

# Psoriasis: gender perspective on disease characteristics and treatment

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**Summary.** Psoriasis is a chronic multifactorial skin disease, characterized by inflammation and a strong genetic predisposition. The prevalence of psoriasis ranges between 0.4 and 5% worldwide. Psoriasis is often associated with a poor quality of life and high physical and psychosocial burden. Several therapies are now available for the treatment of psoriasis. Patients are treated with different drugs, depending on the severity of disease, as indicated by the PASI (Psoriasis Area Severity Index) score. Mild-to-moderate subjects are usually treated with topical treatments, while moderate-to-severe psoriatic patients often require systemic treatments. Among the systemic drugs, biological therapies have been revolutionizing the treatment of psoriatic patients. These are target-specific drugs, mainly monoclonal antibodies and receptor fusion proteins. Biologics are able to improve therapeutic outcomes, and have a favorable tolerability. Biological therapies used in psoriasis include antagonists of cytokines or their receptors, such as anti-TNF agents, anti-IL12/23, anti-IL17, anti-IL17-receptor, and anti-IL23 antibodies. Biologic agents lead to a significant improvement in symptoms; however, psoriasis remains a condition with no permanent resolution. Thus, innovative mechanisms of action are currently being investigated, in order to identify new possible therapeutic targets. The prevalence of psoriasis among men and women is known to be balanced. However, the severity of the disease can vary between genders: several studies show that, in fact, female patients are less severely affected by psoriasis than males. The median PASI score is often lower in women, regardless of age, thus female patients receive systemic treatments less frequently. However, in many cases women suffer from a greater psychological distress. For all these reasons, physicians should consider gender perspective in the management of psoriatic patients and their comorbidities. No clear differences have been observed in the response to treatment of psoriatic patients, regardless of their lifestyle, race/ethnicity, geographic location or gender. In spite of their higher cost, biologics are currently the treatment of choice of moderate-to-severe psoriatic patients, due to their favorable safety and efficacy profiles.

**Keywords.** Psoriasis, biological therapies, gender, treatments, quality of life.

**Psoriasi: caratteristiche, trattamenti e differenze di genere**

**Riassunto.** La psoriasi è una patologia infiammatoria cronica e multifattoriale con una forte predisposizione genetica.

La prevalenza della psoriasi varia a livello globale tra lo 0,4 e il 5%. I pazienti affetti da psoriasi spesso hanno una bassa qualità di vita, poiché la malattia ha un impatto molto grave a livello sia fisico sia psicologico.

Diverse sono le terapie a oggi disponibili per il trattamento della psoriasi. I pazienti psoriasici sono trattati con farmaci differenti in base alla severità della malattia stessa, misurata tramite il PASI (*Psoriasis Area Severity Index*). I pazienti affetti da psoriasi lieve o moderata sono generalmente curati con trattamenti topici, mentre quelli affetti da malattia moderata o severa richiedono spesso trattamenti sistemici.

Tra i farmaci sistemici, le terapie biologiche hanno recentemente rivoluzionato il trattamento dei pazienti psoriasici. I biologici includono anticorpi monoclonali o proteine di fusione, sono target-specifici e hanno un profilo di tollerabilità favorevole. I farmaci biologici utilizzati nella psoriasi appartengono a diverse classi, e includono antagonisti delle citochine e dei loro recettori, come per esempio anticorpi anti-TNF, anti-IL12/23, anti-IL17, anti-recettore dell'IL17 e anti-IL23. Le terapie biologiche portano a un importante miglioramento dei sintomi clinici, tuttavia la psoriasi rimane una patologia senza una cura definitiva. Per questo motivo, si stanno tuttora studiando meccanismi di azione innovativi, allo scopo di identificare nuovi potenziali target terapeutici.

Diversi studi hanno evidenziato che la prevalenza della psoriasi è simile tra uomini e donne. Tuttavia, la severità della malattia può avere delle differenze di genere: la letteratura riporta di frequente che le donne sono affette da patologia meno severa rispetto agli uomini, e mostrano un livello medio di PASI inferiore, indipendentemente dall'età. Per questo motivo le donne sono meno frequentemente trattate con terapie sistemiche rispetto agli uomini, malgrado spesso la malattia abbia un impatto psicologico maggiore su di loro. Per tutte queste ragioni, i dermatologi dovrebbero tenere sempre in considerazione la prospettiva di genere nella gestione dei pazienti psoriasici e delle loro comorbidità.

Infine, non sono state evidenziate differenze chiare nella risposta ai trattamenti dei pazienti con psoriasi, a prescindere dal genere, ma anche dallo stile di vita, dalla razza o dall'etnia e dalla localizzazione geografica.

I biologici sono attualmente i trattamenti d'elezione per i pazienti affetti da psoriasi moderata o severa, grazie al loro favorevole profilo di sicurezza ed efficacia, malgrado i costi più elevati.

**Parole chiave.** Psoriasi, biologici, genere, trattamenti, qualità di vita.

## Introduction

Psoriasis is a chronic systemic disease characterized by skin inflammation. Psoriasis is immune-mediated, therefore it involves dendritic cells, T cells and Tumor Necrosis Factor  $\alpha$  (TNF- $\alpha$ ). There are several clinical phenotypes of psoriasis, with chronic plaque accounting for 90% of cases.

Psoriasis is a wide-spectrum disease characterized by a variable morphology, extension, severity, and development. It is a papule-squamous disease that can involve different body areas and can display different cutaneous manifestations. Well-demarcated erythematous plaques – covered by silvery-white scales that typically occur in the elbows, knees, trunk and scalp, with a symmetrical distribution – are the most frequent features of psoriasis.<sup>1,2</sup>

It has been demonstrated that both genetic and environmental factors could be responsible for this condition. Psoriasis is frequently associated with other systemic comorbidities (i.e., cardiovascular and metabolic changes).<sup>1,3</sup>

The prevalence of psoriasis varies by geographic location, ranging between 0.4 and 5% worldwide. Its onset may occur during pediatric age, and the majority of patients is diagnosed before 40 years of age.<sup>4,5</sup>

Psoriasis is associated with chronic pain, and also presents a high physical and a psychosocial burden, with a significantly negative impact on the quality of life (QoL) of the patients affected, which is often related to the extent of skin lesions.<sup>6,7</sup>

In some cases, psoriatic patients have a very low QoL with regard to patients with other chronic diseases, such as cardiovascular and metabolic. Social exclusion, discrimination and stigma are frequent in psoriatic patients. These factors are associated with a higher rate of depression and suicidal thoughts.<sup>8-10</sup>

The pathogenesis of psoriasis has been deeply investigated during the last decades. The acquired knowledge of the mechanisms underlying this disease led to the discovery and the development of safer and more effectively targeted therapies. These innovative biological drugs have dramatically changed the treatment paradigm of this condition, and are significantly better tolerated than the traditional systemic drugs currently available. Even before the arrival of these new therapies, the psoriasis treatment pattern was wide, and included topical treatments, phototherapy and traditional systemic agents. Such traditional therapies can be combined with the biological ones.

The severity of psoriasis depends on the extension and the location of the lesions, the degree of inflammation and the presence of comorbidities (i.e., psoriatic arthritis), the response to treatment and the impact on QoL. Conventionally, the severity of psoriasis can be established based on the PASI (Psoriasis Area Severity

Index) score. Patients are classified as affected by mild, moderate or severe disease.

Moderate-to-severe psoriatic patients are usually treated with systemic therapies (either conventional or biological), while topical agents are generally used to treat mild-to-moderate subjects. However – despite several therapies to treat this disease and its manifestations are helpful in mitigating the symptoms – a permanent cure for psoriasis is not available yet.

Biological therapies are designed and developed to target specific pathogenic immunological pathways [including tumor necrosis factor (TNF), interleukin (IL)-12/23, IL17 and IL23]. This specificity leads to the favorable therapeutic outcomes and tolerability of biologics. These compounds, in particular the anti IL17, have a rapid action, and the improvements in the patients' symptoms are indeed visible already in the first weeks of treatment. Anti-TNF compounds, instead, have a slower effect, but in 3 months they also achieve a visible improvement in the patient's symptoms.

The management of psoriatic patients is sometimes complicated by the presence of comorbidities, which should be carefully considered before choosing a systemic treatment. Indeed, a multidisciplinary approach in the treatment of psoriatic patients with comorbidities is necessary, since these patients have higher hospitalization rates and mortality.

## Gender perspective

Gender medicine has been achieving a steadily increasing importance during the last few years. Scientific and medical communities are now contemplating the differences between genders in the management of patients, particularly in the prevalence and severity of diseases, and in the treatment dosage and outcomes.

It is well known that the prevalence of psoriasis in the population is balanced between males and females, despite the higher prevalence in the latter of autoimmune chronic inflammatory diseases,<sup>11,12</sup> in particular those involving skin and joints.<sup>13</sup> In fact, it has been demonstrated that women have a more reactive immune system. This characteristic may be favorable during the response to infective pathogens, but it could also cause a higher susceptibility to autoimmunity. Differences in immunity between men and women can be explained both by X-encoded genes and the hormonal profile.<sup>14-17</sup>

The GENDER ATTENTION study was designed to investigate the influence of gender and the hormonal profile in psoriatic patients treated with cyclosporine.<sup>17</sup> This is a prospective study involving fertile and menopausal women, conducted to evaluate the number and severity of adverse events in an Italian clinical practice setting. Since cyclosporine dosage is weight-dependent,

this can be a good model to evaluate the potential differences between genders during treatment. Nine hundred patients were enrolled, the majority of whom developed only mild or moderate adverse events. Fertile women displayed a higher number of mild adverse events than postmenopausal ones. The occurred adverse events included neurological, musculoskeletal, gastrointestinal, metabolic and cutaneous symptoms. The adverse events incidence rate was slightly higher in women than age-matched men for both fertile and postmenopausal females (37% and 18%, respectively). However, these differences were not statistically significant. A statistically significant result was observed in the adverse event incidence rate ratio of fertile vs postmenopausal women (0.67; 95% CI 0.49-0.92). Furthermore, both men and women without any adverse event showed statistically different hormone levels, compared to patients with at least one adverse event reported. In particular, postmenopausal women with no events showed higher levels of follicle-stimulating hormone (FSH) and cortisol, and men with no events had dehydroepiandrosterone (DHEA) sulfate levels 10% higher than patients with adverse events. Together, all this data suggests the potential influence of the hormone profile on the tolerability of cyclosporine treatment.

In general, it is important to evaluate the impact of gender and hormones on the response to drugs, in order to conveniently tailor pharmacological treatments to each patient. This point should be addressed in future studies, in order to have a clear evidence on how hormones could affect treatment choices.

Furthermore, other differences between genders are reported in the literature for psoriatic patients.<sup>18</sup> Disease severity is usually higher in men than in women, as reflected by higher PASI scores. This can affect both the type of treatment and the outcomes.

A cross-sectional observational study was performed using the Swedish national registry of psoriasis systemic treatment (PsoReg). This study enrolled 5,438 patients with moderate-to-severe psoriasis. Women showed statistically significant lower median PASI scores than men, regardless of their age and the treatment received before enrollment. This difference is consistent in all affected areas, except for the head.<sup>19</sup>

Differences in the severity of psoriasis and its clinical characteristics were observed. Male patients generally have a higher BMI and bad lifestyle habits (higher alcohol consumption and smoking).<sup>20</sup> The onset of psoriasis is at  $\geq 20$  years of age in men, and their PASI score is  $\geq 10$  at baseline. Conversely, women show a more frequent joint involvement and family history of diabetes, and they often have different clinical type of psoriasis.

Psoriasis-associated comorbidities have a different prevalence between genders. Indeed, it was noted that dyslipidemia is more frequent in moderate-to-severe

psoriatic male patients, while a greater percentage of females is affected by hypertension.<sup>21</sup>

Furthermore, it was previously reported that male psoriatic patients have a lower incidence of psychosocial morbidity than women.<sup>22</sup> However, a recent study reports that no gender differences are observed in the appearance and socialization life aspects, but men are usually affected by a more severe work-related stress.<sup>23</sup>

With regard to QoL, some studies demonstrated that women have a lower quality of life than men, since they suffer from greater psychological distress. An online survey among 3,164 psoriatic patients showed that pruritus was the most disabling QoL-limiting factor, particularly for female patients.<sup>24</sup>

An Italian study shows that, among the 936 psoriatic patients hospitalized, females have a poorer QoL, and suffer from depression or anxiety.<sup>25</sup> This study suggests the importance of paying attention to the psychological aspects of the patients affected by psoriasis. Indeed, clinical severity could be associated with higher distress and lower QoL.

Men and women affected by psoriasis also showed differences in the burden of disease and in treatment needs. Significant differences between genders in patients' needs and expectations were observed. Female patients rated 20 out of 25 parameters as more important. Relevant differences were reported in depression, sleep quality and everyday productivity. This study underlines the importance of an individualized and targeted therapy.<sup>26</sup> A multicenter Italian study (PSYCHAE) showed that female psoriatic patients suffer from a psychological distress more than males, regardless of the severity of the disease.<sup>27</sup> Furthermore, a Sweden annual report including 2,450 psoriatic patients compared men and women based on the treatment prescribed and the disease characteristics. No gender differences were observed in the level of treatment; however, a greater burden of disease was observed in women, since they showed a significantly higher score on subjective activities than men.<sup>28</sup> This result could be explained by the fact that physicians usually do not take into account subjective measures during the choice of treatment, resulting in an under-treatment of female patients.

Gender differences were observed also in the choice of the physician. A questionnaire filled by 1,060 patients showed that female patients visit their general practitioner more frequently, while men rely on dermatologists.<sup>29</sup> Both women and men expect to achieve an improvement of the disease (80%), rather than a cure (20%). They also have the same expectation with regard to receiving information about self-treatment and professional care; however, female patients give more importance to the politeness of the physician than men. Both sexes' expectations are fully met; nevertheless, almost half of the men interviewed reported that they did not achieve the level

of improvement expected. Finally, the results highlighted that men consume more healthcare resources than women, while the latter incur higher out of pocket expenditures. Gender differences were also observed in the response to biologic treatments. A US study on the CORONA registry showed that female patients usually have a lower response ( $p = 0.46$ ) to anti-TNF $\alpha$  molecules (adalimumab, etanercept or infliximab) than males.<sup>30</sup> The same result was confirmed by a prospective English study conducted in a pharmacovigilance cohort of 3,523 psoriatic patients (BADBIR study). The study was designed to assess the factors predicting the survival rate of biological therapies. The multivariate analysis showed that current female smokers who have a higher baseline DLQI index usually present a higher rate of discontinuation of anti-TNF $\alpha$  biologic treatments (adalimumab, etanercept or infliximab).<sup>31</sup> A retrospective analysis (the OSCAR study) enrolled 650 psoriatic patients in Italy. The results showed that being female and being treated with adalimumab or infliximab, together with traditional systemic drugs, were independent predictors of treatment discontinuation.<sup>32</sup> Moreover, to evaluate the reasons for the discontinuation of anti-TNF $\alpha$  biologic drugs, a Cox regression analysis was conducted on the data from the BioCAPTURE registry. Results showed that a higher BMI and female sex are predictors of a higher discontinuation rate, since they cause lower effectiveness and a higher incidence of side effects, respectively.<sup>33</sup>

In a Treatment Satisfaction Questionnaire for Medications (TSQM), the 'side-effects' and 'global satisfaction' domains were used to highlight any differences in treatment satisfaction between genders in patients enrolled in the BioCAPTURE registry. It was observed that, after one year of treatment with biological therapies, men are usually more satisfied than women.<sup>34</sup>

No differences in the incidence of drug-related serious adverse events were generally observed between male and female psoriatic patients. However, a post-hoc analysis on side effects established that women treated with biologics suffered from fungal and herpes simplex infections more than men.

In conclusion, most of the studies showed that male patients are usually more satisfied with their psoriasis treatment, and that they generally respond better to biological therapies, despite often suffering from a more severe disease. Conversely, women seem to usually suffer a greater psychological impact and a lower QoL than men, regardless of the severity of the disease and the level of treatment received. In order to achieve a higher adherence to treatment and more adequate outcomes, the subjective perceptions of female patients deserve more attention.

It is therefore essential to always consider a gender perspective, in order to better manage psoriatic patients and their comorbidities.

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## Key messages

- Psoriasis is a debilitating disease, with a great impact on quality of life (QoL).
- Biological therapies revolutionized the treatment of psoriatic patients, improving symptoms with a favorable tolerability.
- Gender differences have been identified in the severity of psoriasis, but not in its prevalence.
- Female psoriatic patients often have a poorer QoL, and they suffer from a greater psychological distress.



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