A DE MEDICINĂ ŞI FARMACIE CRAIOVA

Abstract

PhD Thesis

MODERN THERAPEUTIC MEANS AND METHODS IN TREATMENT OF PSORIAZIS COMPARATIVE STUDY

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Summary

Key words: psoriasis, treatment, methotrexate, biologic preparats

onic evolution and characterized by erythematous, scaly plaques and placards disseminated on the trunk and limbs. The incidence of the disease is between 3 and 5%.

Although the disease has been known since the time of Hippocrates, it is not yet known a curative treatment. There are known many therapeutic methods that can reduce or almost eliminate the symptoms of psoriasis, in such a way that a patient can live an almost normal life. There is not a single treatment modality for all patients, but any of the chosen methods have an effect on the evolution of the disease.

In this thesis we present some of the means and methods of treatment in psoriatic disease.

The work was divided into two parts. The first part provides an overview of etiopathogenic, clinical, and treatment issues of the psoriatic disease, and the second part presents my clinical findings in the treatment of psoriatic disease.

State of knowledge – theoretic information.

The general part is divided into four chapters:

- Etiopathogenic study;
- Clinical aspects in psoriasis;
- Histological aspects in psoriatic disease;
- Psoriasis treatment.

The first chapter describes the etiopathogenic aspects of psoriatic disease, presenting in detail:

- Genetic predisposition,
- Triggers of the psoriatic disease (infective, neuropsychological, neuroendocrine, drugs, food, alcohol, tobacco and traumatic),
- Immunological disorders in psoriatic disease
- Biochemical abnormalities.

In the second chapter are presented the clinical aspects of the psoriasis.

We have described the clinical aspects of the psoriasis vulgaris, its clinical forms, depending on the:

- Appearance and size of the elements (guttate, nummular, plaque and placards, figurative or circinat psoriasis)
- Look of squamous (rupioid, warts, squamous very fine, seborrheic, eczema),

e head, face, folds, presacral region, palmoplantar, nail,

- Evolution of lesions (psoriasis unstable, inveterate).

We have described the clinical aspects of **exudative psoriasis**:

- Erythrodermic psoriasis;
- Pustular psoriasis with its clinical forms (generalized: type von Zumbusch, impetigo herpetiformis, exanthema, annular centrifugal; located: type Barber, continues Hallopeau acrodermatitis);
- Psoriasis arthropatic.

The third chapter presents the histological aspects in psoriatic disease, describing the appearance of psoriasis vulgaris, erythrodermic and pustular under an optical and electronic microscope.

The fourth chapter described in detail the means and methods of treatment of psoriatic disease. At the beginning of the chapter is made a brief history of treatment and the fact that there is no universally accepted scheme for the treatment of this disease.

The traditional approach of the psoriasis treatment involves a start with less aggressive therapeutic modalities (such as topical therapy, phototherapy) and, if the answer to this is unsatisfactory, a move to a more aggressive therapy (systemic, biological preparations).

Local treatment is the most common method, being usually the first choice, especially for small and medium-sized forms of psoriasis. There are several categories of local treatments:

- Keratolytic agents: salicylic acid, prepared at various concentrations from 2 to 10%. It can be used alone, but more often in combination with a dermatocorticoid; urea, lactic acid.
- Oxidation reduction agents: vegetable tars (anthralin, cignolin), wood tars, coal tars or bituminous rock tars.
- Topical corticosteroids: For more than four decades the topical corticosteroids were used generally in the treatment of skin diseases and specifically in the psoriatic disease. The topical corticoids remain the main treatment of psoriasis, despite the introduction of new topical non-steroidal.
- Vitamin D Analogs: calcipotriol, the most used product, especially in combination with topical corticoids; maxacalcitolol and tacalcitol.
- Topical Retinoids: topical tazarotene

f the key therapeutic options for patients with moderate

Currently are in use different treatment schemes that use phototherapy sources. These are: PUVA therapy, broadband UVB, narrowband UVB, selective phototherapy (selective ultraviolet phototerapy SUP). It has to be mentioned also the heliomarine cure.

In the **systemic treatment** of psoriasis there are used multiple agents, providing a good control of the disease to most of patients and also improving the life quality indices. Often it is used a combined therapeutic scheme to increase the efficiency of medications. There have been described in detail the following systemic agents:

- **Methotrexate**, used for patients with psoriasis vulgaris who have more than 10-20% body surface area affected, pustular psorazis, erythrodermic psoriasis, arthropatic psoriasis and, not least, for patients with psoriasis vulgaris resistant to other therapeutic modalities (local or phototherapy);
- **Cyclosporine** is an immunosuppressive agent with the same indications as methotrexate;
- **Aromatic retinoids** (etetrinat and acitretin) designate the compounds whose action reproduce the biological effects of vitamin A. They are used mainly in the treatment of psoriasis vulgaris and pustular psoriasis.

The biological medication represents an edge of the medical technology and research, being used in the treatment of psoriasis. The preparations currently used in the treatment of psoriasis are:

- TNF alpha targeting agents: etanerceptum, infliximabum, adalimumabum
- Lf T-targeting agents: alefacept.

In order to reduce the toxicity of the systemic therapies, there are used combinations of various medications or the so-called rotation therapy or combination therapy, in which the systemic medication is subsequently replaced by another. The phototherapy is often associated with systemic and topical therapy. Rarely are made associations between two systemic therapies.

The use of combination therapy is more effective than monotherapy; more, the toxicity of individual treatment may be decreased, because the doses are often lower.

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3.1.1. Objective

The study that I propose aims a comparative assessment of the main therapeutic means and methods, local or general, used so far in psoriatic disease.

3.1.2 Materials and methods

The group comprised 268 patients diagnosed with psoriatic disease (especially psoriasis vulgaris). They were included in the study between January 2005 - December 2010 from the Department of Dermatology of the Clinical Emergency Hospital of Brasov, and its ambulatory. Some patients diagnosed with psoriasis, especially those with extensive and severe forms of psoriasis were hospitalized, and those with mild and moderate were followed through the specialty ambulatory.

The patients involved in the study were carefully selected by taking into account their compliance, their possibility of making visits over a period of almost one year, their readiness to perform laboratory investigations and / or histopathological examinations.

3.2. Epidemiological studies on the group of patients

The gender distribution of patients with psoriatic disease in the study group showed a slight predominance of male compared to the female (sex ratio male / female was 1.37 / 1).

The patients were from both urban and rural areas with a predominance of the those from urban areas (55.33%).

The age of patients in the study group was between 18 and 74 years, with a mean age of 39.92 years. Analyzing the distribution by age, it was found that the most numerous patients were classified in the age group 18-30 years (34.70%), followed by the age group 46-60 years (32.46%).

Regarding age of onset of the psoriatic disease, we noticed a higher incidence in the age group 21-30 years (24.63%), followed by the age group 11-20 years (22.39%).

Of the 268 patients analyzed, 68 patients (23.88%) were included in the study in the first year of disease onset, and all 68 patients (23.88%) within 1-5 years after the onset.

A family history psoriasis could be noticed in 58 patients (21.64%).

From the point of view of medical history, antecedents could be seen for some of the patients over 45 years old. Hypertension was the most common comorbidity in these patients (37.93%), followed by dyslipidemia (30.17%) and cardiovascular disease (25.86%). One explanation is the presence of chromosome 10 on the gene TNFAIP3, both in the psoriasis and cardiovascular disease.

ects in psoriasis

ms of the psoriasis, 242 patients (90.30%) had psoriasis vulgaris and 26 patients (9.70%) had an exudative form of psoriasis.

The patients with psoriasis vulgaris were classified according to: the appearance of the eruption, the location of lesions and the affected body surface.

A large majority of patients had the classic form of psoriasis vulgaris, the plaques and placards (205 patients, accounting for 84.71%), 17 patients had guttate form of psoriasis (7.02%), 9 patients (3.72%) had nummular psoriasis and 10 patients (4.13%) psoriasis circinat or figuratively.

An important clinical feature of psoriasis is the location of lesions. Thus, for 230 studied patients (95.04%) the location of psoriasis lesions was on the trunk and limbs. In addition to this location, patients have lesions on the hairy head skin (167 patients representing 69.04%), on the pleats in the form of psoriasis inverted (9 patients representing 3.81%), and palmar-plantar (14 patients representing 5.71%).

An important criterion in the choice of therapy of the psoriasis vulgaris is the Body Surface Area (BSA) affected by it. According to the European Consensus Programme (ECP) the psoriasis severity is defined as: BSA Ò10% corresponds to easy psoriasis and BSA> 10% to moderate-severe psoriasis. BSA Ò 10% was found in 144 patients (59.50%), and BSA> 10% in 98 patients (40.50%). The patients with BSA Ò10% respond well to local treatment or phototherapy, and for the patients with BSA > 10 the indication is a systemic therapy, either classic with methotrexate, either new modern therapies with biological preparations.

The PASI score is the most used tool in the determining of the severity of psoriasis. It is the gold standard in the assessment of psoriasis. The value of PASI score for patients in the studied group ranged between 2.1 and 41.5 with an average of 10.41.

Among the forms of psoriasis exudative, 14 patients (53.84%) had pustular psoriasis, of which 9 (34.62%) had palmar-plantar, 4 patients (15.38%) had centrifugal ring and one patient (3.85%) von Zumbusch generalized type.

The arthropatic psoriasis, especially oligoarticular asymmetric, had been encountered in 9 patients (34.62%), and the erythrodermic psoriasis, in 3 patients (11.54%).

3.4. Considerations on the psychosocial implications of the psoriatic disease in the group of studied patients

The psoriasis has a profound impact on the patients quality of life, both physically, emotionally and socially. Some of the patients studied (89 patients) responded to a

ions in order to assess the impact of psoriasis on their

After analyzing the patients responses, it has been observed that psoriasis have a negative impact on quality of life and daily activities.

3.5. Assessment of psoriatic disease treatment based on personal experience

The choice of the therapeutic method depends on the clinical form of the psoriasis and its severity. So, in cases of mild psoriasis (PASI <10), or affecting less than 10% of the body surface the treatment consisted of topical and / or phototherapy. In the severe forms of psoriasis (PASI> 10) I opted for systemic treatment, which was associated or not with phototherapy. In some cases, the systemic therapy can not be administered, and there were used local treatment schemes.

In my case I tried to use therapeutic schemes as much adapted to the clinical-evolutive particularities of each studied patient, in order to assess the results as much accurate possible. For this purpose I used several schemes, monotherapeutical or combined, dividing patients into several groups, as follows:

- group I of 38 patients received treatment with topical dermato-corticoids, in this case clobetasol propionate (Dermovate) and mometazonum furoate (Elocom)
- In the second group of 43 patients we applied local treatment with topical dermato-corticoids, topical keratolytic (salicylic acid 2-10%) and phototherapy SUP;
- Group III: 29 patients received local treatment with topical dermato-corticoids, topical keratolytic to which I associate oxide reducers (ointment cignolin in increasing doses)
- In group IV, 29 patients received the same treatment as the patients in group III to which was associated phototherapy SUP.
- Lot V of 14 patients affected only with palmar-plantar form followed a combined treatment with topical dermato-corticoids (clobetasol propionate ointment) and 40% urea ointment.
- group VI of 26 patients received systemic therapy with methotrexate at a dose of 15 mg / week over 16 weeks.
- Lot VII of 45 patients received the same systemic treatment with methotrexate 15 mg / week over 16 weeks at which was associated phototherapy SUP.
- Lot VIII of 18 patients followed a treatment with biological preparations, (7 with Etanercept (Enbrel) and 11 patients with adalimumab (Humira)).

e applied treatment schemes were evaluated as follows: oups at 2, 4 and 8 weeks, the patients results in groups VI, VII and VIII were assessed at 16 weeks.

Assessment of the therapeutic results was as follows:

- PASI > 75% ï lesions reduced over 75% (very good results)
- PASI 50-75% ï lesions reduced between 50-75% (good results)
- PASI 25-50% ï lesions reduced between 25-50% (moderate results)
- PASI < 25% ï lesions reduced less than 25% (treatment failure or no response to treatment).

The results were as follows:

- group I: PASI Ó75% after 8 weeks of treatment for 86,84% of patients, with fewer side effects from treatment dermato-corticoids (7.89% folliculitis corticosteroid);
- group II PASI Ó 75% after 8 weeks of treatment for 95,35% of patients. The results were compared with those in group I, observing slightly favorable results to the patients from group II. Side effects in patients in group II were minor asemnea (4.64% folliculitis and purpuric spots due to dermato-corticoids and 6.98% had the solar erythema after phototherapy);
- in group III and group IV: PASI Ó75% after 8 weeks was 68,96% in group III and 75,86% in group IV; The most common side effect in both groups was crisofanic erythema (18.26%);
- group V: after 8 weeks we have obtained good results in 11 patients (78.51%);
- group VI ’Hi group VII: PASI Ó 75% for 57,69% of the patients of group VI and 66,67% of the patients of group VII after 16 weeks of treatments; we noted that patients in group VI experience side effects such as skin itching, nausea, and the patients from group VII had fever, headache and erythema accentuated after systemic treatment, similar to that ones following exposure to solar UV;
- group VIII: PASI 75% was obtained after 16 weeks to 77,78% of patients treated with Adalimumab and to 50% of patients treated with Etanercept.

current disease that affects approximately 3-5% of the population. Regarding this, the data from the literature is variable.

2. In the study group 90.30% of patients presented psoriasis vulgaris and 9.70% had an exudative form (pustular, arthropatic and eritodermic)

3. Gender distribution of patients with psoriasis showed that 57.84% of patients were male and the remaining 42.16% being female, with a sex ratio male: female 1,37:1.

4. The distribution of age groups of patients showed no big variations depending on the decades of age: (Group 18-30 years ï 34,70%; Group 31-45 years ï 24,26%; Group 46-60 years ï 32,46%; Over 60 years ï 8,58%).

5. The age of onset of psoriasis presented two peaks of increased incidence; thus the first peak age of onset was between 21 and 30 years 24.63% and the second peak age of onset between 41 and 50 years 17.16%.

6. A family history of psoriasis was recorded in 21.64% of patients.

7. In the study group, most patients with psoriasis vulgaris presented the classic form of plaques and placards (84.71%). The remaining clinical forms were gutted psoriasis (7.44%), psoriasis Nummular (3.72%) and psoriasis figurative (4.13%) .

8. In terms of location of the psoriasis lesions, most patients showed an extended form on the trunk and limbs (95.04%) but also in the other known locations: hairy head skin psoriasis (69.01%), psoriasis reversed (3, 72%), palmar-plantar psoriasis (5.76%), nail psoirazis (15.29%), generalized psoriasis (2.48%).

9. The PASI score of patients diagnosed with psoriasis vulgaris was between 2.1 and 41.5, with an average of 10.41. In 53.73% of patients PASI score was under 10 and over 10 to 35,44%. The treatment was chosen (local or systemic) based on this score.

10. Regarding the treatment of psoriasis, which is also the main aim of my PhD thesis, a first conclusion is necessary. The therapeutic methods cannot be assessed comparatively, due to the fact that they are addressed to patients with different clinical forms, specially selected, in accordance with all of the clinical-evolutive particularities of the case.

11. The local treatment with potent topical corticoids is addressed to patients with a PASI score under 10, with a shorter duration of disease development; thus it was applied in 38 patients, with a PASI Ó 75% response after 8 weeks in 86.84% patients. The side effects consists of corticosteroid folliculitis for 7.89% of patients. Recurrence was seen in 5.26% of patients.

pical corticoids, topical keratolytic, phototherapy SUP) PASI score under 10, with a short duration of evolution was administered to 43 patients, and the results showed an improvement in PASI Ó75% at 8 weeks to 95.35% of patients. Minor side effects (folliculitis to 2.32% to 2.32% purpuric spots and solar erythema to 6.98%)

13. In the combined treatment with three methods (topical dermato-corticoids, topical keratolytic, oxide-reduction) and the one with 4 methods (topical dermato-corticoids, topical keratolytic, oxide-reduction, phototherapy SUP) addressed to the patients with PASI < 10, but also to patients with PASI Ó 10 which had systemic therapy contraindications. The good results (PASI Ó75%) at 8 weeks were 68.96%, respectively 75.86%, with the mention of a light erythema at 10.34% and a crisofanic erythema 18.96% patients.

14. Classical systemic treatments with methotrexate 15 mg / week methotrexate in monotherapy vs. 15 mg / week associated with phototherapy SUP were addressed to patients with a PASI score over 10 and with a long disease duration. The comparative results of the two methods showed an improvement in PASI Ó75% after 16 weeks of treatment to 57.69%, respectively 66.67%.

15. The treatments with biologic preparations (Etanercept and Adalimumab) were also addressed to patients with a PASI score over 10, who had not responded to any other conventional method of treatment. PASI Ó 75% after 16 weeks of treatment was achieved in 77.78% of patients having an adalimumab treatment and 50% in those who followed a regimen with etanercept. These results are less conclusive, since the number of patients treated with monoclonal antibodies was very low.

16. Finally, we can afford to consider that all methods used today in the treatment of the psoriatic disease give satisfactory results to a higher or lower number of patients, on condition to a strict therapeutic schemes adaptation to the peculiarities of each clinical case.

17. In the management of the therapy of the psoriatic disease there will be made more additions in relation to modern acquisitions, without neglecting a very important aspect, that of the psychological impact of psoriasis on each patient.

18. Currently with all the progress and whatever therapeutical schemes used, more or less sophisticated, we still can not speak about a standardization of the treatment of the psoriatic disease, neither about a lasting cure.