Research article

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Benefit of a topic ointment as co-medication with biologic drugs for the management of moderate-severe psoriasis: a prospective, observational real-life study

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Abstract

Background. Psoriasis is a multifactorial chronic inflammatory skin disease characterized by erythemato-squamous lesions with a chronic relapsing course.

The desease clinical activity (PASI) and the patient's quality of life (DLQI) are the main elements to assess for setting up a correct therapeutic management.

Objective. The aim of the study was to evaluate the management of the patient with moderate-severe psoriasis in therapy with biological drugs and to establish the difference in the achievement of PASI 90 and DLQI 0-1 between a group of patients treated with only biological drugs and a group of patients receiving biologic therapy in combination with a topical ointment.

Methods. we conducted a prospective, observational real-life study enrolling 60 patients with moderate to severe psoriasis and divided in two groups: Group A patients treated with biological drugs, Group B patiens treated with biological drugs in association with an ointment composed of betamethasone, salicylic acid and ammonium sulphoichtyolate, applied 2 times a day. PASI and DLQI were evaluated at study beginning (T0) for both study groups, after 12 weeks (T3) for sample in therapy with biological drugs and after 24 weeks (T6) for sample in co-medication therapy.

Results. The two-way ANOVA method was used to evaluate the standard deviations (SD): at T3 and T6 Group B obtained a significant PASI reduction and improvement of DLQI (* p value <0.05) compared to Group A.

Conclusion. Our study shown that the patients treated with biologics in co-medication with topical therapy reached a significantly higher PASI and DQLI compared with those treated with only biologics. Furthermore we observed that the association with topical oinment showed more efficacy in the treatment of areas such as palm-plantar region, that is often difficult-to-treat region, even for biologic drugs.

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Key words: *psoriasis, HIV, psoriasis treatment*

Introduction

Psoriasis is a multifactorial chronic inflammatory skin disease characterized by erythemato-squamous lesions with a chronic relapsing course. Psoriasis is associated with numerous comorbidities such as psoriatic arthritis (PsA).

The etiology of psoriasis and PsA is not completely understood, but both are immune-mediated disorders involving dendritic cells (DCs), macrophages, and T cells[1].

These immune cells secrete cytokines such as TNF-α, interleukin (IL)-1β, IL-6, and IL-22 that induce inflammatory signals and chemokines secretion[1].

Psoriasis poses a significant public health challenge and affects millions of people around the world[2]. Inadequate treatment and delayed access to care represent critical issues regarding psoriasis. In Italy, psoriatic patients in therapy are scanty and patient's misinformation could interfere with access to care[3].

The clinical severity is not necessarily related only to the location and extent of the disease, but to the impairment of the patient's quality of life.

Establishing the severity of the disease and its impact on the patient's life is useful to draw a profile on the evolution of the disease[4].

The response to treatments in psoriatic patients is quantitatively monitorated by evaluating clinical severity and quality of life indexes, in particular the psoriasis area severity index (PASI) and the dermatology life quality index (DLQI) are currently the most widely used[5].

Moreover with the introduction of improved treatment strategies, such as biologic drugs, more patients with moderate to severe psoriasis achieve PASI 90 and PASI 100[6].

Although it is evident that biologics constitue an effective treatment, a significant number of patients discontinue the therapy due to loss of efficacy over time, a condition defined biologic fatigue, especially when difficult areas are involved[7].

In particulary, some body areas (scalp, nails, palms and soles) are often recalcitrant to therapy due to slow responses, side effects and lack of adherence to the treatment[8].

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Topical treatment remains first choice in patients with isolated involvement of these sites, while systemic therapy is justified for aggravated stages of isolated lesions or in the case of systemic lesions or refractory to topical therapy[8,9]. In these cases combination regimen of biologics with other agents could be considered as a treatment option[10].

There are numerous topical medications used in clinical practice[11]. Among these, the ointment based on betamethasone 17-valerate 21-acetate, salicylic acid and ammonium sulpho-ichtyolate has shown a synergy of action among its components[12]. Betamethasone 17-valerate 21-acetate has an anti-inflammatory and anti-reactive properties. The ammonium sulpho-ichtyolate has antiexudative, keratoplastic and decongestant properties[13]. Finally salicylic acid has respectively keratolytic, flaking, slightly disinfectant and antipruritic actions[14].

Method

We conducted a prospective, observational real-life study included 60 patients diagnosed with moderate to severe psoriasis, both male and female, over the age of 18.

This spontaneous clinical study, that enclosed psoriatic patients in biological therapy without satisfactory results, was designed as two-arm study. The first group continued with biologic grugs, while the second underwent biologic treatment in association with the local therapy. In the second group, all patients who adhered to topical therapy where placed.

The number of patients in both group was the same.

The patients enrolled in the study had been on therapy for at least 12 consecutive weeks with biological drug (anti-TNFalpha, anti-IL12-23 or anti-IL17).

Group A: 30 patients treated only with the biological drug for at least 12 consecutive weeks.

Group B: 30 patients treated with the biological drug for at least 12 consecutive weeks, who have associated an ointment based on betamethasone, salicylic acid and ammonium sulfoitriolate to be applied 2 times a day.

Patient data were collected in three steps:

At time T0 (base line): age, weight, height, smoking habit, alcohol consumption, involved areas, presence of comorbidity, type of biological drug, PASI and DLQI were detected.

At time T3, after 12 weeks of treatment with biological drug, PASI and DLQI values were collected.

At time T6, after 24 weeks of treatment in both groups, PASI and DLQI values were taken up.

Statistical Analysis

The statistical analysis was carried out by evaluating the means ± the standard deviations (SD) for general parameters reported in tables A, B and C, and using the two-way ANOVA method, followed by Bonferroni test for post-hoc analysis, as regards the elaboration of the graphs.

The analysis of variance (ANOVA) is a set of statistical techniques belonging to the inferential statistics that allow to compare two or more groups of data by comparing the internal variability of these groups with the variability between the groups. The two-way variance analysis (two-way ANOVA) is an extension of the one-way ANOVA (one-way ANOVA), and examines the influence of two different independent categorical variables on a continuous dependent variable. The two-way ANOVA not only aims to evaluate the main effect of each independent variable, but also if there are reciprocal interactions.

Results

The study population is represented by 32 males (53.33%) and 28 females (46.67%) with an average age of 54.53 years ± 10.79 SD.

Palm-plantar involvement was reported in 38.3%, while scalp involvement was reported in 41.7%.

The patients were distributed as follows: 53.33% was in therapy with anti-TNFalpha drugs, 20.33% with anti-IL12-23 drugs and the remaining 13.33% with anti-IL17 drugs.

The characteristics of the sample of 30 patients belonging to group A are listed in Table A (Tab. A).

Tab. A Group A patients

Group A	n° tot 30Patients
Male (%)	19 (63.33%)
Female (%)	11 (36.67%)
Age (anni)	54,37 ± 9,43
Weight (kg)	74,9 ± 13,26
Height (cm)	171,37 ± 8,92
BMI (kg/m^2)	25,47 ± 3,94
Smoking habits	14 (46.67%)
Alcool	8 (26.67%)
PASI T0	16,2 ± 3,86
DLQI T0	16,97 ± 4,94
palmo-plantar involvment (%)	10 (33.33%)
Scalp involvment (%)	10 (33.33%)
Anti-TNFα	15 (50%)
Anti-IL12-23	11 (36.67%)
Anti-IL17	4 (13.33%)

The Group A is represented by 19 males (63.33%) and 11 females (36.67%) with an average age of 54.37 years ± 9.43 SD.

The sample was overweight with an average BMI of 25.47 ± 3.94 SD and associated with incorrect lifestyles: 46.67% had smoking habit and 26.67% was habitual alcohol users.

Patients had an average baseline PASI (PASI T0) of 16.2 ± 3.86 SD and an average baseline DLQI (DLQI T0) of 16.97 ± 4.94 SD.

Palmar-plantar involvement was reported in 33.33%, while scalp involvement was reported in 33.33%.

The patients were distributed as follows: 50% was in therapy with anti-TNFalpha drugs, 36.67% with anti-IL12-23 drugs and the remaining 13.33% with anti-IL17 drugs. The characteristics of the sample of 30 patients belonging to group B are listed in Table B (Tab. B)

Tab. B Group B patients

Group B	n° tot 30 Patients
Male (%)	13 (43.33%)
Female (%)	17 (56.67%)
Age (anni)	54,7 ± 12,17
Weight (kg)	76,2 ± 10,89
Height (cm)	169,4 ± 7,91
BMI (kg/m^2)	26,54 ± 3,11
Smoking habits	10 (33.33%)
Alcool	8 (26.67%)
PASI T0	15,3 ± 4,68
DLQI T0	15,53 ± 5,45
Palmo- plantar involvment	13 (43.33%)
Scalp involvment	15 (50%)
Anti-TNFα	17 (56,67%)
Anti-IL12-23	9 (30%)
Anti-IL17	4 (13,33%)

The Group B is represented by 13 males (43.33%) and 17 females (56.67%) with an average age of 54.7 years ± 12.17 SD.

The sample was overweight with an average BMI of 26.54 ± 3.11 SD and associated with incorrect lifestyle: 33.33% had smoking habit and 26.67% was habitual alcohol users.

Patients had an average baseline PASI (PASI T0) of 15.3 ± 4.68 SD and an average baseline DLQI (DLQI T0) of 15.53 ± 4.45 SD.

Palm-plantar involvement was reported in 43.33%, while scalp involvement was reported in 50%.

The patients were distributed as follows: 56.67% was in therapy with anti-TNFalpha drugs, 30% with anti-IL12-23 drugs and the remaining 13.33% with anti-IL17 drugs.

The PASI and DLQI at time T3 of group A are indicated in Table C (Tab.C).

Tab. C Group A PASI T3 and DLQI T3

Group A	n° tot 30 Patients
PASI T3	5,67 ± 1,6
DLQI T3	5,67 ± 1,47

The sample had an average PASI at time T3 of 5.67 ± 1.6 SD and an average DLQI at time T3 of 5.67 ± 1.47.

The PASI and DLQI at time T3 of group B are indicated in Table D (Tab. D).

Tab. D Group B PASI T3 and DLQI T3

Group B	n° tot 30 Patients
PASI T3	5,53 ± 2
DLQI T3	3,93 ± 1,8

The sample had an average PASI at time T3 of 5.53 ± 2 SD and an average DLQI at time T3 of 3.93 ± 1.8 SD.

The PASI and DLQI at time T6 of group A are indicated in Table E (Tab. E).

Tab. E Group A PASI T6 and DLQI T6

Group A	n° tot 30 Patients
PASI T6	2,87 ± 1,46
DLQI T6	3,03 ± 2,16

The sample had an average PASI at time T6 of 2.87 ± 1.46 SD and an average DLQI at time T6 of 3.03 ± 2.16.

The PASI and DLQI at time T6 of the group B are indicated in Table F (Tab. F)

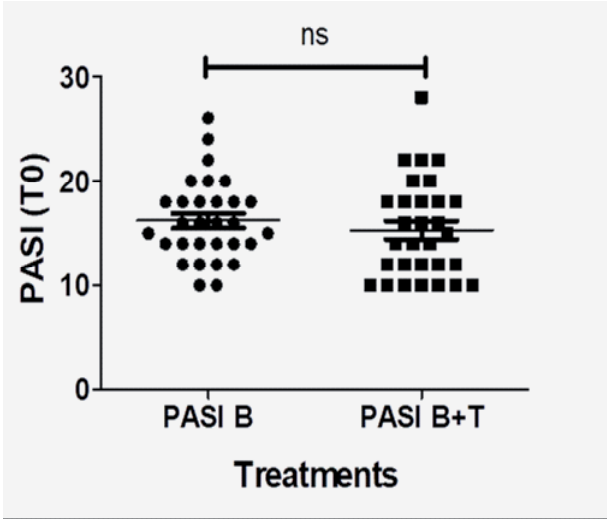
Tab. F Group B PASI T6 e DLQI T6

Group B	n° tot 30 Patients
PASI T6	1,57 ± 1,48
DLQI T6	0,7 ± 0,88

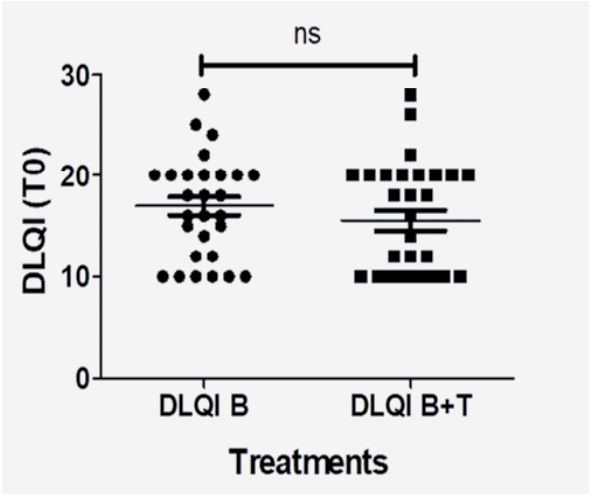
The sample had an average PASI at time T6 of 1.57 ± 1.48 SD and an average DLQI at time T6 of 0.7 ± 0.88 SD.

The comparison of the distribution of PASI values at time T0 between the monotherapy group (group A "PASI B") and the combination group (group B "PASI B + T ") is shown in Graphic 1.

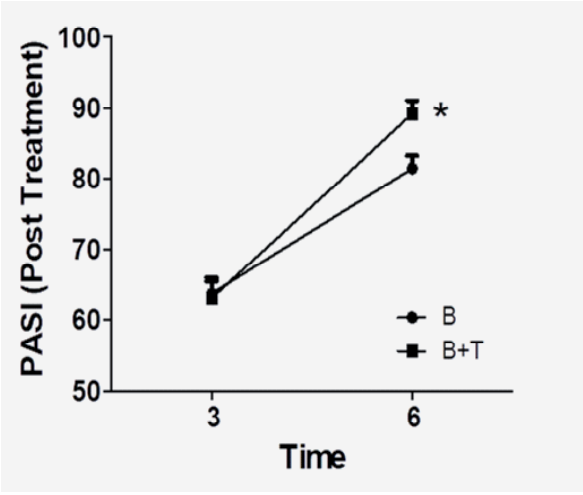
Similarly, the comparison of the distribution of DLQI values at time T0 between the monotherapy (group A "DLQI B") and the combination group (group B "DLQI B + T") is shown in Graphic 2.



Graphic 1. Comparison of the distribution of PASI values at time T0 between Group A (PASI B) and Group B (PASI B+T)



Graphic 2. comparison of the distribution of DLQI values at time T0 between Group A (DLQI B) and
Group B (DLQI B+T)



Graphic 3. Comparison of the reductions in% of the PASI from time T3 to time T6 between Group A (B) and Group B (B+T).

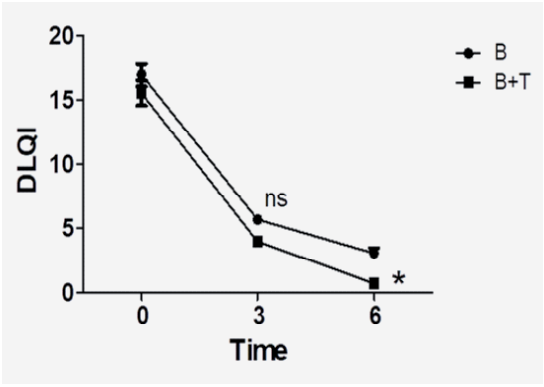
Graphics 1 and 2 rapresent that the samples (PASI B and PASI B + T for Graphic 1, DLQI B and DLQI B + T for Graphic 2) are homogeneous. This means that the sample of patients enrolled in the study is homogeneous and representative: the patients in the two groups are equally distributed between the values of PASI and DLQI at T0.

Graphic 3 represents a comparison of the reductions in% of the PASI from time T3 to time T6 in the two study samples (B and B + T).

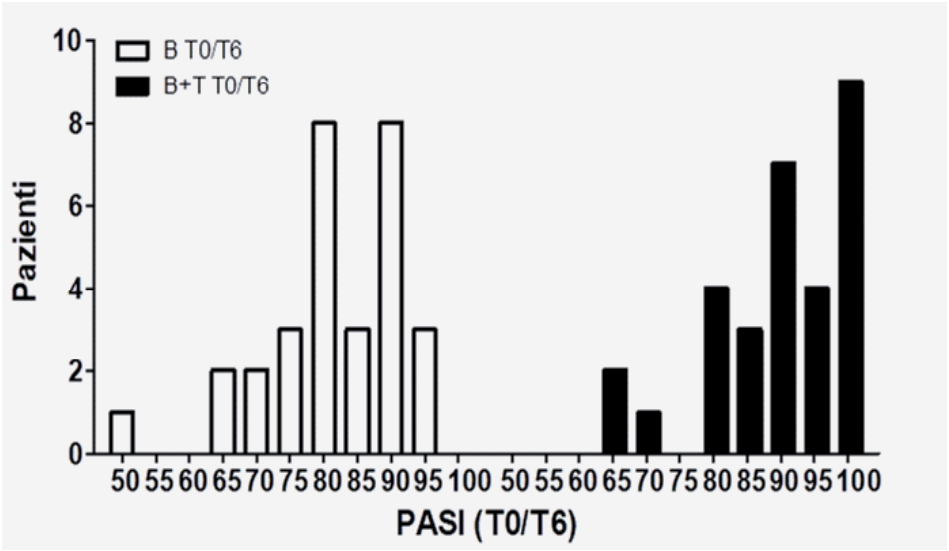
Similarly, Graphic 4 represents a comparison of the reductions of the DLQI from time T3 to time T6 in the two study samples (B and B + T).

Graphic 3 shows that, between T3 and T6, the sample treated with the association of the biological drug and the topical drug (B + T) obtained a significant PASI reduction (* p value <0.05) compared to the sample treated with biological drug only (B).

Graphic 4 shows that, between T3 and T6, the combination group (B + T) obtained a significant reduction of



Graphic 4. Comparison of the reductions of the DLQI from time T3 to time T6 between Group A (B) and Group B (B+T).



Graphic 5. Comparison between PASI reduction frequencies in Group A (in white) and Group B (in black) at T0 and T6

DQLI (* p value <0.05), compared to the monotherapy group (B).

Therefore, by comparing the reduction of the PASI and DLQI values to T6, a significant "gap" is observed between the two groups: patients in group B (sample B + T) reach PASI 90 statistically significantly (p value <0.05) and show a significant reduction in the DLQI (p value < 0.05).

Graphic 5 shows a comparison between the PASI reduction frequencies in the two study groups (B in white, B + T in black) between time T0 and time T6.

In Graphic 5 the histograms represent the number of patients who belong to a certain interval of reduction of PASI (in%) at time T6 for each treatment. It is evident that the PASI 100 was achieved in group B (in black) significantly,

Discussion

We conducted this prospective, observational, real-life study to evaluate the management of the patient with moderate-severe psoriasis in therapy with biological drugs and to establish the difference in the achievement of PASI 90 and DLQI 0-1 between a group of patients treated with only biological drugs and a group of patients receiving biologic therapy in combination with a topical ointment based on betamethasone 17-valerate 21-acetate, salicylic acid and ammonium sulpho-ichtyolate.

We are aware that randomized controlled studies (RCTs) are recognized as a gold standard for evaluating treatment outcomes and ensure both selected patients and ideal conditions for procedures[15]. Anyway, in a clinical practice, clinical investigators should consider costs of therapy, their availability and variables that can influence the outcomes. In particular, in real life setting, it is not necessary a washout period for different topical therapy, so patients are proposed to use an alternative agent in case of therapy failure, without restricted inclusion and exclusion criteria.

The statistical validity of the study was verified: at time T0 (recruitment time) the populations compared were homogeneous, because the differences between the PASI and DLQI values of the two distributions were not statistically significant (NS).

From the comparison of the characteristics of the samples in the study, results that group B is more represented by women (56.67%) than group A (36.67%).

Furthermore, in both groups the calculated average BMI were found to be above the normal range (BMI range: 18.5-24.9), equal to 25.47 ± 3.94 SD for group A and 26.54 ± 3, 11 SD for group B: therefore, patients recruited were overweight (BMI range: 25-29.9).

Besides, patients belonging to both groups showed a similar involvement of difficult areas, with higher percentages in group B (43.33% palm-plantar area and 50% scalp in group B, compared to 33.33% palm-plantar area and 33.33% scalp in group A).

As for the other parameters assessed (age, smoking habit and alcohol intake) there were no significant differences between the two groups.

The biological drugs used in the study (anti-TNFα, anti-IL12-23, anti-IL17) showed a similar efficacy profile.

At time T3, PASI and DLQI values reached in group A were 5.67 ± 1.6 SD and 5.67 ± 1.47 SD respectively; while in group B the values of PASI and DLQI at time T3 were 5.53 ± 2 SD and 3.93 ± 1.8 SD respectively. There were no significant differences between the PASI and DLQI values reached in the two groups at time T3.

At time T6, PASI and DLQI values reached in group A were 2.87 ± 1.46 SD and 3.03 ± 2.16 SD respectively; while in group B the values of PASI and DLQI at time T6 were 1.57 ± 1.48 SD and 0.7 ± 0.88 SD respectively.

To date, the literature on psoriasis co-medication therapy are dated and designed to assess primarly the clinical activity of Betametasone or its well known combination with Calcipotriolo, usually prescribed as a first-line treatment in mild to moderate psoriasis[16-19].

Furthermore other authors, anecdotally, investigated the therapeutic effect of cannabinoids or phytocannabinoids-ointment in the treatment of several dermatologic disorders[20], nevertheless, we followed standardized treatment protocols in our investigation.

Clinical studies focused on direct comparisons of biological agents and topical therapies haven't been carried out.

Main limitations of our study include the uncontrolled design study and the small clinically heterogeneous cohort.

Conclusions

Psoriasis is a chronic inflammatory skin disease that requires long-term, safe and effective treatment. The therapy aims are correct disease management and the prevention of recurrence, with improvement of patient's quality of life and consenquently better adherence to therapy[20].

The main therapeutic objective is the achievement of PASI 90 and DLQI ranged 0-1[21].

Although the efficacy of biological drugs with the initial PASI response could be significant, psoriatic lesions often continue to persist in difficult areas, mainly the palm-plantar region, scalp, nails, genital area etc. So, the other strategies in these psoriatic patients are requested in order to obtain long-term remission that otherwise can be difficult to achieve[9].

The present study suggests that the treatment with the association of biological drug and ointment based on betamethasone, salicylic acid and ammonium sulpho-ichtyolate, obtained a significant reduction of PASI and DQLI, compared to treatment with biological drug alone.

The oinment efficacy in treatment of difficult areas explain the adherence of patients in the daily application.

Our study showed that it is crucial for clinicians choose a combination strategy with the aim to increase efficacy, adherence and safety of treatment as well as to achieve and maintain adequate disease control.

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