

# Concept of Remission in Chronic Plaque Psoriasis

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**ABSTRACT.** Psoriasis is a lifelong chronic inflammatory disease affecting 2–3% of the worldwide population. Current understanding of the pathogenesis of psoriasis assigns central importance to an interaction between acquired and innate immunity. The disease is characterized by a series of linked cellular changes in the skin, including hyperplasia of epidermal keratinocytes, angiogenesis, and infiltration of T lymphocytes, neutrophils, and other types of leukocytes in the affected skin. Plaque psoriasis is the most common clinical form and is characterized by red and scaly plaques generally localized at extensor sites such as elbows and knees. Major determinants of psoriasis severity include the extent of skin involvement; localization in highly affected areas such as scalp, palms, and soles; pruritus; presence of comorbidities including psoriatic arthritis; and impairment on quality of life. About one-third of patients have moderate to severe psoriasis defined as PASI (Psoriasis Area and Severity Index) and/or Dermatology Life Quality Index > 10, and/or affected body surface area > 10%. The optimal treatment goal is to safely achieve complete or almost complete skin clearance. Treatments available are various and they are chosen according to disease features, comorbidities, and patient characteristics and priorities. Topical treatments including corticosteroids and Vitamin D analogs are reserved for mild disease. Phototherapy, cyclosporine, methotrexate, acitretin, or biologics such as tumor necrosis factor- $\alpha$  antagonists and ustekinumab are reserved for the moderate to severe forms. (J Rheumatol Suppl. 2015 Nov; 93:57–60; doi:10.3899/jrheum.150638)

## Key Indexing Terms:

PSORIASIS

COMORBIDITIES

CONVENTIONAL TREATMENTS

BIOLOGICAL THERAPIES

TREATMENT TARGET

Psoriasis is an immune-mediated chronic inflammatory disease affecting 2–3% of the white population, being less common in Asians (about 0.1%), and rarely seen in blacks<sup>1</sup>. It can occur at any age, although the majority of cases occur before the age of 40 years and it is uncommon in children<sup>1</sup>. Psoriasis affects genetically predisposed individuals with 20 chromosome regions harboring psoriasis susceptibility genes<sup>2</sup>. A major locus consistently identified is the class I region of the MHC antigen cluster, which harbors the HLA Cw6, associated with early onset psoriasis as well as better response to ustekinumab therapy<sup>3</sup>. Environmental factors are also involved in the pathogenesis of the disease, including infections, typically pharyngitis caused by *Streptococcus*

*pyogenes*, and drugs such as interferon and lithium salts. The disease is characterized by a series of linked cellular changes in the skin, including hyperplasia of epidermal keratinocytes, angiogenesis, and infiltration of T lymphocytes, neutrophils, and other leukocytes in the affected skin<sup>4</sup>. Current understanding of the molecular pathogenesis of psoriasis assigns central importance to an interaction between acquired and innate immunity<sup>4</sup>. At onset of the disease, plasmacytoid dendritic cells are activated in the epidermis and dermis and produce interferon- $\alpha$  (IFN- $\alpha$ ), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and interleukin 23 (IL-23), which promote development of Th1 and Th17 cells<sup>5</sup>. These T cells secrete several mediators including IFN- $\gamma$ , TNF- $\alpha$ , IL-6, IL-22, and IL-17, which are responsible for inflammatory changes and epidermal hyperplasia<sup>6</sup>.

Plaque psoriasis is by far the most common clinical form of the condition (90% of patients with psoriasis) and is characterized by well-delineated red, scaly plaques. The extent of involvement varies, ranging from a few localized plaques at extensor sites to generalized involvement (Figure 1). Rarely, psoriasis may involve the whole body, leading to erythroderma. Flexural (also known as inverse or intertriginous) psoriasis refers to plaque psoriasis at submammary, groin, axillary, and genital regions, and is typically less or not scaly. Guttate psoriasis is characterized by an acute eruption of small scaly papules, which appear generally after streptococcal infection. Distinctive nail changes occur in around 50% of all those affected and are more common in patients with psoriatic arthritis (PsA). Major determinants of

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Figure 1. Plaque psoriasis disseminated on the back, upper limbs, and sacral area.

psoriasis severity include extent of skin involvement; pruritus; localization in visible areas such as the scalp, palms, and soles; presence of comorbidities; and impaired quality of life<sup>5</sup>. Several epidemiological studies have confirmed that chronic plaque psoriasis is significantly associated with comorbidities including PsA, inflammatory bowel diseases, and cardiometabolic disorders such as myocardial infarction, hypertension, obesity, diabetes, dyslipidemia, fatty liver disease, and metabolic syndrome<sup>7</sup>. Patients with psoriasis have impaired quality of life as well as reduced levels of employment and income<sup>8</sup>. The effects of psoriasis encompass functional, psychological, and social dimensions. Several factors contribute to this burden such as symptoms specifically related to the skin (for example, chronic itch, pain, and scaling), problems related to treatments (messy, unpleasant odor, inconvenient), comorbidities (e.g., pain and functional impairment due to PsA), and the effect of living with a highly visible, disfiguring skin disease (difficulties in relationships and poor self-esteem)<sup>9</sup>.

### Therapy of Chronic Plaque Psoriasis

Psoriasis shows a chronic-relapsing course and requires longterm management. Treatments available for psoriasis are various and they can be topical and systemic (Table 1). Topical therapies include keratolytics, corticosteroids, Vitamin D analogs, retinoids, and topical calcineurin

Table 1. Treatments of chronic plaque psoriasis.

Topical Therapies	Conventional Treatments	Biological Agents
Corticosteroids	Acitretin	Adalimumab
Vitamin D3 analogs	Methotrexate	Etanercept
Topical retinoids (tazarotene)	Cyclosporine	Infliximab
Topical calcineurin inhibitors (tacrolimus and pimecrolimus)	Nb-UVB (311-313 nm) and PUVA	Ustekinumab
	Fumaric acid esters	

Nb-UVB: narrow band ultraviolet B; PUVA: psoralen and ultraviolet A.

inhibitors, which are reserved for mild forms<sup>10</sup>. Phototherapy, which includes either narrow-band ultraviolet (UV) B light and photochemotherapy (i.e., psoralen plus UVA light), and conventional systemic agents such as cyclosporine (CSA), methotrexate (MTX), and acitretin are reserved for moderate to severe cases. In the event of intolerance, inefficacy, or contraindication to phototherapy or conventional systemic treatments, patients are eligible for biological agents, which include TNF- $\alpha$  antagonists [adalimumab (ADA), etanercept (ETN), infliximab (IFX)], or the anti-IL12/23 monoclonal antibody ustekinumab<sup>11</sup>.

The retention rate of biological agents is higher than conventional treatments because they are better tolerated in the case of continuous and longterm treatment<sup>12</sup>. Several elements are considered when selecting treatment for psoriasis, including factors related to the disease, the patient, and the treatment. In particular, disease severity is a driving factor for the choice of a systemic therapy. According to the rule of tens proposed by Finlay, a systemic treatment is indicated when Psoriasis Area and Severity Index score (PASI), and/or Dermatology Life Quality Index (DLQI) is greater than 10, and/or body surface area (BSA) involvement > 10%<sup>13</sup>. However, a systemic therapy could also be indicated in the case of involvement of the most visible or problematic skin areas (i.e., scalp, genitals, palms and/or soles, and nails), high-intensity symptoms such as pruritus, and/or presence of recalcitrant plaques not responsive to topical therapy.

Treatment choice is also influenced by the concomitance of metabolic comorbidities, because MTX, CSA, and acitretin may worsen comorbidities. In particular, MTX should be prescribed with caution in the case of overweight/obese patients, high alcohol consumption, and diabetes mellitus due to the increased risk of developing liver fibrosis<sup>14</sup>. CSA can induce or worsen arterial hypertension, alter glucose tolerance, and/or interfere with fatty acid metabolism, favoring dyslipidemia<sup>15</sup>. Consequently, CSA is contraindicated in patients with well-established metabolic syndrome. Acitretin may induce or worsen either hypercholesterolemia or hypertriglyceridemia. It is also very important to take into account several patient-related factors including age and sex, failure with previous therapies, likelihood of adherence, expectation of remission, and fear of side effects.

Although criteria for selection of a systemic treatment are well established, the undertreatment in moderate to severe psoriasis is still an open issue. A recent population-based, multinational survey of 3426 patients from 139,948 screened households in North America and Europe found that only 11% of patients with affected BSA > 10% were receiving a systemic agent for psoriasis; 52% were receiving topical treatment alone and 37% were untreated<sup>16</sup>.

### Concept of Remission in Psoriasis

The natural course of the psoriasis can be highly variable, from mild or benign to persistent and aggressive forms. Remission of psoriasis is achieved in longterm efficacious control of skin lesions.

In an expert consensus meeting that was carried out to define goals for treatment of plaque psoriasis with systemic therapy and to improve patient care, 19 dermatologists from different European countries met face-to-face for discussion and to define items through a 4-round Delphi process<sup>17</sup>.

For systemic therapy of plaque psoriasis, 2 treatment phases were defined: (a) the induction phase: treatment period until Week 16; and (b) the maintenance phase: for all

drugs, the treatment period after the induction phase. For the definition of treatment goals in plaque psoriasis, change in PASI from baseline until time of evaluation ( $\Delta$ PASI) and absolute DLQI were used. After induction and during maintenance therapy, treatment can be continued if a reduction in PASI is  $\geq 75\%$ . The treatment regimen should be modified if improvement of PASI is  $< 50\%$ . In a situation where the therapeutic response improved  $\geq 50\%$  but  $< 75\%$ , as assessed by PASI, therapy should be modified if the DLQI is  $> 5$ , but can be continued if the DLQI is  $\leq 5$ <sup>17</sup>.

Whether psoriasis remission should be achieved using a continuous or intermittent treatment regimen has not been definitely established. The choice of continuous versus intermittent treatment greatly depends on the drug being prescribed. Regarding conventional therapies, a major limitation for continuous longterm treatment is cumulative toxicity, including liver toxicity from MTX, renal toxicity from CSA, and skin carcinogenesis from phototherapy, particularly psoralen ultraviolet A. In contrast, in the case of treatment with biologics, a continuous regimen has greater efficacy and safety compared to an intermittent regimen<sup>18</sup>. The risk of adverse effects and/or developing antidrug antibodies is significantly higher in those patients receiving IFX and ADA as an intermittent regimen. In contrast, ETN is formally approved for continuous and intermittent regimens because of its lower immunogenicity<sup>19</sup>.

Similarly, it has not been fully investigated whether stopping biological therapy is indicated in those patients who achieve continuing psoriasis remission. A recent international consensus agreed that stopping biologic therapy is not generally recommended<sup>20</sup>. However, if agreed to by the patient (and after achieving complete remission for a minimum of 1 yr), stopping biologic therapy can be considered with careful followup. Subgroups in which stopping therapy might be considered are those patients who clearly require treatment interruption, in the absence of significant comorbidities including PsA, and in the case of low impairment of quality of life<sup>20</sup>. Another consideration is that resolved psoriasis lesions retain expression of a subset of disease-related genes. Gene-expression profiling was used to determine the extent to which psoriasis genes were reversed after 3 months of ETN treatment in patients who responded to treatment. Many cellular markers do approach nonlesional levels, although 4 inflammatory genes were not downregulated: *IL-12p35*, *IL-22*, *IL-17*, and *IFN- $\gamma$* , i.e., there is a “residual disease genomic profile,” according to a study by Suárez-Fariñas, *et al*<sup>21</sup>. That study shows that even when the epidermal reaction in psoriasis is fully reversed, expression of key cytokines and chemokines is not completely resolved in treated lesions.

There are no studies, to our knowledge, investigating whether the dose of biologic therapy could be reduced in cases of sustained clearance without loss of efficacy, so this is not a recommended option in clinical practice. Finally,

patients with moderate to severe psoriasis are candidates for cardiovascular risk reduction. Nonpharmacological intervention, such as body weight loss, should be recommended to obese patients. Indeed, it has been reported that a low-calorie diet inducing moderate weight loss (i.e., 5 to 10% of body weight) increases responsiveness to systemic treatments of obese patients with moderate to severe chronic plaque psoriasis<sup>22</sup>.

Achievement of PASI 75 is the treat-to-target objective in the therapy of psoriasis, although it is likely that the incoming biological treatments including IL-17 (i.e., secukinumab, ixekizumab, and brodalumab) and the IL-23 inhibitors (tildrakizumab and guselkumab) will raise the standard of therapy to PASI 90/100 response<sup>23</sup>. Continuous therapy is generally required to achieve longterm psoriasis control, and biological therapies are more effective and safe when administered in a continuous regimen. Further research is needed to identify biomarkers of treatment response to offer patients with psoriasis a more predictable and personalized therapy.

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