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Study protocol

"Impact of clinical and psychological factors on treatment satisfaction in psoriatic patients in biological therapy"

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ACRONYM STUDY: PSOSAT

1. Summary of the study

Psoriasis is an inflammatory disease with a chronic-relapsing course with a significant impact on the physical and mental well-being of patients. Fortunately, in recent years, the introduction of increasingly selective biological therapies has allowed to obtain an excellent control of the disease, with high rates of complete (PASI100) or almost complete (PASI90) remission in treated patients.

At the same time, however, various studies have shown that the quality of life of these patients and satisfaction with these therapies do not always correlate with the high levels of effectiveness of these drugs and this often represents a limit, as it has negative feedback on adherence to treatment.

This study aims to identify, through the use of questionnaires, demographic, clinical and psychological factors that could better correlate with the satisfaction of psoriatic patients in systemic therapy with biological drugs for more than a year belonging to the Dermatology Clinics of the A. Gemelli-IRCCS University Hospital.

1. Scientific background

Psoriasis is a chronic inflammatory disease with a significant impact on the quality of life of those affected. The introduction of monoclonal antibodies directed against key cytokines in the pathogenesis of the disease has so far allowed to obtain excellent results not only in terms of objective clinical response (PASI90, PASI100), but also in terms of quality of life (DLQI) thanks to the speed of action, the long-term response and the better safety profile compared to so-called "traditional" drugs, such as cyclosporine, methotrexate and acitretin.

Patient satisfaction is one of the main elements to ensure the success of a systemic therapy for a chronic disease such as psoriasis, as it is closely related to adherence to treatment.

Although the literature suggests that treatment satisfaction derives mainly from objective data such as the extent of residual disease, there are no unequivocal data on which values of the disease severity index (PASI) are associated with greater patient satisfaction. Recent studies have also shown that a certain percentage of patients who achieve optimal responses with biological therapies (PASI90, PASI100, absolute PASI <2), still report an impact of the disease on their quality of life (assessed by DLQI) (2021 Life Basel Kirsten et al Which PASI OutcomeIs Most Relevant to the Patients in Real-World Care?) This paradox has been partly explained by the localization of residual disease in so-called sensitive sites and by the presence of a possible associated symptomatology, but it is still partially unexplored how the psychological profile of the patient can influence this aspect. (DermatolTher 2022 Lebwol M. et al "Evolution of Patient Perceptions of Psoriatic Disease: Results from the Understanding Psoriatic Disease Leveraging Insights for Treatment (UPLIFT) Survey").

In particular, it remains to be clarified the weight of some psychopathological characteristics of patients and how these can negatively affect the quality of life and consequently satisfaction with treatment.

On the other hand, it is known that there is an increased prevalence of numerous psychiatric pathologies in psoriatic patients: depression, bipolar disorder, anxiety, psychosis, cognitive impairment, sexual disorders, sleep disorders, eating behavior and personality disorders. (Rev. Neurosci 2018 Amanat M. et al "Neurological and psychiatricdisorders in psoriasis").

With regard to personality alterations, several studies have shown an increased prevalence (37.4%) of a particular personality profile, Type D, in patients with psoriasis: this is a personality profile characterized by negative emotionality, often associated with a higher incidence of psychiatric diseases (such as anxiety and depression) and which could affect satisfaction with therapies.

1. Objectives of the study

Primary objective

The primary objective of the study is to evaluate the effect of objectively measurable clinical variables such as:

1. age of onset and duration of illness
2. the presence of comorbidities
3. possible combination with other treatments
4. the residual localization of disease
5. the presence/absence of psoriatic arthritis

6. the residual PASI
7. PASI improvement compared to baseline
8. DLQI
9. DLQI improvement compared to baseline
10. the achievement of an optimal response in terms of:
    1. ABSOLUTE PASI <2
    2. 90% and 100% reduction in PASI score from baseline
    3. DLQI between 0-5

on satisfaction with the treatment of psoriatic patients, who have been on therapy for at least a year with a biological drug. Satisfaction will be expressed in terms of the score derived from the Treatment Satisfaction Questionnaire for Medication (TSQM-9).

Secondary objective

As a secondary objective, the relationship of specific psychopathological characteristics (Type D personality, Depression) with treatment satisfaction will also be evaluated.

Duration design and setting of the study

It is an observational study with monocentric drug.

The study will last 12 months including enrolment and will begin after the ethics committee has delivered a favourable opinion.

It will be conducted at the Institute of Dermatology and Venereology of FPG.

1. Study population

Patients diagnosed with psoriasis belonging to the Dermatology and Venereology clinics of FPG already treated with a systemic biological drug for at least one year will be included.

Inclusion criteria:

-Patients with age>18 years, of both sexes;

-Diagnosis of plaque psoriasis, with or without concomitant arthritis;

-Patients who have been receiving systemic biologics for at least one year and have disease severity (PASI) and quality of life (DLQI) data available at baseline (prior to initiation of treatment);

-Signature of the written informed consent;

Exclusion criteria:

-Presence of a psychiatric pathology already diagnosed

-Patients with psoriasis variants (pustular, guttate, palmoplantar)

1. Tools and Variables

For each patient, the basic socio-demographic characteristics (age, sex, level of education) and the presence of comorbidities, any comedications, age of onset and duration of illness will be recorded. The severity of psoriasis at the time of enrollment will also be evaluated: absolute PASI at the time of enrollment, possible presence of disease localizations in "special" locations (scalp, nails, genitals, palmoplantar), presence or absence of psoriatic arthritis.

We will also record the characteristics of the ongoing biological treatment: PASI at baseline, duration of treatment, molecule, number of systemic therapies previously used, possible concomitant therapy with another systemic drug.

The PASI (Psoriasis Activity and Severity Index) is an index created to assess the severity of psoriatic lesions and their extension through the indication of the percentage of body area that presents lesions and a definition of the intensity of some local signs such as erythema, infiltration and desquamation, psoriasis is considered mild with a PASI <10, moderate if the PASI is between 10 and 20 and severe if greater than 20.

Treatment satisfaction will be assessed using the Treatment Satisfaction Questionnaire for Medication (TSQMv.II). The TSQM-II is an 11-item questionnaire developed to assess treatment satisfaction with any treatment. There are four scales: treatment effectiveness (two elements), side effects (three elements), treatment convenience (three elements) and overall satisfaction (two elements). Patients rate their experiences with treatment during the last 2-3 weeks between "Extremely dissatisfied" and "Extremely satisfied" on five- or seven-point Likert-type scales. Higher TSQM-II scores indicate greater satisfaction with treatment. The questionnaire refers to a period of 2-3 weeks before the time of completion of the questionnaire.

We will also evaluate the psychological structure of patients and in particular the presence of a "Type D Personality" through a special validated questionnaire (DS14) that identifies this type of personality in those who obtain scores of "Negative Affectivity" or "Social Inhibition" higher than

10. In addition, the PatientHealth Questionnaire-9 (PHQ-9) will assess the possible presence and severity of depression by means of a short scale specific to General Practice (Spitzer et al., 1999) consisting of two questions. The first investigates the presence "in the last two weeks" of the 9 symptoms of depression according to the DSM-IV also taken up in the DSM-5. Only this question determines the score of the PHQ-9. Each symptom is assessed on a 4-point scale. The second question assesses the functional impairment that depression causes on the normal course of the patient's life. This question does not count towards the PHQ-9 score.

The PHQ-9 score ranges from 0 to 27. Scores between 5 and 9indicate the presence of a subthreshold depression. The score of 10 is the optimal cut-off to highlight clinically relevant depressions (Gilbody et al., 2007) with three different levels of severity depending on the score (MacArthur & MacArthur, 2009).

Finally, the dermatological quality of life will be evaluated through DLQI (Dermatology Life Quality Index), a questionnaire of 10 questions that evaluates with a score from 0 to 30 the impact of the disease on the patient's quality of life (a score higher than 10 identifies a strongly compromised quality of life)

1. ENDPOINT

Primary ENDPOINT

Effect of objectively measurable clinical variables on satisfaction - assessed by TSQMv.II - towards treatment, in a sample of psoriatic patients who have been treated for more than one year with a biological drug. This evaluation will be carried out by:

1. the possible localization of the residual disease, measurable through the quantitative definition (body surface area-BSA: percentage of skin surface area with disease residue) and

qualitative (PASI) of the disease residue compared to baseline;

2. the improvement of the PASI and DLQI scores compared to the baseline, quantifiable through the measurement of the difference between the score at the last clinical reassessment (Tlast) and the score at the baseline (T0) (respectively delta PASI and delta DLQI);

3. the evaluation of the efficacy of the treatment in terms of i) proportion of patients who achieve a reduction of 50%, 75%, 90%, 100% of the PASI score (PASI50, PASI75, PASI90, PASI100) compared to baseline, ii) achievement of an absolute PASI <2 at the last clinical reassessment (Tlast), iii) proportion of patients achieving a DLQI between 0-5 at the last clinical re-evaluation (Tlast);

effect/association of clinical factors on/with satisfaction at treatment;

Secondary ENDPOINT

The impact of psychopathological characteristics on treatment satisfaction, assessed by TSQMv.II, will be carried out through:

4. Evaluation of the psychopathological effect of psoriasis on the patient using questionnaires: PatientHealth Questionnaire-9 (PHQ-9) and DS14

1. Safety/adverse event management

Definitions

"Adverse event" means any harmful clinical event that occurs in a person who has been given a medicinal product and who does not necessarily have a causal relationship with such treatment.
"Adverse reaction" means the unintended and unintended reaction resulting not only from the authorised use of a medicinal product under normal conditions of use but also from medication errors and uses not in accordance with the indications given in the marketing authorisation, including misuse and abuse of the medicinal product.
"Serious adverse reaction" means an adverse reaction that causes:
-death
- life threatening,
- hospitalisation or prolongation of hospitalisation,
- severe or permanent invalidity,
- congenital anomalies/birth defects,
- other clinically relevant condition.

Management of adverse events

All adverse events will be collected, recorded and evaluated by severity and relationship to investigational and non-investigational medicinal products for the purpose of identifying suspected adverse reactions.

Any suspected adverse reaction will be reported to the National Competent Authority - AIFA, regardless of the severity, according to the post-marketing pharmacovigilance flow, provided for by DM 30 April 2015 and GVP (Good Vigilance Practices) module VI, by communication to the Local Pharmacovigilance Manager for inclusion in the National Pharmacovigilance Network and, where required, to the Ethics Committee.
Suspected adverse drug reactions should be reported to the Local Pharmacovigilance Manager within 48 hours of becoming known, and suspected adverse reactions from biological medicinal products should be reported no later than 36 hours.

9. Statistical analysis

Sample size

The calculation of the sample size was carried out taking into account the subgroup analysis carried out by Schaarschmidt et al (Acta DermVenereol 2015) which evaluated the associations between

sociodemographic characteristics, disease severity and duration of the same with treatment satisfaction, expressed in terms of TSQM score. In this work a DLQI score between 0-5 is associated with a higher average TSQM score.

Considering a significance level (α) of 0.05 and a potency (1-β) of 0.80, the estimated sample size for each of the two subpopulations (patients with DLQI between 0-5 and greater than 5) is 52.

We therefore estimate to include in our study at least 104 patients with psoriasis who have been treated for at least one year with biological drugs.

Statistical analysis

Categorical variables will be described as absolute frequencies and percentages, while variables continuous as mean and standard deviation (±SD) and in the case of non-Gaussian distribution as median and interquartile range (IQR).

Several optimal response endpoints will be considered and compared: absolute PASI <2, 90% and 100% reduction in PASI score compared to baseline after one year of treatment (PASI 90, PASI 100), DLQI improvement >4 points, DLQI achievement between 0-5.

The ANOVA test (analysis of variance) followed by the Tukey HSD, Bonferroni, Sidak or Scheff tests to adjust the p value in the case of multiple comparisons, will be used to perform subgroup analysis and satisfaction assessed by TSQM score. You will consider transformations of the TSQM satisfaction score to obtain a normal distribution. Subgroup analyses to compare the best treatment ever obtained by participants will be performed with the χ2 test or with the exact Fisher test for small numbers of participants within the subgroups.

Multivariate linear regression analysis will be performed to estimate the association between the

TSQM defined as dependent variable and the BSA score (%), residual PASI (both as continuous and categorical variable i.e. PASI<2 versus PASI>=2), delta PASI (continuous variable), proportion of patients who achieved PASI50, PASI75, PASI90, PASI100, DLQI (both as a continuous and categorical variable i.e. DLQI 0-5 versus DLQI>5) and delta DLQI (continuous variable), possible presence of depression (presence / absence and level of severity if present), possible presence of type D personality, defined as independent variables, considering sex, age (in years) duration of the disease (in years), possible presence of psoriatic arthritis (yes / no), possible presence of disease localizations in "special" sites (scalp, nails, genitals, palmoplantar) (yes / no), possible combination of the biological drug with a traditional systemic therapy (yes/no) as confusing.

A standardized regression coefficient β will be calculated for each independent variable, which indicates the magnitude of the change in the TSQM as the respective variable changes, keeping the others constant.

In addition, a ROC curve with a logistic regression model will be estimated, inserting the TSQM (dichotomous variable of global satisfaction >=75 and <75, Mekies C et al. Patient Preference and

Adherence, 2018) as an objective variable and the residual PASI score as an explanatory variable, the psychological profile of the patient both in terms of presence/absence of personality D-trait and PHQ-9 score as covariates, to evaluate the cut-off value of the PASI score using the Youden index.

The unmatched data test will be used to perform bivariate analyses on the effects of sex, age, PASI, DLQI, disease duration, psoriatic arthritis on satisfaction assessed by TSQM score. Subgroups will be defined according to gender, age (< 50 or ≥ 50 years), PASI (<2 or >=2), DLQI (0-5 or > 5), duration of disease (0-10 or > 10 years) and presence or absence of psoriatic arthritis.

Associations and differences will be considered statistically significant with a $p \leq 0.05$.

All analyses will be performed with the software STATA/BE v.17.0