Influence of Genetic Polymorphisms on Response to Biologics in Moderate-to-Severe Psoriasis

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Abstract: Psoriasis is a chronic inflammatory skin pathology of autoimmune origin and unknown etiology. There are various therapies for treating it, including a wide range of biopharmaceuticals indicated in moderate-to-severe psoriasis. Depending on their therapeutic target, they are classified as tumor necrosis factor inhibitors (anti-TNF) or cytokine inhibitors (interleukin-12, 23, and 17 antagonists). Although they have proved effective and safe, in clinical practice, many patients show a short- and long-term suboptimal response and even varying degrees of toxicity. This variability in response may be influenced by genetic factors, such as polymorphisms in the genes involved in the pathological environment, metabolism or mechanism of action of the drug that could affect the effectiveness and toxicity of biological therapies. This review assesses pharmacogenetic studies of the impact of genetic factors on response to biopharmaceuticals and toxicity in patients diagnosed with moderate-to-severe psoriasis. The results suggest that polymorphisms detected in the HLA genes, in genes that encode cytokines (TNF, IL genes, TNFAIP3), transporters (PDE3A-SLC12A8), receptors (TNFRSF1B, CD84, FCGR2A and FCGR3A, IL17RA, IL23R, TLR genes, PGLYRP4) and associated proteins (TNFAIP3, L9y6, TIRAP, FBXL19), as well as other genes implicated in the pathogenesis of psoriasis (CDKAL1, CARD14, PTG1, MAP3K1, ZNF816A, GBP6, CTNNA2, HTR2A, CTLA4, TAPI) can be used in the future as predictive markers of treatment response and/or toxicity with biological therapies in patients diagnosed with moderate-to-severe psoriasis, tailoring treatment to the individual patient.

Keywords: psoriasis; pharmacogenetics; biological therapies; polymorphisms; response; biomarkers; personalized medicine; adalimumab; etanercept; ustekinumab

1. Introduction

Psoriasis is a chronic and recurrent inflammatory autoimmune skin disease with a worldwide prevalence of up to 8.5% in adults and 2.1% in children [1,2]. Apart from exceptional cases of erythrodermic or pustular psoriasis, the skin manifestations are not life-threatening. However, it severely affects quality of life, with a similar impact to diabetes or chronic obstructive pulmonary disease [3]. Furthermore, it is associated with other pathologies, such as erectile dysfunction in 35% of patients and potentially incapacitating arthropathy in 40% [4–6]. In short, psoriasis is regarded as a systemic entity rather than an exclusively dermatological disease [7].

Its etiology is unclear, although it is thought that it could be due to a combination of genetic, immunological and environmental factors (such as stress, trauma, medications and microorganism infections, among others) (Figure 1) [8]. It has been found that the incidence
differs between ethnicities and that it is greater among relatives and even more between monozygotic twins [9]. In addition, genetic variants in molecules that influence developing epidermal hyperplasia led to an increased susceptibility to develop this pathology. In particular, the HLA-Cw*06 alleles (also known as HLA-C*06:02) have been described as the first-factor risk of psoriasis. Remarkably, HLA-Cw*06 was found to mediate autoimmunity against melanocytes through the ability of its protein product to present ADAMTSL-like protein 5 (ADAMTSL5). In fact, this complex is recognized by epidermal CD8+ T cells, which directly target melanocytes and produce inflammatory cytokines (such as TNF-α and IL-17) that, in turn, are able to alter melanocyte functions and proliferation, leading to dysregulation of skin homeostasis [10].

Abnormalities in cutaneous immune responses, both innate and adaptive, are responsible for the development and maintenance of psoriatic inflammation [8,11]. One of the main pathogenic mechanisms is based on the activation of plasmacytoid dendritic cells, keratinocytes, natural killer cells and macrophages that secrete cytokines (IFN-β and IFN-γ, IL1B, TNF). Activated dendritic cells promote the production of IL-12 and IL-23, which regulate the differentiation and proliferation of helper T lymphocytes (Th1, Th17 and Th22), which produce more cytokines (TNF, IFN-γ, IL22, IL-17). This inflammatory cascade produces a hyperproliferation of keratinocytes in the epidermis and in the vascular endothelium, giving rise to epidermal hyperplasia and psoriasis development. Targeted therapy with monoclonal antibodies inhibits different cytokines of this pathway (TNF, IL12/23, IL17, IL23), preventing the development of the inflammatory cascade and subsequently epidermal hyperplasia, typical of psoriasis. Genetic variations, such as single nucleotide polymorphisms in genes encoding these cytokines, receptors or proteins involved in this mechanism, can be associated with response or toxicity to treatment with biologic therapies. Plasmacytoid DC: plasmacytoid dendritic cells; NK cells: natural killer T cells; Myeloid DC: myeloid dendritic cells; Th: T helper lymphocytes; IFN: interferon; IL: interleukin; TNF: tumor necrosis factor; Anti-TNF: TNF inhibitor drugs; Anti-IL drugs: cytokine inhibitor drugs.
differentiation and proliferation of helper T lymphocytes (Th1, Th17 and Th22). Th1 cells produce TNF and IFN-γ, Th2 cells produce IL-22, while Th17 cells, as well as producing TNF and IL-22, also secrete IL-17. These cytokines activate the proliferation of keratinocytes in the epidermis, and this inflammatory cascade produces a hyperproliferation of keratinocytes in the epidermis and in the vascular endothelium, giving rise to epidermal hyperplasia and psoriasis development (Figure 1) [13]. Furthermore, the status of keratins and collagen has been linked to the development of keratinocyte hyperproliferation, typical of psoriatic lesions. Keratins are involved in cell proliferation and inflammatory response by mediating interactions between cells or cells and the extracellular matrix, while collagen supports stabilization of tissue, strength and resilience. Currently, 54 keratin genes (KRTs) have been identified, and six genetic variations that consequently produce abnormal keratinocytes in the psoriatic epidermis (KRT1, RT6A, KRT6B, KRT10, KRT16 and KRT17). Moreover, altered collagen structure and function due to relevant mutations can affect all tissues or organs and cause various pathological phenotypes. Specifically, two genetic variants of the collagen (COL) genes, COL8A1 and COL8A2, have been shown to be associated with the extracellular matrix remodeling and angiogenesis that occurs in psoriasis. In addition, the impact of genetic variants in COL may be associated with the development of psoriatic arthritis in patients with cutaneous psoriasis [10].

Finally, the relationship of the human microbiome with the immune system and the skin barrier should be highlighted. Analysis of the microbiota of psoriatic lesions revealed the presence of bacteria (Staphylococcus aureus, Streptococcus pyogenes), viruses (Human papillomavirus) and fungi (Candida Albicans), suggesting that developing this pathology may be related to an excessive immune response to microbial pathogens. It has been observed that C. Albicans could even exacerbate skin dysfunction by disrupting the physiological activity of immune-related factors, including TLR [10].

Therefore, the co-occurrence of genetic, epigenetic and non-genetic factors could explain specific skin phenotypes and the differential susceptibility to psoriasis [10].

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Ninety percent of patients develop clinical manifestations in the form of erythematous plaques covered by whitish scales on the scalp, elbows, knees and back [14–16]. The severity of the lesions is measured with the psoriasis area severity index (PASI), body surface area (BSA) and dermatology life quality index (DLQI) indicators. The latest consensus document on the evaluation and treatment of psoriasis established that moderate-to-severe psoriasis is diagnosed with PASI > 10, BSA > 10 and DLQI > 10 [17]. In addition, the effectiveness of treatment is evaluated by absolute PASI or percentage improvement in PASI; for example, a 90% reduction (PASI 90) [1].

The treatments used are aimed at blocking the inflammatory response. As an exceptional non-pharmacological treatment, exposure to sunlight is recommended [18]. However, pharmacological treatment depends on the severity of psoriasis, and topicals, phototherapy, traditional oral immunomodulators, or biological therapy may be used [19]. In mild psoriasis, the treatment is based mainly on topical and symptomatic therapy (corticosteroids, calcineurin inhibitors, topical retinoids vitamin D analogs) [20]. When the disease is more severe (BSA > 10, PASI > 10 and DLQI > 10), systemic therapy (methotrexate, cyclosporine, acitretin, apremilast, fumaric acid esters), phototherapy (UV, UVB, PUVA) or photochemotherapy [therapy based on psoralens plus ultraviolet A radiation (PUVA)] are recommended. As a last option, when the severity indicators are greater than 10, and there is no response to previous treatments or contraindicated, treatment with biologics is used [17].

There is a wide range of biopharmaceuticals indicated in moderate-to-severe psoriasis [21]. They are classified into two groups according to the therapeutic target: tumor necrosis factor inhibitor (anti-TNF) therapies, such as infliximab (INF), etanercept (ETN), adalimumab (ADA) and certolizumab (CTL), and cytokine inhibitors: ustekinumab (UTK), secukininumab (SCK), ixekizumab (IXE), brodalumab (BDL), guselkumab (GSL), tildrakizumab (TDK), the recently approved risankizumab (RSK) and another two new drugs that are undergoing trials (bimekizumab and mirikizumab).
The first treatment options for moderate-to-severe plaque psoriasis are the anti-TNF drugs ADA and ETN and the IL-12/23 inhibitor UTK [22,23]. Second-line treatments include the IL-17 inhibitors SCK and IXE and BDL targeting the IL-17RA receptor [24,25]. There are also GSL, TDK and RSK, which inhibit IL-23 or its receptor IL-23R (Figure 1) [26,27].

Anti-TNFs were the first biologics indicated in psoriasis to be marketed. A network meta-analysis has indicated that INF is the most effective (80% of patients reached PASI 75 at week 10), followed by CTL and ADA, with similar degrees of efficacy (n early 80% of patients reached PASI 75 at week 16), and finally ETN (49% of patients reached PASI 75 at week 12) [28]. In addition, four recent meta-analyses have evaluated the short-term efficacy of all the biological therapies (anti-TNFs and cytokine inhibitors), and the two with the largest numbers of patients (77 studies/34816 patients and 28 studies/9940 patients) showed that the most effective drugs (PASI 90 at 12–16 weeks of treatment) are RSK (80.9%), BDL (76.8%), IXE (71.6%) and GSL (76.8%), followed by SCK (66%), INF (56%), UTK (58–43.6%, depending on dosage) and finally the anti-TNFs ADA (44.2%), CTL (38.8–43.7%, depending on dosage) and ETN (16.8–26.3%, depending on dosage) [24,26,29,30]. These results were confirmed in head-to-head clinical trials, demonstrating that the IL-17 or IL-23 inhibitor drugs are more effective than the IL-12/IL-23 inhibitors and anti-TNFs [31]. However, BDL, IXE and SCK have the highest probability of maintaining long-term efficacy (40–64 weeks) (97, 83 and 77%, respectively) [32].

As regards safety, all of them have proved to be very safe; patients show no increase in rates of severe infections or internal malignancies [33]. It should be noted that UTK and SCK have the lowest rates of adverse effects (compared to other anti-TNF biological therapies), even in patients with comorbidities, in the case of SCK [34,35].

Despite the confirmed efficacy and safety of these medications, not all patients obtain good results. Some do not show the expected response in the induction phase (16–24 weeks with the treatment) or undergo a loss of response in the maintenance phase (from 24 weeks to several years) [36]. Moreover, certain patients experience various degrees of toxicity. This variability in short- and long-term response, as well as toxicity, may be due to genetic factors. Therefore, this genetics variant can be used in the future as predictive markers of treatment response and/or toxicity with biological therapies in patients diagnosed with moderate-to-severe psoriasis, tailoring treatment to individual patients.

In light of all the foregoing, the object of this review of pharmacogenetic studies of candidate genes is to assess the impact of genetic variants on the response to treatment with biopharmaceuticals in patients diagnosed with moderate-to-severe psoriasis.

### 2. Materials and Methods

A PubMed search included key words “psoriasis”, “psoriatic”, together with “treatment”, “biological therapy”, “etanercept”, “infliximab”, “adalimumab”, “ustekinumab”, “secukinumab”, “certolizumab pegol”, “guselkumab”, “tildrakizumab”, “brodalumab”, “ixekizumab”, “risankizumab” and “polymorphisms” and “response” or “toxicity”. Data regarding gene, SNP, year of publication, number of patients, population, drugs, response (time and outcome measure), results (odds ratio, 95% confidence interval and \( p \)-value), and allele or genotype of response were recorded. Figure 2 shows a flow chart regarding study selection.
3. Pharmacogenetics of Biological Therapies in Psoriasis

Alterations in the genes involved in the pathological environment of the disease, metabolism or mechanism of action may influence the effectiveness of biopharmaceuticals in psoriasis. Specifically, genetic polymorphisms in the human leukocyte antigens, cytokines, receptors, transporters and associated proteins, as well as other genes implicated in the physiopathogenesis of the disease, have been shown to play a crucial role in interindividual variability in response to these drugs (Tables 1–3).
| Gene               | SNP                  | Year | N   | Population  | Drugs         | Response | Results | Responsive Allele or Genotype | PMID       |
|--------------------|----------------------|------|-----|-------------|---------------|----------|---------|--------------------------------|------------|
| Haplotype HLA-A/   | rs9260313/           | 2018 | 109 | Spain       | INF           | 6        | PASI75  | <0.05<sup>a</sup>             | 28921458   |
| TRAF3IP2           | rs13190932           |      |     |             | ADA           |          |         |                                |            |
| Haplotype HLA-B    | HLA-B*46             | 2012 | 74  | China       | ETN           | 3        | PASI50  | 1<sup>b</sup>                   | 21985130   |
| HLA-B/MICA         | rs13437088           | 2017 | 81  | Spain       | ETN           | 3        | PASI75  | 2.71–128,614.40                | 28470127   |
|                    | rs12191877           | 2016 | 144 | Spain       | Anti-TNF      | 3        | PASI75  | 0.30                            | 27670765   |
|                    | rs1048554            | 2016 | 250 | Greece      | Anti-TNF      | 6        | PASI75  | 3.94                            | 27043841   |
|                    | rs610604             |      |     |             | ADA           |          |         | 0.05<sup>b</sup> <sup>a</sup> |            |
| HLA-C              | rs12191877           | 2013 | 109 | Spain       | Anti-TNF      | 6        | PASI75  | 85.1                            | 23662788   |
|                    | rs13437088           | 2016 | 144 | Spain       | Anti-TNF      | 6        | PASI75  | 1.11–13.3                       | 28130758   |
|                    | rs11001104           |      |     | Greece      | ADA           |          |         |                                 |            |
|                    | rs12191877           | 2013 | 123 | Italy       | ETN           | 3        | PASI75  | >0.05                           |            |
|                    | -                    |      |     | United Kingdom and Ireland | ADA |          |         |                                 |            |
|                    | -                    |      |     |             | ETN           |          |         |                                 |            |
|                    | -                    | 2014 | 138 | Spain       | Anti-TNF      | 3        | PASI75  | >0.05                           | 24758522   |
| HLA-Cw*06/LCE3C    | LCE3B del/ins        | 2015 | 116 | Spain       | Anti-TNF      | 3        | PASI75  | 3.14                            | 25794162   |
|                    | -                    | 2016 | 96  | Italy       | ETN           | 3        | PASI75  | >0.05                           | 27348478   |
|                    | -                    | 2017 | 122 | Italy       | ADA           | 3        | PASI75  | 1.11                            | 28130758   |

<sup>a</sup> OR, 95% CI, and p-value are significant at the 0.05 level.

<sup>b</sup> OR, 95% CI, and p-value are significant at the 0.01 level.
Table 1. Cont.

| Gene            | SNP                  | Year | N     | Population | Drugs | Response | Results | Responsive Allele or Genotype | PMID   |
|-----------------|----------------------|------|-------|------------|-------|----------|---------|-------------------------------|--------|
|                |                      |      |       |            |       | Time     | Outcome Measure | OR   | CI<sub>95%</sub> | p-value |                        |        |
|                |                      |      |       |            |       | (Months) |                      |      |              |         |                          |        |
|                |                      | 2013 | 51    | Italy      | UTK   | 1        | PASI75   | 5.36 | 1.24–23.1 | 0.024   | (+)                      | 23521149 |
|                |                      |      |       |            |       | 3        | PASI75   | 13.4 | 1.6–12.6  | <0.008  |                        |        |
|                |                      |      |       |            |       | 3        | PASI90   | 4.6  | -          | 0.02    |                        |        |
|                |                      |      |       |            |       | 10       | PASI75   | 3.9  | 2–7.37    | 0.014   |                        |        |
|                |                      |      |       |            |       | 10       | PASI90   | 8.7  | -          | 0.012   |                        |        |
|                |                      | 2016 | 134   | Italy      | UTK   | 3        | PASI75   | 4.1  | -          | 0.001   | (+)                      | 26775778 |
|                |                      |      |       |            |       | 13       | PASI75   | 3.7  | -          | 0.003   |                        |        |
|                |                      | 2017 | 255   | Belgium, Italy, Netherlands | UTK | 3        | PASI75   | 3.28 | 1.92–5.59 | <0.001  | (+)                      | 28207934 |
|                |                      |      |       |            |       | 13       | PASI75   | 3.82 | 1.88–7.73 | <0.001  |                        |        |
|                |                      | 2014 | 66    | China      | UTK   | 4        | PASI75   | 0.28 | 0.11–0.68 | 0.005   | (+)                      | 24734995 |
|                |                      |      |       |            |       | 3        | PASI75   | -    | -          | <0.05<sup>b</sup> | (+)          | 27476722 |
| HLA-Cw6/L12B   | rs3212227            | 2016 | 64    | Italy      | UTK   | 1        | PASI75   | 10.49 | 50–0       | 0.009   | (+)/C                    | 26678060 |
|                |                      |      |       |            |       | 13       | PASI75   | 5.21 | 83.3–44.4 | 0.007   |                        |        |
| HLA-Cw6/IL12B  | rs6887695            |      |       |            |       | 1        | PASI75   | 6.11 | 23.5–10.5 | 0.031   | (+)/GG                   |        |
|                |                      |      |       |            |       | 13       | PASI75   | 4.75 | 82.4–42.1 | 0.006   |                        |        |
| HLA-Cw6 y IL6  | rs1800795            |      |       |            |       | 1        | PASI75   | 6.52 | 38.5–0    | 0.027   | (+)/C                    |        |
|                |                      |      |       |            |       | 13       | PASI75   | 4.99 | 84.9–46.7 | 0.005   |                        |        |
|                |                      | 2019 | 1048  | Caucasians and Asian | UTK | 6        | PASI75   | 0.24 | 0.14–0.35 | <0.001  | (+)                      | 30994858 |

<sup>b</sup> Indicates significant difference.
### Table 1. Cont.

| Gene     | SNP                  | Year | N    | Population                     | Drugs | Response Time (Months) | Outcome Measure | OR  | CI95%   | p-value | Responsive Allele or Genotype |
|----------|----------------------|------|------|--------------------------------|-------|------------------------|----------------|-----|---------|---------|-------------------------------|--------|
| HLA-G    | 14-pb ins/del        | 2014 | 11   | Italy                          | Anti-TNF | 4                     | PASI75          | -  | -       | 0.7 b   | (+)                           | 24909182|

| N: number of patients; OR: odds ratio; CI95%, 95% confidence interval; ADA: adalimumab; ETN: etanercept; INF: infliximab; UTK: ustekinumab; anti-TNF: inhibitors TNF drugs; PASI: psoriasis area and severity index; PASI75:75% improvement from baseline PASI; PASI90:90% improvement from baseline PASI; (+) presence of allele HLA-C*06:02; (-) absence of allele HLA-C*06:02; a p-value for chi-squared test; b p-value for Fisher’s test. The script means that the paper did not provide any information on this parameter.

### Table 2. Gene polymorphisms involved in response to biological therapies.

| Gene     | SNP            | Year | N    | Population | Pathology | Drugs | Response Time (Months) | Outcome Measure | OR  | CI95% | p-value | Responsive Allele or Genotype | PMID   |
|----------|----------------|------|------|------------|-----------|-------|------------------------|----------------|-----|-------|---------|-------------------------------|--------|
| TNF-α-238| rs361525       | 2013 | 109  | Spain      | PS        | Anti-TNF | 6                     | PASI75          | -  | -     | 0.049 f | G                             | 23662788|
|          |                |      |      |            |           |        | -                      | BSA             | -  | -     | 0.004 f |                                |        |
|          |                |      |      |            |           |        | -                      | PASI            | -  | -     | 0.009 f |                                |        |
|          |                |      |      |            |           |        | 6                     | PASI75          | -  | -     | 0.006 f |                                |        |
|          |                |      |      |            |           |        | 3                     | PASI75          | -  | -     | 0.047 f | TT                            |        |
|          |                |      |      |            |           |        | 6                     | PASI75          | -  | -     | 0.038 f |                                |        |
| TNF-α-308| rs1800629      | 2015 | 807  | Caucasians | AE        | Anti-TNF | -                     | -               | 2.005 | 1.417–2.838 | 0.000086 | G                             | 26244882|
| TNF-α-238| rs361525       | 2015 | 500  | Caucasians | IBD       | Anti-TNF | 2                     | 1.965           | 1.161–4.154 | 0.016   | G                             | 26244882|
| TNF-α-857| rs1799724      | 2015 | 483  | Caucasians | APS       | Anti-TNF | -                     | 1.779           | 1.13–2.802  | 0.013   | C                             | 26244882|
| TNF-α-857| rs1799724      | 2015 | 177  | Caucasians | PS        | ETN    | -                     | 2.238           | 1.319–3.798 | 0.003   | C                             | 26244882|

N: number of patients; OR: odds ratio; CI95%, 95% confidence interval; AE: atopic dermatitis; IBD: inflammatory bowel disease; APS: ankylosing spondylitis; PS: psoriasis; Anti-TNF: inhibitors TNF drugs; AE: atopic dermatitis; IBD: inflammatory bowel disease; APS: ankylosing spondylitis; PS: psoriasis; ETN: etanercept; INF: infliximab; UTK: ustekinumab; anti-TNF: inhibitors TNF drugs; PASI: psoriasis area and severity index; PASI75:75% improvement from baseline PASI; PASI90:90% improvement from baseline PASI; (+) presence of allele HLA-C*06:02; (-) absence of allele HLA-C*06:02; a p-value for chi-squared test; b p-value for Fisher’s test. The script means that the paper did not provide any information on this parameter.
Table 2. Cont.

| Gene  | SNP             | Year | N   | Population | Pathology | Drugs     | Time (Months) | Outcome Measure | OR     | CI 95%   | p-value | Responsive Allele or Genotype | PMID       |
|-------|-----------------|------|-----|------------|-----------|-----------|--------------|-----------------|--------|----------|---------|-------------------------------|------------|
| IL1-β | rs1143623       | 2017 | 376 | Denmark    | PS        | Anti-TNF  | 3            | PASI75          | 0.35   | -        | 0.0041  | GG                             | 28696418   |
|       | rs1143627       | 2017 | 376 |           | PS        | Anti-TNF  | 3            | PASI75          | 0.28   | -        | 0.0016  | AA                             |            |
| IL6   | rs1800795       | 2012 | 60  | Italy      | PS        | Anti-TNF  | 6            | PASI75          | 2.00   | 1.19–3.38 | <0.05  | GG                             | 22158445   |
|       | rs2546890       | 2017 | 78  | Spain      | PS        | APS       | 6            | PASI75          | 11.92  | 1.07–132.67 | 0.044 | G                             | 28470127   |
|       | rs3213094       | 2017 | 66  | Netherlands| PS        | UTK       | 3            | ΔPASI           | -3.15  | -5.724–0.586 | 0.017 | CT                            | 27560482   |
| IL12β | rs763780        | 2015 | 67  | Spain      | PS        | UTK       | 4            | PASI75          | 12.23  | 1.17–127.36 | 0.022 | CT                            | 26347322   |
|       | rs610604        | 2013 | 51  | Italy      | PS        | UTK       | 10           | PASI75          | 1.6    | -         | 0.75    | -                             | 23521149   |
|       | rs610604        | 2016 | 64  | Italy      | PS        | UTK       | 3            | PASI75          | -      | -         | >0.05   | -                             | 26678060   |
|       | rs6920220       | 2017 | 66  | Netherlands| PS        | UTK       | 3            | ΔPASI           | 3.490  | 0.329–6.650 | 0.031 | GG                            | 27564082   |
|       | rs11045392/rs3794271 | 2019 | 20  | Spain      | PS        | APS       | 3            | % EQ-VAS        | -10.6  | -20.71–0.048 | 0.041 | AC/CC                         | 30653751   |
| Gene       | SNP      | Year | N   | Population | Pathology | Drugs     | Response | Results | Responsive Allele or Genotype | PMID   |
|------------|----------|------|-----|------------|-----------|-----------|----------|---------|--------------------------------|--------|
|            |          |      |     |            |           |           | Time (Months) | Outcome Measure | OR | CI95% | p-value |                      |        |
| TNFRSF1B   | rs1061622| 2012 | 80  | Greece     | PS        | Anti-TNF  | ETN      | 6        | PASI75 | -     | -      | 0.019 f                  | 22111980 |
|            |          | 2015 | 90  | Spain      | PS        | Anti-TNF  | 6        | PASI50  | 2.96  | 1.09–8.02 | 0.03             | G       | 25537528 |
|            |          | 2015 | 929 | Caucasians | CD        | Anti-TNF  | 3        | ∆PASI   | −2.028 | −3.794–0.261 | 0.025        | AG      | 27564082 |
|            |          | 2015 | 170 | Germany    | CD        | Anti-TNF  | 6        | PASI75  | 13.32 | 1.67–106.50 | 0.015        | 131HH   | 27044681 |
|            |          | 2015 | 133 | Spain      | RA        | Anti-TNF  | 6        | PASI75  | 2.96  | 1.60–5.527 | 0.0018       | 158 V   | 27044681 |
| FCGR2A     | rs1801274| 2013 | 70  | Spain      | PS        | Anti-TNF  | 6        | dBSA    | -     | -      | 0.03 d                  | 131HH   | 24048425 |
|            |          | 2015 | 115 | Spain      | PS        | Anti-TNF  | 6        | PASI75  | -     | -      | 0.1 e                  | -       | 26398016 |
|            |          | 2016 | 100 | Greece     | PS        | Anti-TNF  | 6        | PASI75  | -     | -      | 0.882 e                | H131R   | 27044681 |
| IL17RA     | rs4819554| 2018 | 238 | Spain      | PS        | Anti-TNF  | 3        | PASI75  | 1.86  | 1.05–3.27 | 0.03             | A       | 27670766 |
| IL23R      | rs11209026| 2013 | 109 | Spain      | PS        | Anti-TNF  | 6        | PASI90  | -     | -      | 0.006 f                | GG      | 23662788 |


| Gene  | SNP          | Year | N   | Population | Pathology | Drugs | Response | Results | responsive Allele or Genotype | PMID  |
|-------|--------------|------|-----|------------|-----------|-------|----------|---------|-----------------------------|-------|
| TLR2  | rs4696480    | 2017 | 376 | Denmark    | PS        | Anti-TNF | Time (Months) 3 | OR 0.22, CI95% 0.08–0.59, p-value 0.0032 | A     | 28696418 |
|       | rs11938228   |      |     |            |           |        |          |         |                             |       |
|       | rs11465996   | 2017 | 230 |            |           | UTK    | Time (Months) 3 | OR 0.33, CI95% 0.15–0.71, p-value 0.0044 | C     |       |
| TIRAP | rs8177374    | 2017 | 230 |            |           |        |          |         |                             |       |
| TLR5  | rs5744174    | 2017 | 376 |            | Anti-TNF  | Time (Months) 3 | OR 9.42, CI95% 1.96–45.3, p-value 0.0051 | C     |       |
|       |              |      |     |            |           |        |          |         |                             |       |
| TLR9  | rs352139     | 2017 | 376 |            |          | Anti-TNF  | Time (Months) 223 | OR 2.42, CI95% 1.32–4.44, p-value 0.0044 | G     |       |
| PGLYR4-24 | rs2916205    | 2016 | 144 | Spain      | PS        | Anti-TNF  | Time (Months) 3 | OR 3.62, CI95% 1.00–13.07, p-value 0.05 | C     | 27670765 |
| CDKAL1| rs6908425    | 2015 | 116 | Spain      | PS        | Anti-TNF  | Time (Months) 6 | OR 3.14, CI95% 1.40–7.05, p-value 0.005 | CC    | 26563541 |
|       |              | 2016 | 133 | Spain      | PS        | Anti-TNF  | Time (Months) 6 | OR 0.14, CI95% 0.03–0.66, p-value 0.013 | T     | 27670765 |
| CARD14| rs11652075   | 2016 | 116 | Spain      | PS        | Anti-TNF  | Time (Months) 6 | OR 3.71, CI95% 1.30–10.51, p-value 0.01 | CC    | 26854129 |
| PTTG1 | rs2431697    | 2017 | 78  | Spain      | PS        | APS ETN | Time (Months) 3 | OR 29.80, CI95% 1.16–765.68, p-value 0.04 | C     | 28470127 |
| MAP3K1| rs96844      | 2017 | 78  | Spain      | PS        | APS ETN | Time (Months) 3 | OR 0.01, CI95% 0–0.33, p-value 0.009 | C     | 28470127 |
|       |              | 2016 | 144 | Spain      | PS        | Anti-TNF  | Time (Months) 6 | OR 0.17, CI95% 0.05–0.56, p-value 0.017 | C     | 27670765 |
| ZNF816A| rs9304742    | 2017 | 78  | Spain      | PS        | APS ETN | Time (Months) 3 | OR 8144.11, CI95% 13.03–5089337.0, p-value 0.006 | CC    | 28470127 |
|       |              | 2016 | 144 | Spain      | PS        | Anti-TNF  | Time (Months) 3 | OR 7.66, CI95% 1.37–42.70, p-value 0.02 | CC    | 27670765 |
| GBP6  | rs928655     | 2017 | 68  | Spain      | PS        | APS ETN | Time (Months) 6 | OR 0.14, CI95% 0.03–0.67, p-value 0.014 | G     | 28470127 |
| CTNNA2| rs11126740   | 2016 | 144 | Spain      | PS        | Anti-TNF  | Time (Months) 3 | OR 20.56, CI95% 2.75–153.69, p-value 0.003 | AA    | 27670765 |
| HTR2A | rs6311       | 2017 | 68  | Spain      | PS        | Anti-TNF  | Time (Months) 6 | OR 5.6, CI95% 1.10–28.63, p-value 0.038 | T     | 27670765 |

N: number of patients; OR: odds ratio; CI95%: 95% confidence interval; ADA: adalimumab; ETN: etanercept; UTK: Ustekinumab; anti-TNF-α: inhibitors TNF-α drugs; EQVAS: European quality of life visual analog scale; PASI: psoriasis area and severity index; PASI75:75% improvement from baseline PASI; PASI90:90% improvement from baseline PASI; dBSA: decrease of BSA; DS: drug survival; APS: psoriatic arthritis; CD: Crohn’s disease; EA: ankylosing spondylitis; IBD: inflammatory bowel disease; Ps: psoriasis; RA: rheumatoid arthritis; a: weeks; b: days; c: beta; d: p-value adjusted by age, sex, initial BSA, and the efficacy of the anti-tumor necrosis factor agent (percentage of PASI improvement) in week 6; e: p-value for the chi-squared test; f: p-value for Fisher’s test. The script means that the paper did not provide any information on this parameter.
Table 3. Gene polymorphisms involved in toxicity to anti-TNF-α therapies in psoriasis patients.

| Gen  | SNP          | Year | N   | Results         | Responsive Allele or Genotype | PMID       |
|------|--------------|------|-----|------------------|-------------------------------|------------|
|      |              |      |     | OR               | Cl<sub>95%</sub> | p-value |              |                |
| CTLA4| rs3087243    | 2016 | 161 | 0.001            | 0.012 AG/GG                | 26194362   |
| FBXL19| rs10782001  |      |     | 32.85            | 0.0028 GG                  |            |
| IL23R| rs11209026   |      |     | 11,011.59        | 0.005 AG                   |            |
| SLC12A8 | rs651630   |      |     | 0               | 0.011 AA                   |            |
| TAP1 | rs1800453    |      |     | 0.009            | 0.018 AG                   |            |

N: number of patients; OR: odds ratio; Cl<sub>95%</sub>: 95% confidence interval.
3.1. Human Leukocyte Antigens (HLAs)

The human leukocyte antigens (HLAs) are part of the major histocompatibility complex (MHC) and help to identify exogenous proteins that may trigger an immune response. The HLA system is located at the PSORS1 locus of chromosome 6 and encodes a large number of HLAs with different functions [37]. They are grouped into three classes: class I (A, B and C) is responsible for presenting peptides of intracellular origin, while class II presents antigens to T cells, and class III encodes enzymes, some complement proteins, and other proteins that interfere in antigen presentation, but are not HLAs [38].

Many variant alleles of HLA-I and HLA-II genes have been described, and their association with the risk of developing psoriasis or relationship to response to biological therapy (anti-TNF and UTK) have been studied (Table 1). The HLA-A rs9260313 (T > A, C) polymorphism has been studied in a cohort of Spanish patients (n = 109), finding an association between the GT haplotype (TRAF3IP2 rs13190932 and HLA-A rs9260313, respectively) and response (PASI 75 at eight months) to INF and ADA, but not to ETN (p < 0.005) [39]. However, this association was not statistically significant when the TRAF3IP2 rs13190932 and HLA-A rs9260313 polymorphisms were studied separately.

In addition, several studies have evaluated the usefulness of HLA-B as a predictor of response to biologics in patients diagnosed with moderate-to-severe psoriasis [40,41]. A study with Spanish patients (n = 81) found that the HLA-B/MICA rs13437088 polymorphism was related to response to ETN at 3 months (OR = 589.99, CI95% = 2.71–128,614.40, p = 0.02) [40]. Another study assessed the impact of the HLA-B haplotype (HLA-B*46) in Asian patients (from China) treated with ETN or UTK (n = 74), without obtaining statistically significant results (ETN: n = 45, p = 1.0; UTK: n = 29, p = 0.32) [41].

The HLA-C haplotype has been extensively studied in psoriasis. In particular, the rs12191877 polymorphism was associated with response to anti-TNF medication (PSA 75) at 3 months in 144 Spanish patients (HLA-C rs12191877-T: OR = 0.30, CI95% = 0.11–0.88, p = 0.027) [42]. Similarly, a study performed in Greek patients (n = 250) showed that the rs1048554 polymorphism, situated close to the HLA-C locus, was associated with better response to anti-TNF drugs (PASI 75 at 6 months: OR = 3.94, CI95% = 1.16–13.3, p = 0.0032), specifically with ADA (p = 0.0007) [43]. Moreover, patients carrying the rs610604-A allele (situated at the HLA loci) showed a better response to ADA (p = 0.05) [43].

The HLA-Cw*06 alleles (also known as HLA-C*06:02) have been shown to confer a high risk of suffering from psoriasis, but its association with response to anti-TNF drugs and cytokine inhibitors is contradictory [20,39,44–46]. A study in Spanish patients (n = 109) observed that patients carrying the HLA-Cw*06 allele had a lower probability of responding (PASI 75 at week 24) to ADA, ETN or INF (OR = 58.1, CI95% = 71.7–93.8, p = 0.049) [47]. In addition, a study with 116 Spanish patients showed that those are carrying the HLA-Cw*06 alleles together with the deletion of the two late cornified envelope genes (LCE3C_LCE3B-del), which has been evaluated independently without statistically significant results, had a higher probability of responding to treatment with anti-TNF drugs (OR = 3.14, CI95% = 1.07–9.24, p = 0.034) [48–51]. However, it was not possible to predict the response to anti-TNF medication in a study with patients from the United Kingdom and Ireland (n = 138) treated with ADA or ETN [45]. In an Italian population the HLA-Cw*06 allele was not associated with response to ADA or ETN (n = 123 and n = 96; PASI 75 at 3 months; p > 0.05) [44,52]. Similarly, in an Italian population, Talamonti et al. found no association between the HLA-Cw*06 allele and response to anti-TNF medication (n = 122), but in patients treated with UTK (n = 51) they observed that the HLA-Cw*06 allele could be a predictor of good response (PASI 75 or PASI 90 at week 12) (PASI 75: OR = 13.4, CI95% = 1.6–12.6, p < 0.008; PASI 90: OR = 4.6, p = 0.02), rapid response (PASI 75 at week 4) (OR = 5.36, CI95% = 1.24–23.1, p = 0.024) and lasting response (PASI 75 or PASI90 at week 40) (PASI 75: OR = 3.9, CI95% = 2–7.37, p = 0.014; PASI 90: OR = 8.7, p = 0.012) to UTK [49,53].

These results were confirmed in two larger cohorts of patients treated with UTK (n = 134; PASI 75 at week 12 (OR = 4.1, p = 0.001) and week 52 (OR = 3.7, p = 0.003), and n = 255; PASI 75 at week 12 (OR = 3.28, CI95% = 1.92–5.59, p < 0.001) and week 52.
14-pb Ins/Del polymorphism (rs66554220) with response to anti-TNF treatment

HLA-G allele and had developed psoriatic arthritis (PASI 90 at 6 months: OR = 2.95, HLA-Cw*06 (OR = 5.21, CI = 0.14–0.35, p < 0.001) [46]. However, this association was not statistically significant in Asian patients (2 studies/140 patients) [64]. In line with these results, a study performed in Spanish patients diagnosed with moderate-to-severe psoriasis (n = 109) showed that patients with the TNF-238 rs361525-G allele showed a better response to anti-TNF treatment (PASI 75 at 6 months) (p = 0.049) [47]. The impact of the TNF-857 rs1799724 (C > T) polymorphism on the response to anti-TNF...
drugs was evaluated in Caucasian (4 studies/483 patients) and Asian patients (1 study/100 patients); Caucasian patients carrying the TNF-857 rs1799724-C allele showed a better response (OR = 1.779, CI95% = 1.130–2.802, p = 0.013), which was not confirmed in Asian patients [64,66]. Specifically, a meta-analysis comprising 2 studies and 177 Caucasian patients with psoriatic disease treated with anti-TNF medication found that patients carrying the TNF-857 rs1799724-C allele responded better to treatment with ETN (OR = 2.238, CI95% = 1.319–3.798, p = 0.003) [64,67,68]. Similar results were also obtained in a study with 109 Spanish patients diagnosed with moderate-to-severe psoriasis and treated with anti-TNF drugs; TNF-857 rs1799724-C patients had better BSA (83.1% vs. 92.7%, p = 0.004) and PASI (82.7% vs. 92.6%, p = 0.009) scores and better response at 6 months (PASI 75:71.4% vs. 96.3%, p = 0.006) [47].

Finally, in the promoter region of the TNF gene is the TNF-1031 rs1799964 (T > C) polymorphism. A study with 109 patients of Spain diagnosed with psoriasis showed an association between patients carrying the TT genotype of the TNF-1031 polymorphism and anti-TNF response at 3 and 6 months (3-month PASI 75:90.8% vs. 75.7% (p = 0.047); 6 month PASI 75:85.5% vs. 65.7% (p = 0.038)); specifically, INF achieved the highest response at 3 months (PASI 75:84.2% vs. 42.9%, p = 0.024; PASI 90:73. 7% vs. 28.6, p = 0.015) and at 6 months (PASI 75:94.1% vs. 53.8%; p = 0.025; PASI 90:76.5% vs. 30.8%, p = 0.025; ΔPASI:94.1% vs. 64.7%, p = 0.019) [47].

3.2.2. Interleukin 1 Beta (IL1B)

In the 2q14.1 region of chromosome 2 is the interleukin 1 beta gene (IL1B or IL1F2), which encodes a protein crucial to developing acute-phase response [69]. The IL1B cytokine induces prostaglandin synthesis, neutrophil influx and activation, T-cell activation and cytokine production, B-cell activation and antibody production, as well as promoting differentiation of T-helper 17 (Th17) cells and combining with IL-12 to induce IFN-γ synthesis from Th1 cells [70]. In short, IL1B is a very potent proinflammatory cytokine, and possible genetic alterations could greatly influence the response to anti-TNF drugs or cytokine inhibitors. There are two known genetic alterations in IL1B, rs1143623 (C > A/C > G) and rs1143627 (G > A), associated with response to anti-TNF treatment and to UTK [71].

A study with 478 patients from Denmark diagnosed with moderate-to-severe psoriasis and treated with anti-TNF medication (n = 376) and with UTK (n = 230) assessed the effect of these polymorphisms on the treatment response (PASI 75 at 3 months) [71]. Patients carrying the IL1B rs1143623-GG or IL1B rs1143627-AA genotypes showed worse response (IL1B rs1143623 treated with anti-TNF drugs (OR = 0.35, p = 0.0041, q = 0.19) and with UTK (OR = 0.25, p = 0.0049); IL1B rs1143627 treated with anti-TNF (OR = 0.28, p = 0.0016, q = 0.19) and with UTK (OR = 0.24, p = 0.0042, q = 0.19)) [71].

3.2.3. Interleukin 6 (IL6)

Cytokine 6 (IL6), also known as interferon-β2, is a protein encoded in humans by the IL6 gene located on chromosome 7 (7p15.3). This cytokine acts in the acute phase of inflammation and in B-cell maturation [72]. Therefore, genetic alterations in the IL6 gene may give rise to a modification of the response to anti-TNF drugs.

The IL6 rs1800795 (C > G,T) polymorphism has been studied in a small cohort of the Italian population treated with anti-TNF medication (n = 60) [73]. It was observed that obese patients carrying the IL6 rs1800795-GG genotype had a worse response to anti-TNF drugs than patients carrying the CG and CC genotypes (OR = 2.00, CI95% = 1.19–3.38, p ≤ 0.05) [73].

3.2.4. Interleukin 12B (IL12B)

The interleukin 12B (IL12B) gene, also known as natural killer cell stimulatory factor 2, is located on chromosome 5 (5q33.3) [74]. This gene codes for the p40 subunit of IL12, which acts on T and natural killer cells; it is important for maintaining Th1 memory cells and associates in turn with IL23A to form interleukin 23 (IL-23). Interleukin 23 induces
developing inflammation and may, therefore, be responsible for autoimmune inflammatory diseases [74]. Genetic alterations in IL12B may influence the response to biologics indicated for the treatment of moderate-to-severe psoriasis, especially UTK, an IL-12/23 inhibitor. Two clinically significant polymorphisms have been found: IL12B rs2546890 (A > G) and IL12B rs3213094 (C > G,T).

The IL12B rs2546890 polymorphism has been evaluated in two studies conducted simultaneously with Spanish patients treated with ETN (n = 78) or anti-TNF drugs (ADA, ETN, INF) (n = 144) [40,42]. Patients diagnosed with plaque psoriasis, who developed psoriatic arthritis treated with ETN for 6 months and, who carried the IL12B rs2546890-G allele showed worse response (PASI 75: OR = 11.92, CI 95% = 1.07–132.67, p = 0.044) [40]. Subsequently, it was confirmed that for patients carrying the IL12B rs2546890-G allele, anti-TNF drugs are less effective (PASI 75) at 3 months (OR = 3.22, CI 95% = 1.23–8.40, p = 0.017), at 6 months (OR = 4.14, CI 95% = 1.23–13.81, p = 0.022) and after a year of treatment (OR = 2.79, CI 95% = 1.02–7.64, p = 0.046), compared to patients with the IL12B rs2546890-A allele [42].

In addition, the IL12B rs3213094 polymorphism was studied in patients from the Netherlands treated with ETN, ADA and UTK (n = 234) and an association were found with the response to UTK (n = 66) (∆PASI at week 12) [50]. Patients with the IL12B rs3213094-CT genotype showed a better response to UTK than those carrying the IL12B rs3213094-CC genotype (beta = −3.16, CI 95% = −5.72–−0.59, p = 0.017). However, no statistically significant results were found for ETN and ADA. [50].

3.2.5. Interleukin 17 (IL17) Genes

The IL17A and IL17F genes, belonging to the interleukin 17 (IL17) family, are located on chromosome 6 (6p12.2) and encode the IL-17A and IL-17 F cytokines, which bind to the IL-17RA receptor [75]. Cytokine 17 performs an important role in the innate and adaptive immune system, activating and recruiting neutrophils as an antibacterial defense in areas of infection [76]. They have also been associated with autoimmune and inflammatory diseases, such as psoriasis since IL-17 values are increased in psoriasis lesions [77]. The impact of this gene on certain autoimmune and inflammatory diseases, such as psoriasis, has led to the development of two drugs aimed at blocking this cytokine (SCK and IXE) [78]. Recent studies show an association between polymorphisms of IL17 genes and response to anti-TNF medication and UTK [79–81].

A study in Spanish patients (n = 194) showed that the IL17F rs763780 polymorphism was a useful predictor of response to UTK (n = 67) and to the anti-TNF medications INF (n = 35) and ADA (n = 62) [81]. In particular, patients carrying the IL17F rs763780-CT genotype showed worse response to UTK (PASI 75 at week 16: OR = 12.23, CI 95% = 1.17–127.36, p = 0.022, and at week 28: OR = 14.18, CI 95% = 1.35–149.42, p = 0.016). This genotype (IL17F rs763780-CT) was also associated with worse response to ADA treatment (n = 62) (PASI 75 at week 28: OR = 14.00, CI 95% = 2.15–91.12, p = 0.0044). Conversely, in patients treated with INF (n = 35), the IL17F rs763780-CT genotype was associated with better treatment response (PASI 75 at week 16 (p = 0.023) and week 28 (p = 0.02)) [81].

3.2.6. Tumor Necrosis Factor Alpha-Induced Protein 3 (TNFAIP3)

The tumor necrosis factor-alpha-induced protein 3 (TNFAIP3) gene is located in the 6q23.3 region [82]. The protein encoded by this gene inhibits NF-κB activation, as well as TNF-mediated apoptosis, and has ubiquitin ligase and deubiquitinase activity involved in the cytokine-mediated immune response [83,84]. The genetic alterations of TNFAIP3 have been extensively studied in various pathologies. In psoriasis, however, only the effect of the TNFAIP3 rs610604 (G > T) and TNFAIP3 rs6920220 (G > A) polymorphisms have been evaluated.

The TNFAIP3 rs610604 polymorphism has been assessed in four studies, with inconclusive results. First, the influence of this polymorphism on the response to UTK (PASI 75 at 40 weeks) was studied in the Italian population diagnosed with moderate-to-severe psoriasis
(n = 51), without finding any statistically significant association (OR = 1.6, p = 0.75) [49]. Similarly, it was not possible to associate the TNFAIP3 rs610604 polymorphism with UTK response (PASI 75 at weeks 4, 12, 28, 40 and 52) in 64 Italian populations (p > 0.05) [58]. Subsequently, a study with 66 patients from the Netherlands diagnosed with psoriasis showed a significant association between the TNFAIP3 rs610604 polymorphism and response to UTK (APASI at week 12). In particular, patients carrying the GG genotype had a worse response to UTK (beta = 3.49, CI95% = 0.33–6.65, p = 0.031). Moreover, the regression model adjusted to those patients who developed psoriatic arthritis showed an association between the polymorphism and treatment response (beta = 11.23, CI95% = 0.48–7.07, p < 0.001). However, no significant association was found in patients treated with ADA or ETN (n = 282; p > 0.05) [50].

Recently, a preliminary study with 20 Spanish patients diagnosed with psoriasis and psoriatic arthritis assessed the relationship between these polymorphisms (TNFAIP3 rs610604 and TNFAIP3 rs6920220) and improvement in the quality of life of patients treated with anti-TNF drugs (European quality of life visual analog scale (EQ-VAS) score at 3 and 6 months), finding statistically significant results at three months of treatment (TNFAIP3 rs610604-AC/CC: OR = −10.60, CI95% = −20.71–−0.48, p = 0.041; TNFAIP3 rs6920220-AA: OR = −25.83, CI95% = −47.969–−3.698, p = 0.025) [85].

3.3. Transporters, Receptors and Associated Proteins

3.3.1. Phosphodiesterase 3A (PDE3A)-Solute Carrier Organic Anion Transporter Family Member 1C1 (SLCO1C1)

The PDE3A and SLCO1C1 genes are located on chromosome 12 (12p12.2). PDE3A is expressed mainly in cardiac tissue and codes for a phosphodiesterase responsible for internal control of nucleotide signaling, whereas SLCO1C1 encodes a sodium-independent transporter with a high affinity for the thyroid hormones in brain tissue and is related to various pathologies [86,87].

The SLCO1C1 rs3794271 (G > A, C) and PDE3A rs11045392 (T > A, C) polymorphisms are in linkage disequilibrium and have been evaluated in a study with 130 Spanish patients diagnosed with moderate-to-severe psoriasis and treated with anti-TNF medication (n = 130) [88]. This study demonstrated that patients carrying the SLCO1C1 rs3794271-G allele obtained a better response to anti-TNF drugs (∆PASI at 3 months) (p = 0.00057) [88].

3.3.2. Solute Carrier Family 12 Member 8 (SLC12A8)

The solute carrier family 12-member 8 genes are located on chromosome 3 (3q21.2) and code for a sodium, potassium and chloride transporter related to control of keratinocyte proliferation. On this basis, it is directly implicated in developing psoriasis and is also known as PSORS5 (psoriasis susceptibility 5) [89].

The SLC12A8 rs651630 (G > A) polymorphism was evaluated in a study of predictive biomarkers for the risk of developing toxicity and/or paradoxical psoriasis due to anti-TNF drugs in Spanish patients with moderate-to-severe psoriasis (n = 161) [90]. The patients carrying the SLC12A8 rs651630-AA genotype showed a higher risk of developing paradoxical psoriasis during treatment with anti-TNF medication (OR = 0, CI95% = 0–0.06, p = 0.011) [90].

3.3.3. Tumor Necrosis Factor Receptor Superfamily Member 1B (TNFRSF1B)

The TNF receptor superfamily member 1B (TNFRSF1B) is located on chromosome 1 (1p36.22) and encodes the TNF receptor responsible for recruiting the apoptotic suppressor proteins c-IAP1 and c-IAP2 [91]. This receptor mediates most of the metabolic effects of TNF, as it regulates the activity of this protein. Therefore, alterations in the TNFRSF1B gene may influence the TNF-mediated immune response, mainly in ETN, which inhibits the action of this receptor since ETN is the soluble p75 subunit of the TNF receptor [92].

The influence of the TNFRSF1B rs1061622 (T > G) polymorphism on response to anti-TNF drugs has been assessed in two studies and a meta-analysis [68,93,94]. The TNFRSF1B
rs1061622-TT genotype has been associated with better response (PASI 75 at 6 months) in a study with 80 Greek patients (92.1% vs. 68%, \( p = 0.019 \)), specifically to ETN treatment (100% vs. 60%; \( p = 0.001 \)). However, no statistically significant association was found in treatment with INF (\( n = 22 \)) and ADA (\( n = 14 \)) [68]. The results were confirmed in a study with Spanish patients (\( n = 90 \)) [93]. Patients carrying the TNFRSF1B rs1061622-G allele responded worse to anti-TNF drugs and to UTK (PASI 50 at 6 months) compared to those carrying the T allele (35% vs. 56%, \( p = 0.05 \)), specifically patients treated with anti-TNF therapy (OR = 2.96, CI95% = 1.09–8.02, \( p = 0.03 \)) [93]. In addition, a meta-analysis evaluated the effect of this polymorphism on the response to anti-TNF medication in Asian and Caucasian patients with autoimmune pathologies, such as Crohn’s disease (7 studies/929 patients) [42,102–105]. The TNFRSF1B rs1061622-T allele was associated with better response to anti-TNF drugs (OR = 0.72, CI95% = 0.57–0.93, \( p = 0.01 \)).

3.3.4. CD84 Molecule (CD84)

Located in the 1q23.3 region is the CD84 gene, which encodes a membrane protein belonging to the signaling lymphocytic activation molecule (SLAM) family and to the CD2 subgroup of the immunoglobulin cell-surface receptor superfamily [95]. It is expressed in many types of immune cells, such as B and T cells regulating receptor-mediated signaling, and participates in the adhesion and activation of immune cells [95]. Alterations in this gene are, therefore, related to autoimmune pathologies.

The CD84 rs6427528 (G > A) polymorphism alters the affinities of the transcription factor binding site in the 3′-UTR of CD84, leading to greater expression of the CD84 gene in peripheral blood mononuclear cells, affecting the response to anti-TNF treatment [50]. This was demonstrated in a study in a population from the Netherlands (\( n = 161 \)) where the CD84 rs6427528-AG genotype was associated with better response (ΔPASI at 12 weeks) to ETN treatment (\( \beta = -2.028, \text{CI}_{95\%} = -3.794–0.261, \ p = 0.025 \)) [50]. These results were confirmed in a meta-analysis of a genome-wide association study (GWAS) in Caucasian patients (13 studies/2706 patients) with rheumatoid arthritis treated with anti-TNF medication [96]. In particular, the CD84 rs6427528-AG genotype was associated with greater effectiveness of ETN treatment in those patients (\( n = 733 \)) (\( p = 0.004 \)) [96].

3.3.5. Fc Fragment of IgG Receptors IIA and IIIA (FCGR2A and FCGR3A)

Specific antibody receptors (FcR) are a group of surface receptors present in immune system cells (monocytes, macrophages, neutrophils, natural killer cells, and T and B lymphocytes), which interact with the constant or fragment crystallizable (Fc) region of antibodies. The receptors of the constant fraction of immunoglobulin G receptor gene family, in particular IIA (FCGR2A) and IIIa (FCGR3A), bind to the Fc region of immunoglobulin G (IgG), triggering a cell response of antibody-dependent cellular cytotoxicity (ADCC) mediated by phagocytic or cytotoxic cells [97].

The FCGR2A and FCGR3A genes are located on chromosome 1 (1q23.3), and alterations in these genes modify the affinity of the receptor for the immune complex [98]. The rs1801274 (A > C, G) polymorphism of the FCGR2A gene results in arginine (R) to histidine (H) substitution at position 131, reducing its affinity [99]. However, the FCGR3A rs396991 (A>C,G,T) polymorphism generates a change at position 158 from phenylalanine (F) to valine (V) [100]. It has been shown that the presence of the FCGR3A-V158 variant produces greater affinity for IgG, increasing the complement-mediated cytotoxic immune response and cell apoptosis, as well as the number of FcR receptors expressed on the membrane since patients carrying the FCGR3A-V158 variant express a larger number of these receptors on the surface of natural killer cells [101].

To date, several studies have been conducted evaluating the effect of these polymorphisms on the response to anti-TNF drugs, showing contradictory results [42,102–105]. The FCGR3A-158FF variant was associated with better response to anti-TNF medication at 6
weeks of treatment in a study with 35 American patients diagnosed with psoriatic pathology (n = 5) and rheumatoid arthritis (n = 30) (47.8% vs. 0%; p < 0.01) [102]. Subsequently, the impact of the FCGR3A-V158F and FCGR2A-H131R polymorphisms on anti-TNF response was assessed in a pilot study with biologic-naive Spanish patients diagnosed with moderate-to-severe psoriasis and treated with ADA, INF or ETN (n = 70) [103]. Both alleles were associated with a reduction in BSA at week 6 of treatment (beta = 0.42, p = 0.02 and beta = 0.425, p = 0.03 respectively), although these results were not confirmed at week 12 (p > 0.05) [103]. Batalla et al. corroborated the association between the FCGR3A-158FF polymorphism and anti-TNF response (PASI 75 at week 24) in a study with 115 biologic-naive Spanish patients diagnosed with moderate-to-severe psoriasis (OR = 12.05, CI95% = 1.25–111.11, p = 0.04), although the association between the FCGR2A-131HH allele and anti-TNF response was not confirmed (p = 0.1) [104]. However, Mendrinou et al. evaluated the association between both polymorphisms and response to anti-TNF drugs (PASI 75 at 6 months) in 100 Greek patients diagnosed with moderate-to-severe psoriasis [105]. In particular, patients carrying the FCGR3A-158 V allele showed better anti-TNF response (OR = 2.96, CI95% = 1.60–5.527, p = 0.018), especially to ETN, which achieved the best results (n = 55) (OR = 2.61, CI95% = 1.078–6.402, p = 0.018), but no statistically significant association was found between the FCGR2A-H131R polymorphism and anti-TNF response (p = 0.882) [105]. Finally, a study in Spanish patients (n = 133) confirmed the association of the FCGR2A-H131R polymorphism with response (PASI 75 at week 6) to anti-TNF medication [42]. In particular, patients carrying the GG genotype showed a better response than those with the AG genotype (p = 0.015) [42].

3.3.6. Interleukin 17 Receptor A (IL17RA)

The interleukin 17 receptors A (IL17RA) gene, located on chromosome 22 (22q11.1), encodes a membrane protein (IL17RA) which binds to interleukin 17A and 17 F and generates an inflammatory cascade [77]. This gene, therefore, plays a crucial role in developing psoriasis, being targeted by BDL [106,107].

Recent studies show an association between polymorphisms of IL17RA and response to treatment with biological therapy [80,81]. The rs4819554 polymorphism, located in the promoter region of IL17RA, was associated with response to anti-TNF drugs in Spanish patients (n = 238). Specifically, the IL17RA rs4819554-A allele was associated with better response (PASI 75 at 12 weeks) to anti-TNF treatment (OR = 1.86, CI95% = 1.05–3.27, p = 0.03) [80].

3.3.7. Interleukin 23 Receptor (IL23R)

The interleukin 23 receptor (IL-23R) is a subunit of the IL-23A/IL-23 receptor, which associates with IL-12RB1 to form the IL-23 receptor and induce T-cell, natural killer and macrophage stimulation by binding with IL-23 [108]. IL-23 is considered to be a proinflammatory cytokine, which participates in the acute response to infection in peripheral tissues [90]. The IL23R gene is located on chromosome 1 (1p31.3) and has demonstrated its importance in developing autoimmune inflammatory diseases and tumorigenesis [109,110].

The impact of polymorphisms in the IL23R gene on the response to anti-TNF drugs in biologic-naive patients diagnosed with moderate-to-severe psoriasis has been evaluated in a study with Spanish patients (n = 109). The IL23R rs11209026-GG genotype was associated with better treatment response at 6 months (PASI 90:66.3% vs. 0%, p = 0.006; ∆PASI: 86.8% vs. 67.8%, p = 0.013) [47]. Furthermore, the association between IL23R polymorphisms and the risk of developing toxicity and/or paradoxical psoriasis due to the anti-TNF medication has been demonstrated in a study with Spanish patients (n = 161) [90]. Specifically, the IL23R rs11209026-AG genotype was related to greater risk of developing paradoxical psoriasis during treatment (OR = 11.011.59, CI95% = 17.36–6984187.8, p = 0.005) [90].
3.3.8. Toll-Like Receptors

The Toll-like receptor (TLR) family consists of transmembrane proteins with an essential role in pathogen recognition and activation of the immune response. The external domain recognizes pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), while the TIR-type intracellular domain combines with IL-1, generating an inflammatory cascade.

Toll-Like Receptor 2 (TLR2)

The Toll-like receptor 2 (TLR2) gene is located on chromosome 4 (4q31.3). The function of the TLR2 protein is to recognize bacterial lipoproteins and other components of the microbial cell wall, cooperating with LY96 to mediate the innate immune response [111].

The influence of the TLR2 rs4696480 (T > A) and rs11938228 (C > A, T) polymorphisms has been investigated in 478 patients from Denmark diagnosed with moderate-to-severe psoriasis and treated with anti-TNF medication (n = 376) and UTK (n = 230) [71]. The TLR2 rs4696480-A allele (OR = 0.22, CI_95% = 0.08–0.59, p = 0.0032, q = 0.19) and the TLR2 rs11938228-C allele (OR = 0.30, CI_95% = 0.14–0.64, p = 0.0019, q = 0.19) showed a worse response to anti-TNF treatment (PASI 75 at 3 months) [71]. However, no significant association was found in patients treated with UTK [71].

Lymphocyte Antigen 96 (LY96)

The lymphocyte antigen 96 (LY96) gene, also known as MD2 protein (MD2), is located on chromosome 8 (8q21.11) and encodes a protein, which cooperates with TLR2 and TLR4 in the immune response to the membrane lipopolysaccharides and cell-wall components of Gram-positive and Gram-negative bacteria [112].

Various genetic alterations of LY96 have been studied. Specifically, the LY96 rs11465996 (C > G) polymorphism has been evaluated in a cohort of patients from Denmark diagnosed with moderate-to-severe psoriasis and treated with anti-TNF drugs and UTK (n = 478), showing that patients carrying the LY96 rs11465996-C allele had a worse response to UTK (ΔPASI at 3 months) (n = 230) (OR = 0.33, CI_95% = 0.15–0.71, p = 0.0044, q = 0.19) [71]. However, it was not possible to confirm this association in patients treated with anti-TNF medication [71].

TIR Domain-Containing Adapter Protein (TIRAP)

In region 11q24.2, we find the TIR domain-containing adapter protein (TIRAP) gene, also known as MYD88 adapter-like (MAL) [113]. TIRAP belongs to the group of genes containing a TIR domain and encodes a protein that interferes in the signaling cascade of TLR2 and TLR4 [114,115]. The possible genetic alterations of TIRAP could influence the immune response.

Previous studies have shown that the TIRAP rs8177374 (C > T; L180S) polymorphism interferes in the immune response by attenuating TLR2 signal transduction [113]. A study with 376 patients from Denmark diagnosed with moderate-to-severe psoriasis evaluated the effect of this polymorphism on response to UTK and anti-TNF drugs (PASI 75 at 12 weeks) [71]. In particular, patients carrying the TIRAP rs8177374-C allele showed a better response to UTK treatment (n = 230) compared to patients with the T allele (OR = 9.42, CI_95% = 1.96–45.3, p = 0.0051, q = 0.19) [71]. However, no statistically significant association was found between this polymorphism and anti-TNF response [71].

Toll-Like Receptor 5 (TLR5)

The Toll-like receptor 5 (TLR5) protein recognizes bacterial flagellins and recruits intracellular adapter proteins MYD88 and TRIF, leading to cytokine secretion and generating the inflammatory response. It, therefore, plays an important part in the relationship between the intestinal epithelium and enteric microbes and contributes to the composition of the intestinal microbiota throughout life. Its gene is located on chromosome 1 (1q41) [116,117].
Recently, the association of the TLR5 rs5744174 (A > G) polymorphism with the response to biological drugs indicated in moderate-to-severe psoriasis (anti-TNF: \( n = 376 \); UTK: \( n = 230 \)) has been evaluated in patients from Denmark [71]. Patients carrying the TLR5 rs5744174-A allele showed a better response (ΔPASI at 3 months) to UTK treatment (OR = 5.26, CI\(_{95%}\) = 1.93–14.38, \( p = 0.0012 \), q = 0.19) [71]. However, it was not possible to confirm this association in patients treated with anti-TNF medication (\( p > 0.05 \)) [71].

Toll-Like Receptor 9 (TLR9)

The Toll-like receptor 9 (TLR9) gene is located on chromosome 3 (3p21.2) and codes for a protein responsible for recognizing microbial nucleic acids (cytidine-phosphate-guanosine (CpG) dinucleotides) that induce the proliferation, activation, survival and production of B-cell antibodies [118].

The TLR9 rs352139 (T > C, A, G) polymorphism has been associated with the response to treatment with biological therapy in patients diagnosed with psoriasis. A study conducted in 478 patients of Danish origin with moderate-to-severe psoriasis treated with anti-TNF drugs (\( n = 376 \)) and/or UTK (\( n = 230 \)) showed that patients carrying the TLR9 rs352139-G showed greater effectiveness of anti-TNF treatment (drug survival at 225 days) (OR = 2.42, CI\(_{95%}\) = 1.32–4.44, \( p = 0.0044 \), q = 0.19) [71]. However, this association was not confirmed in patients treated with UTK [71].

3.3.9. Peptidoglycan Recognition Protein 4 (PGLYRP4)

Peptidoglycan recognition protein 4 (PGLYRP4) is responsible for triggering the innate immune response and exercising bactericidal action on recognizing murein peptidoglycans of Gram-positive bacteria [119]. The PGLYRP4 gene is located on chromosome 1 (1q21.3) and is directly implicated in the physiopathogenesis of psoriasis, as it plays an essential role in innate immunity; for this reason, it is also known as PSORS4 (susceptibility to psoriasis 4) [120]. Therefore, possible genetic alterations could greatly influence the response to anti-TNF drugs or cytokine inhibitors.

A study assessed the impact of the PGLYRP4–24 rs2916205 (C > T) polymorphism on the response to anti-TNF drugs (PASI 75 at 3 and 6 months) in patients of Spanish origin diagnosed with psoriasis (\( n = 144 \)) [42] and found an association between the PGLYRP4–24 rs2916205-C allele and worse anti-TNF response at 3 months of treatment (OR = 3.62, CI\(_{95%}\) = 1.00–13.07, \( p = 0.05 \)) [42].

3.3.10. F-Box and Leucine-Rich Repeat Protein 19 (FBXL19)

The F-box and leucine-rich repeat protein 19 (FBXL19) gene is situated in the 16p11.2 region and encodes a member of the Skp1-cullin-F-box family of E3 ubiquitin ligases. FBXL19 binds to the transmembrane receptor IL-1RL1 and regulates its ubiquitination and degradation, activating the innate immune system and MHC class I [121]. This gene has been linked to the regulation of pulmonary inflammation and psoriasis. Therefore, alterations of the FBXL19 gene may influence the response to biologics indicated in moderate-to-severe psoriasis.

The FBXL19 rs10782001 (G > A, C) polymorphism was evaluated in a study of predictive biomarkers for the risk of developing toxicity and/or paradoxical psoriasis due to anti-TNF drugs in Spanish patients with moderate-to-severe psoriasis (\( n = 161 \)) [87]. Patients carrying the FBXL19 rs10782001-GG genotype showed a higher risk of developing paradoxical psoriasis during treatment (OR = 32.85, CI\(_{95%}\) = 1.46–738.37, \( p = 0.0028 \)) [90].

3.4. Other Genes

In recent years, studies have been conducted on other genes implicated in the pathogenesis of psoriasis that may exercise a crucial role in response to treatment with biological therapies in patients diagnosed with psoriatic disease [122].

The protein encoded by the CDKAL1 gene, located on chromosome 6 (6p22.3), belongs to the methylthiotransferase family and catalyzes the methylthiolation of N6-threonylcarba-
moyladenosine, producing 2-methylthio-N6-threonylcarbamoyladenosine at position 37 in the transfer RNA that reads codons beginning with adenine (AAA and AAG) [123]. This gene has been associated with autoimmune pathologies such as non-insulin-dependent diabetes mellitus [124]. There are various genetic alterations of CDKAL1; specifically, the rs6908425 (C > A, T) variant affects the response to anti-TNF drugs, as has been demonstrated in two studies [42,125]. Coto-Segura et al., associated the CDKAL1 rs6908425-C allele with better response (PASI 75 at 24 weeks) in 116 Spanish patients diagnosed with moderate-to-severe psoriasis (OR = 3.14, CI95% = 1.40–7.05, p = 0.005) [125]. Conversely, these results were not validated in a cohort of Spanish patients (n = 133) since patients carrying the CDKAL1 rs6908425-C allele showed worse treatment response at six months (p = 0.013) [42].

The caspase recruitment domain family member 14 (CARD14) gene, which has a mutation named PSORS2 because of its relationship to psoriasis, encodes a scaffolding protein belonging to the membrane-associated guanylate kinase (MAGUK) family of proteins involved in various cellular processes, such as cellular adhesion, signal transduction and control of cell polarity. It has been shown that this protein interacts specifically with BCL10, a protein that positively regulates cell apoptosis and activates NF-κB [126]. Genetic alterations may influence the response to biologics indicated for treating psoriasis. The CARD14 rs11652075 (C > T; R820T) polymorphism produces a change in position 820 from tryptophan (T) to arginine (R), and its usefulness as a predictive biomarker of response to anti-TNF drugs (PASI 75 at week 24) has been evaluated in Spanish patients (n = 116). The results of the study revealed that the patients carrying the CARD14 rs11652075-CC genotype showed better response compared to those with the T allele (OR = 3.71, CI95% = 1.30–10.51, p = 0.01) [127].

On the other hand, a recent study analyzed 124 polymorphisms of a number of candidate genes associated with response to ETN (PASI 75 at 3 and 6 months) in 78 Spanish patients diagnosed with moderate-to-severe plaque psoriasis; it found that the PTTG1 rs2431697 (T > C), MAP3K1 rs96844 (G > A) and ZNF816A rs9304742 (T > C) polymorphisms were associated with good response to ETN at 3 months of treatment (PTTG1 rs2431697-T: p = 0.04; MAP3K1 rs96844-C: p = 0.009; ZNF816A rs9304742-T: p = 0.006). In addition, the G allele of the GBP6 rs928655 (G > A, C) polymorphism has been associated with better response to ETN at 6 months (n = 68; p = 0.014) [40]. The association of the MAP3K1 rs96844 and ZNF816A rs9304742 polymorphisms with good response to anti-TNF medication (PASI 75 at 3 and 6 months) was subsequently confirmed in a study with 144 Spanish patients diagnosed with psoriasis (MAP3K1 rs96844 and ZNF816A rs9304742 polymorphisms with good response to anti-TNF medication (PASI 75 at 3 months: OR = 0.004; at six months: p = 0.045) and ZNF816A rs9304742-T at 3 months (p = 0.02)).

Two further polymorphisms associated with anti-TNF response (PASI 75 at 3 and 6 months) were also identified. In particular, the A allele of the CTNNA2 rs11126740 (A > C, G, T) polymorphism showed worse response at 3 months (n = 144; p = 0.003) and patients carrying the T allele of the HTR2A rs6311 (C > A, T) polymorphism were associated with worse response at 6 months (n = 133; p = 0.038) [42].

Finally, it is worth highlighting the only study that has evaluated the influence of the presence of particular genetic polymorphisms on susceptibility to developing toxicity and/or paradoxical psoriasis due to anti-TNF drugs, conducted in 161 Spanish patients diagnosed with plaque psoriasis (Table 3) [90]. Specifically, it showed that patients carrying the CTLA4 rs3087243-AG/GG or TAPI rs1800453-AG genotypes, or the previously mentioned FBXL19 rs10782001-GG, IL23R rs11209026-AG and SLCL12A8 rs651630-AA, had a higher risk of developing paradoxical psoriasis during treatment (CTLA4 rs3087243-AG/GG: OR = 0.001, CI95% = 0−0.24, p = 0.012; TAPI rs1800453-AG: OR = 0.009, CI95% = 0−0.45, p = 0.018) [90]. There are few statistically significant results between genetic polymorphisms and developing toxicity in patients diagnosed with psoriasis treated with biological therapies. However, in other therapies, such as methotrexate, an association has been found. Particularly, patients carriers of the Betaine-homocysteine
S-methyltransferase (BHMT) rs3733890 variant allele have showed an increased risk of hepatotoxicity (OR = 3.17, CI95% = 1.18–8.49, \( p = 0.022 \)) [122].

### 4. Conclusions

There is a wide range of biologics indicated for moderate-to-severe psoriasis that have proved effective and safe; however, certain patients do not obtain the expected effect in the short or long term and experience various degrees of toxicity. This variability in short- and long-term response and in toxicity may be due to genetic factors. Precision medicine research has assessed the influence of polymorphisms of genes involved in the pathological environment of the disease, metabolism or mechanism of action on the efficacy of these drugs. Specifically, the allelic variants of HLA genes have been extensively studied, but the results are contradictory. The HLA-A rs9260313/TRA3/PIF2 rs13190932 and HLA-Cw*06/LCE3B_LCE3B del/ins haplotypes, together with the HLA-B/MICA rs1347088 and HLA-C rs12191877, rs1048554 and rs610604 polymorphisms, have shown an association with the response to anti-TNF drugs. However, the presence of the HLA-Cw*06 alleles has been shown to be associated with response to UTK but not to anti-TNF drugs. In addition, associations with response to anti-TNF drugs in patients diagnosed with moderate-to-severe psoriasis have been found for polymorphisms of the following genes: TNF (TNF-238 rs361525, TNF-308 rs1800629, TNF-857 rs1799724, TNF-1031 rs1799964), IL6 (rs1800795), IL12B (rs2546890), TNFAIP3 (rs6920220), PDE3A-SLCO1C1 (rs11045392-rs3794271), TNFRSF1A (rs1061622), CD84 (rs6427528), FCGR2A (rs8101274), FCGR3A (rs396891), IL17RA (rs4819554), IL23R (rs11209026), TLR2 (rs4696480 and rs11938228), TLR9 (rs352139), PGLYRP4–24 (rs2916205), CDKAL1 (rs6908425), CARD14 (rs11652075), PTTG1 (rs2431697), MAP3K1 (rs96844), ZNF816A (rs9304742), GBP6 (rs928655), CTNNNA2 (rs11126740) and HTR2A (rs6311). Furthermore, polymorphisms of the following genes have shown an association with response to UTK: IL12B (rs3213094), TNFAIP3 (rs610604), LY96 (rs1145996), TIRAP (rs8177374) and TLR5 (rs5744174), and the IL1B rs1143623 and rs1143627 and IL17F rs763780 polymorphisms have proved to be associated with susceptibility to developing toxicity and paradoxical psoriasis due to anti-TNF drugs.

In conclusion, the results suggest that polymorphisms detected in the HLA genes, in genes that encode cytokines (TNF, IL genes, TNFAIP3), transporters (PDE3A-SLCO1C1, SLC12A8), receptors (TNFRSF1B, CD84, FCGR2A and FCGR3A, IL17RA, IL23R, TLR genes, PGLYRP4) and associated proteins (TNFAIP3, LY96, TIRAP, FBXL19), as well as other genes implicated in the pathogenesis of psoriasis (CDKAL1, CARD14, PTTG1, MAP3K1, ZNF816A, GBP6, CTNNNA2, HTR2A, CTLA4, TAPI1) can be used in the future as predictive markers of treatment response and/or toxicity with biological therapies in patients diagnosed with moderate-to-severe psoriasis, tailoring treatment to the individual patient.
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