UNIVERSITY OF MEDICINE AND PHARMACY
"CAROL DAVILA", BUCHAREST
DOCTORAL SCHOOL
MEDICAL FIELD

Patients with psoriasis vulgaris treated with biological agents - clinical and paraclinical features -

ABSTRACT OF DOCTORAL THESIS

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2024

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SUMMARY OF THE MAIN POINTS

Psoriasis vulgaris is an autoimmune, immune-mediated disease with a high genetic susceptibility. Interleukin 17 is highly expressed, along with other cytokines (overproduction of interferon-gamma (IFN-γ)/tumour necrosis factor-alpha (TNF-α) [1]. In psoriasis vulgaris a "vicious cycle" occurs, the auto-inflammatory process initiated perpetuating itself. [2].

The primary cause of psoriasis is thought to be a dysregulation of the immune responses [3-5]. The latter include physical trauma (the Koebner phenomenon) and infections, which trigger innate immune responses. [6,7].

Psoriatic arthritis is highly prevalent among patients with psoriatic disease, with peripheral and axial involvement and dactylitis - a predictive factor for this condition. It commonly occurs in the 30-50 year old population. Comorbidities are also common: cardiovascular disease, metabolic syndrome (obesity, diabetes, hypertension), depression, uveitis [8]. Psoriasis is a systemic inflammatory disease and is associated with multiple comorbidities, the most common and important being metabolic syndrome (MetS) (obesity, hypertension, diabetes mellitus, hyperlipidaemia and non-alcoholic fatty liver disease associated with obesity). The severity of psoriasis also carries a high risk of developing metabolic syndrome [9].

Positive lifestyle changes and therapeutic management of metabolic syndrome have been shown to improve psoriasis vulgaris. Appropriate screening for metabolic syndrome in patients with psoriasis vulgaris is recommended to identify patients which present a potential risk for cardiovascular disease [10].

Hepatitis B virus (HBVR) reactivation under immunosuppressive therapy has been observed and described [11], and in hepatitis C virus (HCV) infection, the immunosuppressive potential of tumor necrosis factor (TNF) correlates with exacerbation of chronic liver infection and is a primary concern for researchers [12].

According to the national therapeutic protocol for the treatment of psoriasis approved in 2022, due to the high risk of tuberculosis reactivation, patient screening before the initiation of biological therapy is mandatory, performing the following investigations: QuantiFERON

TB test or IDR (intradermal tuberculin test), chest X-ray, pneumological consultation. These are repeated every 12 months for those who have not undergone chemoprophylaxis [13]. The QuantiFERON TB test was approved by the FDA in 2005 as an in vitro test for the diagnosis of Mycobacterium tuberculosis infection for both active and latent disease [14].

In the literature, there is substantial evidence regarding the importance of paradoxical reactions developed in psoriasis patients treated with biologics. These manifestations include: paradoxical psoriasis (generalised plaques, palmoplantar pustulosis), alopecia, neutrophilic dermatitis. Of the anti-TNF agents, the most frequently reported to produce paradoxical reactions was adalimumab, followed by infliximab. In terms of switching between molecules, those who switched to another anti-TNF did not achieve complete remission, and only a small proportion of those switched to another therapeutic class achieved partial resolution [15].

Psoriasis is an important public health problem that benefits from innovative treatments that act not only on the skin but also on systemic inflammation. Fortunately, innovative treatments are constantly being developed. We chose this topic because it is of interest at the present time, considering also the importance of revolutionary biological therapies that can change the lives of our patients today.

In this paper, I aimed to identify the particularities of psoriasis vulgaris patients treated with innovative therapies by comparing their laboratory data with control groups of psoriasis vulgaris patients on classical therapies. To achieve this, we formulated 7 objectives, which we addressed in 7 original studies and 3 published articles.

The general objectives of this scientific research were:

- Describing the comorbidities of the patients with psoriasis vulgaris treated with innovative therapies in the studied groups
- Highlighting the lipid status changes in patients from the two groups
- Quantification of the factors that make up the metabolic syndrome
- Identifying the patients with psoriasis and viral hepatitis (HBV or HCV)
- Studying the degree of joint damage in patients with psoriasis vulgaris
- Highlighting the risk of developing tuberculosis among the patients on innovative treatments
- Analysing of the potential risk of developing neoplasia while undergoing immunomodulatory and immunosuppressive treatments

- Quantification of the coexistence of other associated autoimmune diseases in patients with psoriasis vulgaris (vitiligo, rheumatoid arthritis, inflammatory bowel disease, autoimmune thyroiditis, hidradenitis suppurativa, ankylosing spondylitis)
- Describing the paradoxical reactions which occured during biological therapies administered to patients with psoriasis vulgaris

The common general methodology of this PhD work was based on observational, cohort, analytical studies that included patients diagnosed with psoriasis vulgaris in the dermatology departments of SUUMC Dr Carol Davila and Colentina Clinical Hospital, Bucharest.

The data collection period was from 2008 to 2023. General demographic, clinical, biological data were accumulated through a retrospective methodology for the period 2008-2023.

Data for statistical analysis were processed using SPSS. SPSS version 25 and Microsoft Excel 365 software were used.

Quantitative variables were tested for distribution using the Shapiro-Wilk test and were expressed as means with standard deviations or medians with interpercentile ranges.

Quantitative variables were tested between measurements using the Related-Samples Wilcoxon Signed Rank Test. Independent quantitative variables were tested between groups using the Mann-Whitney U test.

Qualitative variables were expressed as absolute or percentage and were tested using Fisher's Exact Test. Bonferroni-corrected Z-tests were used to detail the results obtained in the contingency tables.

Pearson's correlation coefficient (r) indicates the direction and strength of the linear relationship between two numerical interval variables, but gives no indication of causality. Its values can range from -1 to +1.

The sign of the coefficient indicates the meaning of the link, thus:

- $-1 \leq r < 0$: inverse relationship, so large values of one variable are associated with small values of the other
- $r = 0$: no relationship between the variables analysed
- $0 < r \leq +1$: direct link, so large values of one variable are associated with large values of the other

The strength of the link is given by the absolute value of the coefficient. Among the most commonly used indications of interpretation are the following:

- (0,0;0,2] no correlation
- (0.2;0.4] weak correlation
- (0.4;0.6] moderate correlation
- (0.6;0.8] strong correlation
- (0.8;1.0] very strong correlation

The statistical significance of the correlation coefficient implies the rejection of the null hypothesis r=0, which is done when the p-value (sig.) is below the 0.05 threshold.

When the data analysed are not numerical and of interval type, the Pearson coefficient cannot be used and non-parametric methods are used. A non-parametric method for testing the association between two variables is the chi-square ($\chi 2$) test, which compares the observed distribution of the data with a theoretical distribution expected if the variables were not associated. If the result of the comparison is statistically significant (p-value/sig. > 0.05), then we say that the two values are associated. In the case of nominal variables (categories with no intrinsic order, e.g. gender or type of treatment), Cramer's V, an indicator of the strength of association between the two variables, is calculated from the $\chi 2$ value. Its value is always between 0 (independent variables, no association) and 1 (dependent variables, perfectly associated).

Phi and Cramer's V Phi is a chi-square based measure of association, which involves dividing the chi-square statistic by the sample size and taking the square root of the result. Cramer's V is a chi-square based measure of association.

To compare differences between the mean values of two populations or samples, the t-test is used (for more than 30 observations in each population/sample the results of the t-test are identical to those of the z-test).

If it is desired to compare the means of two variables for the same sample, the t-test for dependent samples (or pairs) is used. It tests for differences obtained for the same respondents, either for two comparable behaviours (e.g. year of psoriasis diagnosis vs year of hp exam) or at two different points in time (e.g. to test the impact of a treatment, comparing before and after values).

In order to test for differences between the means of two independent samples (e.g. a group of patients with and without treatment) it is necessary to test for homogeneity of variances beforehand, because the value of the t-test is calculated differently depending on

whether the assumption of equality of variances is accepted or not. The test used for this purpose is the Levene test. If the Sig. value for this test is greater than 0.05, then the variances are considered equal and the interpretation of the result for the t-test is made using the line for the Levene's test conclusion. The difference between the means of the two communities studied is significant if the Sig. value for the t-test is less than 0.05. The confidence interval for the difference comprises the possible values, with a probability of 0.95, of the difference between the general populations from which the samples on which the analysis is based are drawn.

ANOVA can be considered an extension of the t-test in that it can be used to test differences between more than two samples/populations. As with the t-test, before interpreting the ANOVA results, it is necessary to determine whether or not the variances in the groups analysed are equal. This is important because one of the necessary conditions for obtaining reliable results using ANOVA is that of homogeneity of variances. If this condition is not met, alternative methods will be used to test for differences between group means that are robust to failure to meet the homogeneity of variances condition.

The hypotheses tested in the ANOVA and its robust variants are as follows:

- H0: all group means are equal (no statistically significant difference between group means) - sig.>0.05
- H1: there are statistically significant differences between at least two group means - sig.≤0.05

It becomes clear from the hypotheses tested using the method that using ANOVA we can only find out if there are differences between at least two group means, but we will not have information on which means differ and how many pairs of means are significantly different. To compensate for this shortcoming, ANOVA has been supplemented by post-hoc tests, which determine the statistical significance of differences between all possible combinations of the grouping factor (the one on the basis of which the groups are formed).

Post-hoc tests are also sensitive to equality of variances, so depending on the result of Levene's test, we used Tuckey's b for equal variances and Dunnett's T3 for unequal variances. Using the first post-hoc test we create homogeneous subsets of group means. Basically, for each subset the rule is that there are no statistically significant differences between the group means in the subset, but they differ significantly from the means outside the subset. For the second test, the significance of the difference between each combination of two groups is tested.

Results and discussions

In this paper we collected data on 296 patients, 129 (43.6%) women and 167 (56.4%) men.

Patients in the study had a mean age of 54.1 ± 13.96 years, with a median of 55 years (interpercentile range is 44.25-65), the minimum value being 15 years and the maximum value being 90 years.

The majority of the patients investigated in the study were from urban areas (82.4%).

The most common drugs used in biological therapy were adalimumab (18.9%), ixekizumab (18.9%), etanercept (15.2%) and risankizumab (12.8%).

40.5% of patients had anti-TNF therapy and 59.5% of patients had anti-IL therapy.

The majority of the patients had only one therapy administered (77.7%) (thus having no therapeutic switch), 15.2% of patients had 2 therapies (having one therapeutic switch), 6.1% of patients had 3 therapies (having 2 therapeutic switches) and 3 patients (1%) had 4 therapies (having 3 therapeutic switches).

Out of the total of 296 patients, 17.9% of the patients analysed had arthritis. Differences between groups were statistically significant according to Fisher's test ($p<0.001$), showing that patients with anti-IL therapy were significantly more frequently associated with arthritis (83% vs. 54.2%) compared to patients with anti-TNF therapy (45.8% vs. 17%).

The age distribution in both groups was normal according to the Shapiro-Wilk test ($p>0.05$). Differences between groups were observed to be statistically significant according to Student's t-test ($p=0.002$), patients with arthritis had a significantly younger age (48.66 ± 13.36 years) compared to patients without arthritis (55.29 ± 13.83 years).

In the arthritis patients on treatment with novel molecules group, methotrexate (MTX) was added to 3 (6.4%) patients. In addition, MTX was also added to 3 (1.2%) of 243 patients without arthritis. Although the proportion of patients with arthritis to whom MTX was added was not statistically significantly higher than that of patients without arthritis to whom MTX was added, there was a trend towards statistical significance between the two groups, as expected, $p=0.053$ by Fisher's exact test.

Out of 287 patients*, 50 patients had arthritis and 237 had no joint involvement. Of the 53 patients with joint involvement, 28 (56%) patients had no involvement of particular areas

and the rest had scalp involvement together with other locations (26% patients), only 9 (18%) patients had nail involvement and other locations. There is a statistical significance between joint involvement and presence of special areas ($p<0.001$). (*9 patients did not have confirmed/unconfirmed presence of special areas involvement in medical documents). Our group of patients showed scalp involvement together with other disease locations in 26% of patients. There is a statistical significance between joint damage and the presence of special areas ($p<0.001$). It is a location associated with arthritis risk also in international studies. Yang et al. and Zanolli et al. in studies of 1928 and 459 patients with psoriasis, respectively, demonstrated an increased prevalence of PsA (psoriatic arthritis) in those with scalp lesions compared to those without (90.2% vs. 76.4%, P=0.001, respectively 87% vs. 72%, P=0.0237) [16]. Early onset of arthritis had scalp lesions as a clinical manifestation, and this early joint damage was associated with the axial form in men, respectively family history of psoriatic disease in women [17].

The first group consisted of patients with psoriasis vulgaris without biological treatment and the second group included patients with psoriasis vulgaris with biological treatment (anti-TNF alpha and anti-IL, apremilast).

Regarding the patients with biological treatment, significant differences were observed only in relation to total cholesterol values between week 0 and 24 ($p=0.016$) where values recorded in week 24 (median = 208.4, IQR = 178-237) were significantly higher compared to those recorded in week 0 (median = 199.2, IQR = 173-228).

Differences between groups were observed to be statistically significant according to Welch's test ($p=0.001$), showing that patients with metabolic syndrome were significantly older (62 ± 9.9 years) than patients without metabolic syndrome (53.53 ± 14.05 years). The majority of investigated patients in our study on biologic treatment had an increased BMI value (74.3%). Related to weight gain, patients on etanercept and infliximab treatment demonstrated weight gain at week 12, but returned to baseline weight or lost weight at week 48, unlike adalimumab, which triggered significant weight gain at week 48. Those on ustekinumab showed no change in weight compared to the anti-TNF-alpha class [18].

Of the 296 patients on biological therapy, 6.1% of the patients analysed had HBV infection.

Differences between groups were statistically significant according to Fisher's test ($p=0.011$), patients receiving anti-IL therapy were significantly more frequently associated

with HBV infection (88.9% vs. 57.5%) compared to patients receiving anti-TNF therapy (42.5% vs. 11.1%). Patients in Romania diagnosed with active viral hepatitis with HBV receive treatment with entecavir, adefovir, lamivudine or pegylated interferon α-2a. Entecavir is frequently used in combination with other anti-TNF-alpha molecules in patients with HBV. Of the recommended biologic therapies, etanercept is preferred for administration in these cases [19].

Only one patient out of 296 had HCV (undetectable viremia). She is a 74-year-old urban patient, overweight (BMI =29.7 cm/m2), with psoriasis vulgaris since 2001, histopathologically confirmed in 2001, who started treatment with Etanercept in 2010, who underwent chemoprophylaxis following a positive Quantiferon Gold test. No other comorbidities as per Appendix 2. As a single case statistical analysis was not required.

Of the 296 patients, 34.8% of patients tested positive for tuberculosis with the Quantiferon test. Differences between groups were statistically significant by Fisher's test (p=0.019), males in the study were significantly more frequently associated with a positive test result (66% vs. 51.3%) compared to females (48.7% vs. 34%). Differences between groups were statistically significant by Fisher's test (p=0.001), with rural patients being associated with a significantly more frequent positive test result (28.2% vs. 11.9%) compared to urban patients (88.1% vs. 71.8%). Differences between groups were not statistically significant according to the Fisher test (p=0.708), so the frequency of a positive Quantiferon test result was not significantly more frequently associated with a specific biological therapy. Differences between groups were observed to be statistically significant according to Student's t-test (p=0.002), patients with positive test result had significantly higher age (57.53 ± 12.71 years) compared to patients with negative test result (52.27 ± 14.27 years).

Only 1.7% of the patients analysed had tuberculosis. In our study, one patient with psoriasis vulgaris developed tuberculosis while undergoing treatment with etanercept, and the literature (Kumar et al [20]) revealed that out of 40 cases treated with etanercept, 2 patients had tuberculous lymphadenitis, and out of 77 patients with spondyloarthritis, one patient developed pleural effusion of tuberculous etiology after treatment with biosimilar etanercept [21].

In another report, 10 (5.2%) of 193 patients had a positive QuantiFERON test after starting biologic therapy for psoriasis vulgaris over 11 years. Only 1 patient on infliximab treatment developed active TB [22], in contrast to our study where 2 patients developed active TB on infliximab treatment. Megna M. et al. showed only 3 out of 570 patients (0.5%) with

QuantiFERON test positivity after initiation of anti-TNF-alpha therapy over a mean of 4.8 years [23]. In our study, among the 53 patients with arthritis, only one patient (2.1%), while in patients without arthritis, the QTF test was positive in 12 (4.8%) patients, but there was no statistically significant difference between the two groups, p=0.70 by Fisher's exact test.

Out of 296 patients examined, only 9 patients were diagnosed with a neoplasm. Differences between groups were statistically significant according to Fisher's test (p=0.042), noting that patients on anti-TNF therapy were significantly more frequently associated with neoplasia (83.3% vs. 39.6%) compared to patients on anti-IL therapy (60.4% vs. 16.7%). 2 patients were not included in the statistical analysis, being on Apremilast treatment, due to lack of statistical significance. Of the anti-TNF-alpha class, etanercept and adalimumab therapies had a significant risk of NMSC, particularly SCC, compared to the general US population, without increasing the risk of other cancers [24].

Out of 296 patients with psoriasis vulgaris: 2 patients also associated hidradenitis suppurativa, 1 patient with ulcerative colitis, 3 patients with vitiligo, 5 patients with autoimmune thyroiditis, 2 with spondyloarthritis, 1 patient with rheumatoid arthritis.

The 2 patients with hidradenitis suppurativa (HS) started biological treatment when they had no active HS lesions. They were treated with adalimumab >2 years, similar to patients included in the study by R. Blanco et al [25], but with a different therapeutic schedule: they used 40 mg every 2 weeks, similar to Moul DK et al. [26] while in the study by R. Blanco et al. [25] patients received 40 mg of adalimumab every week. Our patients did not develop severe adverse effects such as facial or lumbosacral infectious cellulitis, epidural abscess compared to previous reports [25].

For our patient with ulcerative colitis we opted for risankizumab treatment because Th17 lymphocytes play a role in the pathogenesis of psoriasis vulgaris and IBD, but anti-IL-17 therapy is not recommended in the treatment of IBD. Many biologic therapies, interleukin 23 inhibitors are effective in both conditions, highlighting common immunological mechanisms [27].

The patients in the study did not report the repigmentation of vitiligo lesions when following a particular biological therapy and also following classical therapy for vitiligo. Biological treatment was used successfully in one patient with psoriasis vulgaris and vitiligo. Secukinumab resulted in remission of psoriasis and vitiligo lesions (hyperpigmentation),

although the patient developed depigmented linear lesions histopathologically diagnosed as lichen striatus [28].

In contrast to the current study group of 296 patients, where we had only 5 cases of autoimmune thyroiditis, only female patients, Vassilatou E et al, showed from a group of 114 patients with psoriasis the frequency of autoimmune thyroiditis was similar between females and males with psoriasis [11/114 (9.6%) vs. 12/114 (10.5%) [29].

We report 3 cases of paradoxical reactions to biologic therapy (ixekizumab pen, without citrate). We also report for the first time a case of paradoxical reaction in the form of palmoplantar pustular psoriasis to secukinumab in a patient with ankylosing spondylitis. Paradoxically, EL-Komy et al. described a case in which secukinumab retreatment was associated with the development of psoriasis and pustular rash in a 46-year-old woman. For financial reasons, the patient had to stop anti-IL-17 therapy for 7 months. When secukinumab was reintroduced, the psoriasis lesions started to reappear, with few plaques in the lower limbs, with pustular lesions on the surface. In contrast to our patient, the author increased the dose of secukinumab and achieved remission of skin lesions [30].

Conclusions and personal contributions

- The PhD thesis highlighted in the first study developed the importance of affecting special, hard-to-treat areas in the management of psoriatic disease. In our report, correlations were made between the severity of these areas, especially the scalp location and joint-type damage in the patients studied;
- The second study enunciate the cardiovascular protective role that innovative biological molecules can have in the context of reducing lipid profile values in patients affected by psoriasis vulgaris;
- Screening for HBV and HCV viral infections in the psoriasis patients included did not identify any cases of HBV reactivation. However, all patients with low anti-HBs antibodies were given prophylactic antiviral therapy;
- The study which aimed to identify patients at risk for reactivation of latent tuberculosis infection or de novo development of this disease identified one case of tuberculosis in a patient on etanercept treatment and 2 cases of tuberculosis during infliximab therapy. As is well known, the therapeutic class who poses a real risk for the development of such pathology remains the class of TNF α blockers, especially Infliximab;
- Analysis of the subjects included in this study revealed the general neoplastic status in these patients treated with biological therapies. The majority of psoriasis patients developed neoplasia during biologic therapy with TNF α inhibitory agents;
- In this study, the first of its kind in Romania to my knowledge, we studied the correlations between psoriatic disease and other autoimmune or immune-mediated diseases, their frequency of occurrence and their nature in the studied group;
- Finally, the last analysis, also the first of its kind in our country, identifies the presence of paradoxical reactions in psoriasis patients on biological therapies in the cohort studied. The results show a higher proportion of these reactions among interleukin inhibitors.

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