCV hepatic diseases; TNF has been shown to inhibit replication of hepatitis B virus favoring T lymphocyte response to eliminating the virus. Therefore, in case of anti TNF-α treatment, an antiviral prophylactic treatment in all patients with HBV hepatic disease should be considered (95). With regard to data on treated patients who have concomitant HCV hepatic disease, although anti TNF-α drugs are not indicated, preliminary results on the possible effect of etanercept treatment in association with antiviral treatment or in monotherapy have been published showing an improvement on both antiviral treatment and hepatic damage (96, 97).

**Therapeutic management of psoriasis in pregnancy (Tables 3, 4)**

Data available on psoriasis course in pregnancy are poor, but a clinical improvement during pregnancy seems to prevail (14). Table 3 summarizes FDA (Food and Drug Administration) risk categories for drug exposure during pregnancy.

With regard to drugs used in the treatment of psoriasis, it should be noted that biological agents, especial-
Psoriasis in elderly patients

Data available in literature report a prevalence of psoriasis in the 55-75 year age range of approx. 4%, which is slightly higher than the general population (103). In elderly patients, the higher frequency of morbidity, including cardiovascular diseases, diabetes and renal disease, is an additional challenge in finding the best approach to available treatments. Comorbidity treatment often involves the use of drugs that may potentially worsen psoriasis (i.e. beta blockers, NSAIDs, ACE-inhibitors, etc.) or interfere with available treatments. Even if the impact of aging on pharmacokinetic and pharmacodynamic changes – which increases the risk of adverse event onset – is not known, greater attention should be given especially to the therapeutic approach to psoriasis involving systemic drugs. In particular, the Medical Board of the National Psoriasis Foundation recommends CsA as second-line treatment after other traditional systemic treatments and biological drugs (103). Anti TNF-α drugs have shown similar efficacy and safety profiles between psoriatic patient population aged < 65 years and >65 years (104-106).

Therapeutic adherence

According to the World Health Organization, therapeutic adherence can be defined as the extent to which the patient follows medical or healthcare professional instructions in following a treatment schedule, a diet or a change in his/her life style (107). In psoriasis, primary adherence (defined as the percentage of patients who start the prescribed drug) does not exceed 50%, while secondary adherence (defined as the correct use of prescribed drugs) is not achieved in 39%-73% of patients (25). Available data on biological drugs come to different conclusions. Gniadecki et al. analyzed the Danish DERMIBIO database including 882 treatment series with anti TNF-α in psoriatic subjects. The results showed a treatment adherence reduction in a number of patients over time, with treatment persistence up to 4 years in 70% of cases with infliximab and approx. 40% with etanercept and adalimumab (108). A study by Clemmensen et al. showed that patients treated with ustekinumab have a greater treatment adherence as compared to those treated with adalimumab or etanercept, and concluded that loss of efficacy with a previous anti TNF-α drug does not compromise clinical response to ustekinumab (109).

Psoriasis in children

Importantly, approx. 30% of psoriatic patients experience disease onset in the pediatric age range (100). Psoriasis in children is a serious issue especially from the therapeutic point of view, since it requires a pharmacological treatment that in most cases is not well-accepted by young patients. Topical treatments have the same indications and limitations as in adult patients (101). Traditional systemic treatments require the same precautions used in adults. Methotrexate and cyclosporin A, always indicated in the most severe forms, have not shown any specific issues, while use of oral retinoids (acitretin) has shown issues related to the risk of onset of bone disorders, as well as the need for adequate contraceptive measures in female adolescents with childbearing potential (101, 102).

With regard to biological drugs, the only possible therapeutic option is etanercept, being the only one approved for the treatment of moderate-to-severe plaque psoriasis in pediatric patients (64, 65).
Conclusions

Over the last few years the therapeutic approach to psoriasis has deeply changed thanks to the availability of new molecules, as well as new increased knowledge on etiopathogenesis and disease-related comorbidities. With regard to this, an important contribution has been provided by a number of Italian research groups. In the context of an overall disease evaluation, dermatologists should focus more on the complexity of a psoriatic patient, and should increasingly implement a multidisciplinary approach by involving other specialists with the purpose of maximizing efficacy, safety and treatment adherence of available therapeutic options.

References


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