Pharmacogenetics of Psoriasis Treatment

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Abstract
Psoriasis is a chronic systemic, immune-mediated disorder of unknown aetiology, usually presenting with typical inflammatory skin lesions and/or joint manifestations, but systemic inflammation that may lead to the development of co-morbidities may also be present. First-line therapy encompasses local cutaneous treatment and phototherapy, but with more severe symptoms or systemic course, systemic treatment with methotrexate (MTX), immunosuppressant cyclosporine, retinoid acitretin or biologicals may be used. Treatment response varies between patients in terms of efficacy and/or toxicity, which could, among other reasons, be due to genetic differences between patients. Approximately 10–30% of patients experience adverse drug reactions with MTX treatment, leading to discontinuation of MTX mostly due to hepatotoxicity. Around 15% of patients experience adverse events when treated with biologicals; however, the most frequent reason for discontinuation is inefficacy or loss of the initially favourable response over time. Inefficacy or occurrence of adverse drug reactions cannot be predicted, so genetic biomarkers of drug response in combination with clinical data could be helpful in treatment planning. Several polymorphic genes have already been associated with treatment outcome, most of them involved in drug metabolism, transport and target pathways. Genetic biomarkers could be helpful in personalized care of psoriasis patients in order to prevent adverse events or predict inefficacy of a certain drug.

Keywords: psoriasis, pharmacogenetics, genetic polymorphisms, personalized medicine, methotrexate, biologic agents

1. Introduction
Psoriasis is a chronic systemic immune-mediated disorder of which etiopathogenesis is not yet fully understood, though there is evidence of genetic, immunologic and environmental factors playing a role in the development and the severity of the disease. The most common symptoms involve typical inflammatory skin lesions, but systemic inflammation may also be
present [1, 2]. Psoriatic arthritis (PsA) is the most frequent systemic manifestation that can accompany the skin lesions and occurs in up to 40% of patients [3]. Systemic inflammation is also one of the reasons for the occurrence of many other comorbidities in patients with psoriasis, such as metabolic syndrome which includes obesity, type 2 diabetes, hypertension and dyslipidaemia, cardiovascular diseases, chronic inflammatory bowel disease and also cancer in some cases [4]. Furthermore, lower quality of life and psychological disorders are also more frequent among psoriasis patients as compared to general population [5, 6]. It is proven that lifestyle, including diet, smoking and alcohol consumption, influences the occurrence and the course of psoriasis and the comorbidities [7]. Elevated body mass index and visceral fat can also increase the probability of more progressive course of the disease [7].

The severity of the disease is evaluated by the Psoriasis Area and Severity Index (PASI) score that takes into account the area of the affected skin, the thickness of skin plaques and the severity of inflammation. PASI score is calculated before the treatment strategy is chosen and is also used to monitor the treatment response. The response to treatment is considered to be good when PASI has decreased for at least 75% from the baseline score in 3–6 months after the first dose was administered (PASI75) [8]. The minimum treatment goal is usually set at PASI decreasing for at least 50% from the baseline score (PASI50). If PASI50 is not met, the treatment plan is usually changed [9]. However, PASI only evaluates the dermatological manifestations of the disease and neglects the psychological aspect. Therefore, Dermatology Life Quality Index (DLQI) is also assessed with a questionnaire to evaluate the impact of psoriasis on a patient’s physical, psychological and social well-being. The treatment goal is to achieve DLQI of zero to one after 2–4 months of treatment, but if this cannot be achieved, at least DLQI below five should be aimed for [9].

The patient’s response to systemic psoriasis treatment cannot be predicted. Furthermore, the interindividual variability in the treatment response is quite extensive and adverse events occur frequently [6]. A study conducted 3 years ago discovered that approximately 75% of traditional systemic drugs are discontinued after 143 days of treatment ($p < 0.0001$), mostly because of adverse events ($p < 0.001$) [8]. Besides the choice and the dose of the drug and patient’s compliance to treatment, many other factors may influence the treatment response, such as patient’s demographic characteristics (age, gender, body mass, ethnicity), the severity of the disease, concomitant treatment with other drugs, patient’s diet, alcohol consumption, cigarette smoking as well as comorbidities. However, a lot of attention has been lately focused on the role of genetic factors that may influence the course of the disease and treatment response [10, 11]. Several pharmacogenetics studies were performed to assess the influence of genetic factors on treatment response, mainly investigating the interindividual variability in genes involved in drug metabolism, transport and mechanisms of action and the association between genetic variability and the efficacy of treatment and the occurrence of adverse events [7, 12].

1.1. Genetic factors are associated with treatment response

Our genetic characteristics are encoded in our genome [13]. Interindvidual differences between people are due to differences in less than 1% of genomic DNA sequence between unrelated individuals. Different variants of the same gene or genetic locus are called alleles. A variant is
called a polymorphism when there are at least two alleles present in the population and the frequency of the less prevalent allele is more than 1%. A great majority of variants are due to single nucleotide polymorphisms (SNPs), which means that alleles differ only in one nucleotide. In addition to SNPs, deletions, insertions, duplications of nucleotides or longer sequences, microsatellites, changes in variable number of tandem nucleotide repeats (VNTR) and others may account for genetic polymorphism. Genetic polymorphisms may influence the process of transcription, translation and/or function of proteins. If variants change the binding site for different regulatory proteins, transcription may be altered. Amino acids are encoded as a sequence of three nucleotides, called codons. If a polymorphism changes a codon, another amino acid can be incorporated into a protein, which can change the characteristics and function of a protein. Insertion of only one nucleotide causes frame shift, which results in a premature stop codon and non-functional protein. The same happens after a stop codon is formed in the middle of an exon or when SNPs alter mRNA splicing. Gene deletions may cause depletion of proteins while, on the other hand, gene duplications lead to excess of the encoded protein [14].

Genetic polymorphisms may also influence expression and function of proteins involved in drug metabolism and transport as well as drug targets and their effector pathways. Because of that, genetic polymorphisms may influence patients’ response to drugs and the occurrence of adverse effects. Pharmacogenetics studies the associations between genetic polymorphisms and the course of disease and response to treatment. The aim of this chapter is to summarize the current knowledge on pharmacogenetic polymorphisms that may influence the response to systemic treatment in patients diagnosed with psoriasis. Such polymorphisms have been investigated as predictive biomarkers of treatment response that would support personalized treatment approaches in patients with psoriasis.

2. Pharmacogenetics of systemic psoriasis treatment

2.1. Low-dose methotrexate

Methotrexate (MTX) is an immunomodulatory drug that is widely used in the treatment of psoriasis and PsA and is frequently the first-line systemic treatment for these two indications. It is usually orally administered once per week in doses of 7.5–30 mg [9]. Good response to treatment is achieved in approximately 50% of cases [8]. On the other hand, from 10 to 30% of patients have to discontinue the treatment because of adverse drug reactions. These include nausea, malaise, gastrointestinal ulcers, depression, infections, nephrotoxicity and most importantly hepatotoxicity and bone marrow suppression [9]. Adverse events are usually mild and can be eliminated by dose reduction. However, some adverse events may be severe or even life-threatening and cannot be predicted. This is the reason why patients treated with MTX are monitored very closely, and liver and kidney functions and blood status have to be checked regularly [8]. With the low doses used for psoriasis treatment, MTX plasma concentrations are too low to be measured, so drug monitoring cannot be used to predict the occurrence of adverse events. It has been therefore proposed that genetic polymorphisms should be investigated as predictors of response to treatment, either efficacy or toxicity [15–17].
MTX is a folate analogue and as such inhibits folic acid metabolism. Folic acid is a donor of methyl group in the process of deoxythymidylate synthesis that is required for DNA synthesis and cell proliferation as well as donor of methyl groups for methionine synthesis that directs the methyl group towards methylation reactions [18].

MTX enters the cell through the reduced folate carrier SLC19A1 and is activated by folypolyglutamate synthase that adds glutamate moieties to the molecule. MTX polyglutamate primarily inhibits dihydrofolate reductase (DHFR), thus inhibiting also thymidylate synthase (TYMS) reaction, which results in inhibition of DNA synthesis. Indirectly it inhibits also other enzymes of folate metabolic pathway and methylation reactions, such as methylenetetrahydrofolate dehydrogenase (MTHFD1), methylenetetrahydrofolate reductase (MTHFR), methionine synthase (MS) and methionine-synthase reductase (MSR) (Figure 1) [19].

MTX is also adenosine pathway inhibitor. It inhibits the enzyme 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase (ATIC), which results in elevated levels of AICAR. AICAR inhibits adenosine deaminase (ADA) and this consequently leads to higher intercellular concentrations of adenosine. Adenosine is released into circulation, and its binding to adenosine receptors on the target cells contributes significantly to the anti-inflammatory effects of MTX (Figure 1) [18].

![Figure 1. Schematic view of MTX mechanism of action on folate and adenosine pathway. SLC19A1—reduced folate carrier, MTX—methotrexate, ABC—ABC transporters (ATP dependent), FPGS—folypolyglutamate synthase, GGH—gamma-glutamyl hydrolase, MTXglu—methotrexate polyglutamate, DHFR—dihydrofolate reductase, THF—tetrahydrofolate, MTHFD1—methyltetrahydrofolate dehydrogenase, SHMT1—serine hydroxymethyltransferase, MTHFR—methylene tetrahydrofolate reductase, MTR—methionine synthase, MTRR—methionine synthase reductase, TYMS—thymidylate synthase, DHF—dihydrofolate, dTMP—deoxothymidine monophosphate, dUMP—deoxyuridine monophosphate, AICAR—5-aminoimidazole-4-carboxamide ribonucleotide, ATIC—ATIC transformylase, THF—tetrahydrofolate, FAICAR—5-formamidoimidazole-4-carboxamide ribotide, ITP—inosine triphosphate, IMP—inosine monophosphate, AMP—adenosine monophosphate, AS—adenylosuccinate, AMPD1—AMP deaminase, ITPA—inosine triphosphatase, ADA—adenosine deaminase.](image-url)
Cells are protected from toxic effects of MTX by transmembrane transporters ABC (ATP-binding cassette), especially ABCB1, ABCC2 and ABCG2. They are ATP dependent, and they actively pump MTX out of the cell. On the other hand, solute carriers (SLC), such as SLC19A1 and SLCO1B1, facilitate MTX transport in the direction of the concentration gradient (Figure 1) [19].

Most of the genes coding for the enzymes in folate and adenosine pathway as well as for folate and MTX transporters are polymorphic. As genetic polymorphisms may lead to differences in expression and activity of enzymes, polymorphisms in the genes coding for the above mentioned proteins (transporters and enzymes) contribute to interindividual variability in therapeutic response and toxicity profile of drugs among patients. Several of the above mentioned polymorphic genes were already studied in relation to MTX treatment response in rheumatoid arthritis (RA) and cancer, but studies regarding psoriasis are scarce. Studies pointing out positive associations between polymorphisms and response to MTX in psoriasis and PsA are listed in Table 1.

| Genes  | Variants | p-value | Predicted effect                                      | Reference |
|--------|----------|---------|-------------------------------------------------------|-----------|
| **Efficacy** |          |         |                                                       |           |
| TYMS   | rs34743033 28-bp repeat | 0.048   | Carriers of the 3R allele susceptible to poor response to MTX | [20]      |
|        |          |         |                                                       |           |
| ABCC1  | rs35592 c.1219-176T>C | 0.008   | Homozygotes for the major allele respond better to MTX | [25]      |
|        | rs2238476 c.3391-1960G>A | 0.02    |                                                       |           |
|        | rs28364006 c.4009A>G | 0.02    |                                                       |           |
| ABCG2  | rs13120400 c.1194+928A>G | 0.03    | Minor allele associated with better response to MTX   | [25]      |
|        | rs17731538 c.204-1592C>T | 0.007   | Major allele associated with better response to MTX   |           |
| DHFR   | rs1232027 g.80619201G>A | 0.02    | Minor allele associated with better response to MTX   | [15]      |
| **Toxicity** |          |         |                                                       |           |
| SLC19A1| rs1051266 c.80A>G | 0.025   | A allele associated with occurrence of adverse events  | [20]      |
|        |          |         |                                                       |           |
|        |          |         |                                                       |           |
|        |          |         |                                                       |           |
|        |          | 0.03    | A allele associated with toxicity                      | [25]      |
| MTHFR  | rs1801131 c.1298A>C Glu429Ala | 0.042   | C allele associated with lower risk of hepatotoxicity  | [20]      |
|        | rs1801133 c.677C>T Ala222Val | 0.04    | Homozygotes for the minor allele more susceptible to liver toxicity | [15]      |
2.1.1. Genetic variability in folate pathway and MTX treatment

The direct target of MTX within folate pathway is DHFR that converts dihydrofolic acid into tetrahydrofolic acid (Figure 1). It is therefore surprising that the impact of DHFR polymorphisms on the efficacy and toxicity of treatment of cutaneous psoriasis have not been studied.

| Genes  | Variants | p-value | Predicted effect                                                                 | Reference |
|--------|----------|---------|----------------------------------------------------------------------------------|-----------|
| TYMS   | rs34489327 nt.1494del6 | 0.015   | Polymorphism increases the risk for hepatotoxicity                                | [20]      |
|        | rs34743033 28-bp repeat | 0.0025  | 3R allele increased risk for adverse events in patients without folic acid supplementation |          |
| ATIC   | rs2372536 c.347C>G | 0.038   | G allele associated with increased risk for MTX discontinuation due to adverse events | [20]      |
|        | rs4672768 c.1660-135G>A | 0.02     | Homozygotes for the major allele more susceptible to MTX toxicity                 | [22]      |
|        | rs2238476 c.3391-1960G>A | 0.01     | Homozygotes for the major allele more susceptible to toxicity                      | [25]      |
|        | rs3784864 c.616-1641G>A | 0.03     | Carriers of at least one major allele more susceptible to toxicity               |           |
|        | rs246240 c.616-7942A>G | 0.0006   | Homozygotes for the major allele more susceptible to toxicity                     |           |
|        | rs3784862 c.615+413G>A | 0.002    | Homozygotes for the major allele more susceptible to toxicity                     |           |
|        | rs1967120 c.489+409G>A | 0.01     | Carriers of at least one major allele more susceptible to toxicity               |           |
|        | rs11075291 c.49-3198G>A | 0.008    | Carriers of at least one major allele more susceptible to toxicity               |           |
|        | rs5760410 g.24815406G>A | 0.03     | Homozygotes for the major allele more susceptible to toxicity                     | [25]      |

Table 1. Genetic polymorphisms in folate and adenosine pathway and MTX transporters associated with MTX treatment outcome in patients with psoriasis or psoriatic arthritis.

2.1.1. Genetic variability in folate pathway and MTX treatment

The direct target of MTX within folate pathway is DHFR that converts dihydrofolic acid into tetrahydrofolic acid (Figure 1). It is therefore surprising that the impact of DHFR polymorphisms on the efficacy and toxicity of treatment of cutaneous psoriasis have not been studied.
TYMS is one of the key enzymes providing deoxythymidylate for DNA synthesis, thus enabling cell proliferation. Two common functional polymorphisms in TYMS gene could influence therapeutic response to MTX [20]. rs34743033 polymorphism in the promoter region (5′UTR) is due to a double or triple tandem 28 bp repeat (2R and 3R). Because the 3R allele is associated with increased transcription/translation of the gene, rs34743033 may contribute to elevated activity of the enzyme and lead to depletion of the substrate for homocysteine methylation (Figure 1). The second most studied TYMS polymorphism, rs34489327, is due to a 6 bp deletion at nucleotide 1494 in the 3′UTR (3′UTR 6bp del) and leads to decreased TYMS formation [21]. The presence of 3R allele (homozygous or heterozygous variant genotype) was significantly related to poor response to treatment (OR = 2.96; p = 0.048), in fact carriers of 3R allele were three times less likely to respond to MTX. Furthermore, among psoriasis patients, the 3R allele was significantly (p = 0.029) more frequent in non-responders (64%) compared to responders (50%). On the other hand, 3′UTR 6bp del allele did not show any association with MTX efficacy. After including only patients not receiving folic acid supplementation, both 5′UTR 3R and 3′UTR 6bp del alleles were more frequent in non-responders compared to responders, but association with treatment response was not significant [20]. The TYMS 3′UTR 6bp del polymorphism showed significant association with occurrence of adverse events (p = 0.025), irrespective of folic acid supplementation. When researchers excluded patients who received folic acid supplementation, both polymorphisms (2R/3R repeat and 6 bp deletion) appeared to influence adverse events occurrence. Patients with TYMS 5′UTR 3R/3R genotype had 13-fold (OR = 13.2) higher chance of experiencing any adverse event, 15-fold (OR = 15.75) higher chance of developing hepatotoxicity and 12-fold (OR = 11.8) higher chance of experiencing a symptomatic adverse event compared to patients with other genotypes. TYMS 5′-UTR 3R allele also conferred risk for MTX discontinuation (p = 0.033) in this group of patients. The 3′UTR 6bp del was more frequent in patients experiencing adverse events or symptomatic adverse events, which may be due to the reduced mRNA expression caused by this polymorphism. Among patients with no concomitant folate supplementation, carriers of 3′UTR 6bp del polymorphism had an eight-fold (OR = 8.4) increased risk of developing elevated ALT levels [20]. Folic acid supplementation during MTX treatment is thus important for decreasing the risk of adverse events.

MTHFR is the central enzyme in folate pathway as it is responsible for the conversion of 5,10-methyltetrahydrofolate, which is a substrate for TYMS, to 5-methyltetrahydrofolate, which is a substrate for homocysteine remethylation (Figure 1). The most studied polymorphisms in MTHFR gene are rs1801133 (c.677C>T, p.Ala222Val) and rs1801131 (c.1298A>C, p.Glu429Ala), which cause reduced activity of the enzyme. Homozygous (TT) or heterozygous (CT) genotypes of the MTHFR 677C>T polymorphism decrease the enzyme’s activity by 70 or 40%, respectively. Furthermore, a homozygous (CC) genotype of the 1298A>C polymorphism decreases the enzyme’s activity for 40%. Due to decreased enzyme activity, patients heterozygous for these polymorphisms could be more susceptible to MTX-induced adverse events [21]. In the first pharmacogenetic study of psoriasis patients that included 203 patients
followed for 3 months after the initiation of treatment, 104 patients experienced at least one adverse event and, out of those, 67 patients (33%) had to discontinue the therapy. The most common adverse event was nausea (35%), closely followed by abnormal transaminase levels (30%). This study reported lower risk of developing hepatotoxicity in patients with 1298C allele \( (p = 0.042) \) and in patients with double heterozygosity 677CT/1298AC not receiving folic acid supplementation [20]. On the other hand, the frequency of \( MTHFR \) polymorphisms did not differ significantly between responders and non-responders [20]. Similarly, no association was found between \( MTHFR \) 677T allele and MTX efficacy in another study that included 330 patients, of which 250 were classified as responders and 80 as non-responders [22]. PsA patients carriers of \( MTHFR \) 677TT genotype suffered higher risk for hepatic adverse events compared to non-carriers (OR = 2.53; \( p = 0.04 \)) [15].

Polymorphisms in \( MTHFD1 \), \( MTR \) and \( MTRR \) genes were not studied in psoriasis patients yet, although they were associated with MTX toxicity in RA patients in some of the studies [19, 23].

2.1.2. Genetic variability in adenosine pathway and MTX treatment

MTX directly inhibits ATIC, the key enzyme in the adenosine pathway (Figure 1). The consequent accumulation of AICAR indirectly leads to accumulation of adenosine in circulation, which acts as an anti-inflammatory factor. The most studied genetic polymorphism in \( ATIC \) is rs2372536 (c.347C>G, p.Thr116Ser), which changes the codon, so serine is incorporated into the protein instead of threonine. According to various studies, this polymorphism does not affect patient’s response to MTX, and its frequency does not differ between responders and non-responders, but it did have a slight influence on the occurrence of adverse events, especially nausea, elevated alanine and aminotransferase levels. Patients who discontinued the MTX therapy had a higher frequency of the 347G allele \( (p = 0.038) \), but genotype distribution was not significantly different. Carriers of \( ATIC \) 347G allele had 1.6-fold increased risk of discontinuing the treatment because of adverse events [10, 20]. A study by Warren et al. investigated several \( ATIC \) polymorphisms and also found association with the outcome of MTX therapy. Two polymorphisms, in particular, rs2372536 and rs4672768, were associated with MTX toxicity \( (p = 0.01 \) and \( p = 0.02 \), respectively) [22].

ADA is the enzyme inhibited because of accumulation of AICAR following MTX treatment. A functional polymorphism \( ADA \) rs73598374 (c.22G>A, p.AsplAsn) lowers the enzyme activity and may be thus associated with higher efficacy of MTX. The association between this polymorphism and toxicity and efficacy of MTX was, however, not confirmed in psoriasis patients [20].

No other polymorphic genes in adenosine metabolic pathway were investigated in psoriasis patients. However, in Slovenian patients with RA, several other genes in adenosine pathway were studied. \( AMPD1 \) rs17602729 (c.34C>T, p.Gln45Ter) polymorphism was associated with better response to MTX. On the contrary, \( ITPA \) rs1127354 polymorphism (c.94C>A, p.Pro23Thr) that may decrease the release of adenosine into the circulation was associated with poor response to MTX [24].
The anti-inflammatory effect of adenosine is directly related to its binding to the adenosine receptors (ADORA). Only one pharmacogenetic study investigated adenosine receptors so far and included 374 patients with chronic plaque psoriasis, who had been treated with MTX for at least 3 months. No significant association was detected between polymorphisms in ADORA1 gene for adenosine receptor A1 and ADORA2A gene for adenosine receptor A2a and the efficacy of MTX. However, there was one polymorphism, ADORA2A rs5760410, that was associated with higher probability of adverse events \( (p = 0.03) \) \[25\].

2.1.3. Genetic variability in folate and MTX transport and MTX treatment

Polymorphisms in transporters may influence intracellular MTX levels and, thus, also influence therapeutic effect. SLC19A1 (RFC1) is a reduced folate carrier, which facilitates the MTX transport into the cell. Many studies investigated the most common functional polymorphism in SLC19A1 (RFC1) gene, rs1051266 (c.80G>A, p.His27Arg) and its influence on MTX treatment outcome. According to some studies, this polymorphism influences toxicity but has no effect on efficacy \[20, 25\]. On the contrary, studies in RA patients showed a better response to MTX in carriers of 80AA genotype \[21\]. Psoriasis patients with documented adverse events had a higher frequency of 80A allele \( (p = 0.025) \) in either homozygous or heterozygous state, so the effect was dominant \( (p = 0.049) \). When specific adverse events were analysed, SLC19A1 (RFC1) 80A allele was associated with higher risk for hepatotoxicity \( (p = 0.053) \) and symptomatic side effects \( (p = 0.043) \). Also, an epistatic effect of the loci, RFC1 and TYMS, was observed. Two-loci genotype RFC1 80A/TS 3'-UTR 6bp del increased the risk of symptomatic side effects nearly three-fold \( (OR = 2.86) \). In addition, two-loci genotype RFC1 80A/ATIC 347G increased the risk for MTX discontinuation \( (p = 0.0076) \). Even the RFC 80A allele alone increased the risk of discontinuation in patients not receiving folic acid supplementation \[20\]. A weak association of this polymorphism to the onset of toxicity \( (p = 0.03) \) was shown in the study by Warren et al. \[25\]. However, in PsA, rs1051266 polymorphism was related neither to efficacy nor to toxicity of MTX \[15\].

On the other hand, polymorphisms in genes coding for the efflux ABC transporters showed association with efficacy as well as toxicity. In the study by Warren et al., two polymorphic transporter genes were investigated in psoriasis patients: ABCC1 and ABCG2. In ABCC1, 40 polymorphisms were tested and three of them were associated with MTX efficacy. The most significant one was rs35592 \( (p = 0.008) \), the other two were rs2238476 \( (p = 0.02) \) and rs28364006 \( (p = 0.02) \). For all the three polymorphisms, the homozygosity for wild-type (major) allele was associated with better response to MTX. They also tested 12 ABCG2 SNPs and two of them, rs17731538 and rs13120400, were associated with response to MTX although the effect was very small. In the case of rs17731538, the wild-type (major) allele was associated with better response \( (p = 0.007; OR = 2.1) \), whereas in the case of rs13120400 the minor allele was associated with better response \( (p = 0.03; OR = 1.8) \) \[25\]. When investigating the influence on toxicity, six ABCC1 SNPs were found to be associated with MTX adverse events. The strongest correlation was found with polymorphisms rs246240 \( (p = 0.001; OR = 2.2) \) and rs3784862 \( (p = 0.002; OR = 2.1) \), in both cases homozygotes for the major allele were at increased risk for toxicity. Carriers of these polymorphisms had up to two-fold higher risk of experiencing an adverse drug reaction, irrespective of the type of the adverse event. Furthermore, the correlation between the onset of
toxicity and rs2238476 was also observed. Carriers of two copies of the rs2238476 major allele had a higher chance of experiencing adverse events ($p = 0.01; \text{OR} = 2.49$). On the other hand, the investigated polymorphisms in $ABCG2$ gene were not associated with toxicity [25].

### 2.2. Cyclosporine

Cyclosporine is an orally administered systemic immunosuppressive drug that may be used to treat the most resistant forms of psoriasis, especially the plaque-type diseases [9]. It inhibits the first phase of T-lymphocyte activation, thus decreasing the levels of inflammatory cytokines, among them interleukin-2 (IL2) and interferon-gamma (IFNG) [26]. It is usually administered in doses of 2.5–5 mg/kg of body weight/day [9]. The current knowledge on cyclosporine pharmacogenetics comes from studies in recipients of solid organ transplants. Bioavailability and clearance of the drug are influenced by polymorphic P-glycoprotein ($ABCB1$) in gastrointestinal tract and CYP3A4 and CYP3A5 in the liver, suggesting that these polymorphisms could also influence the response to cyclosporine treatment in psoriatic patients [27, 28]. There was only one pharmacogenetic study performed on psoriasis patients treated with cyclosporine, and it focused only on $ABCB1$ polymorphisms (Table 2). In this study, rs1045642 (3435C>T) was associated with response to cyclosporine (OR = 2.995; $p = 0.0075$). The frequency of the minor T allele was found to be higher in the non-responders group, which means that T allele carriers have lower chance of good response [29].

### 2.3. Acitretin

Acitretin is a vitamin A derivative that belongs to the second-generation retinoids [30]. It reduces proliferation of epidermal keratinocytes and promotes their differentiation. It is also used as an anti-inflammatory agent. It is administered orally in doses of 0.5–0.8 mg/kg daily. Usually, it is used in combination with topical treatment as well as phototherapy [9]. Studies pointing out positive associations between polymorphisms and response to acitretin in psoriasis are listed in Table 3. The most widely studied polymorphisms lie in the gene coding for vascular endothelial growth factor ($VEGF$). Angiogenesis, especially inappropriate vascular expansion, is indeed a common pathogenic component of psoriasis. Two polymorphisms within $VEGF$, rs2010963 and rs833061, have been implicated in diseases with strong angiogenic background [31]. Besides the influence on treatment response, they may also influence the time of onset of the disease [32, 33]. rs833061 was associated with response to treatment in patients with early onset chronic plaque psoriasis. The frequency of rs833061TT genotype was higher in patients who were non-responsive to acitretin compared to

| Genes   | Variants                  | $p$-value | Predicted effect                                      | Reference |
|---------|---------------------------|-----------|-------------------------------------------------------|-----------|
| $ABCB1$ | rs1045642 c.3435C>T       | 0.0075    | Minor T allele associated with poor response to cyclosporine | [29]      |

Table 2. Genetic polymorphism associated with response to cyclosporine treatment in patients with psoriasis.
good responders ($p = 0.04$). Patients with the TT genotype were almost twice as likely to not respond to therapy as to respond. On the other hand, rs833061 TC genotype frequency was increased in the group of patients that responded well to acitretin compared to non-responders ($p = 0.01$). Patients with TC genotype were almost twice as likely to respond to therapy as to fail [31]. However, no association was found between rs2010963 and therapeutic response [31].

Another study performed on a group of Italian patients found an association between the HLA-G genotype and response to acitretin. HLA-G 14 bp del allele ($p = 0.008$; OR = 7.74) and del/del genotype ($p = 0.05$) were more frequent in responders compared to non-responders [34]. Another pharmacogenetic study investigated polymorphisms in the gene coding for apolipoprotein E (APOE). No association with treatment response was found for polymorphisms APOE rs429358 and rs7412 [35].

### 2.4. Biologic drugs

Biologic drugs specifically bind to their target, usually inflammation mediators or their receptors, and inhibit their action, which results in anti-inflammatory effect. Biologics used in treatment of psoriasis mainly inhibit tumour necrosis factor alpha (TNFα) and several interleukins (IL)—IL17, IL12 and IL23. Among the biologics used for psoriasis treatment, infliximab, adalimumab, etanercept are TNFα inhibitors, while ustekinumab is an IL12/23 inhibitor and secukinumab is IL17 inhibitor [36, 37].

Biologic drugs are relatively safe and well tolerated. Adverse events occur only in approximately 15% of patients, but the symptoms are usually not severe and are not the reason for discontinuation [38]. The most common adverse events are injection-site reaction (pain, erythema, itching and haemorrhage) and different infections, mostly of upper respiratory tract [9]. However, according to a study performed by Levin et al., 48% of patients discontinue treatment due to reasons not related to toxicity [8].

| Genes | Variants | $p$-value | Predicted effect | Reference |
|-------|----------|-----------|-----------------|-----------|
| Efficacy | | | | |
| VEGF | rs833061 c.-958C>T | 0.04 | TT genotype increased the risk of poor response to acitretin | [31] |
| | | 0.01 | TC genotype increased the chance of favourable response to acitretin | |
| HLA-G | 14 bp DEL | 0.008 | DEL allele associated with better response to acitretin | [34] |
| | | 0.05 | DEL/DEL genotype is associated with better response to acitretin | |

**Table 3.** Genetic polymorphisms associated with response to acitretin treatment in patients with psoriasis.
A study conducted in 2015 that included 4309 patients treated with different biologics for 12 months showed that patients experienced dose escalations and discontinuations, restarting the same biologic or switching to a different one. Approximately one-third of patients had their doses increased until month 6 and 39% until month 12 of treatment. On the other hand, half of these patients also discontinued the biologic drug or reduced the dose [6]. This indicates that many patients do not achieve sufficient response or lose an initially favourable response over time. Pharmacogenetic studies have investigated several polymorphisms in genes coding for the targets of biologic drugs and their signalling pathways regarding their contribution to interpatient and intrapatient variability in treatment response to biologics in patients with RA, PsA, Chron’s disease and spondyloarthritis (SA). However, such studies have been rarely performed exclusively in psoriasis patients [39].

2.4.1. Pharmacogenetics of anti-TNFα treatment

The most widely used biologic drugs for systemic psoriasis treatment are TNFα blockers. It is therefore not surprising that the majority of pharmacogenetic studies focused on polymorphisms in the gene coding for TNFα (TNF). TNFα levels are increased in affected skin and serum of patients and correlate well with disease severity measured with PASI score. TNFα inhibition can reduce the symptoms of the disease [40]. Studies pointing out positive associations between polymorphisms and response to anti-TNFα therapy in psoriasis and PsA are listed in Table 4.

| Genes    | Variants                  | p-value | Predicted effect                                      | Reference |
|----------|---------------------------|---------|------------------------------------------------------|-----------|
| Efficacy |                           |         |                                                      |           |
| TNFα     | rs1799724 c.-857C>T       | 0.002   | C allele associated with better response to etanercept | [49]      |
|          |                           | 0.004   | Patients with CT/TT genotypes showed greater improvements in PASI score | [47]      |
|          | rs361525 c.-238A>G        | 0.049   | Patients with GG genotype achieved PASI75 more frequently after 6 months of anti-TNFα therapy | [47]      |
|          |                           | 0.03    | G allele associated with better response to etanercept | [48]      |
|          | rs1799964 c.-1031T>C      | 0.041   | Patients with TT genotype demonstrated superior improvements in PASI after 6 months of therapy | [47]      |
|          | rs80267959 c.186+123G>A   | 0.0136  | G allele favours better response to etanercept in PsA patients | [63]      |
|          | rs1800629 c.-308G>A       | 0.001   | GG genotype associated with better response to etanercept | [48]      |
| TNFRSF1B | rs1061622 c.676T>G        | 0.001   | T allele associated with better response to etanercept | [49]      |
|          | p.Met196Arg               | 0.05    | G allele associated with poor response               | [52]      |
| Genes   | Variants | p-value | Predicted effect                                                                 | Reference |
|---------|----------|---------|----------------------------------------------------------------------------------|-----------|
| TNFAIP3 | rs610604 c.987-152G>T | 0.05    | G allele associated with better response to anti-TNFα therapy                     | [53]      |
|         |          | 0.007   | T allele associated with better response to etanercept                            | [54]      |
| TRAILR1 | rs20575 c.626G>C p.Arg209Thr | 0.048   | CC genotype associated with better response to infliximab in PsA                  | [66]      |
| TNFR1A  | rs767455 c.36A>G p.Pro12=  | 0.04    | AA genotype associated with better response to infliximab in PsA                  |           |
| IL23R   | rs11209026 c.1142G>A p.Arg381Gln | 0.006   | Patients with GG genotype achieved more frequently PASI 90 at 6 months            | [47]      |
| IL6     | rs1800795 c.-237C>G           | <0.05   | Carriers of t C allele respond better to therapy                                  | [55]      |
| IL-17F  | rs763780 c.482T>C p.His161Arg | 0.0044  | TC genotype associated with no response to adalimumab at 6 months                  | [56]      |
|         |          | 0.023   | TC genotype associated with better response to infliximab at 3 months              |           |
|         |          | 0.020   | TC genotype associated with better response to infliximab at 6 months              |           |
| IL17RA  | rs4819554 c.-947G>A           | 0.03    | AA genotype associated with better response at12 weeks                            | [67]      |
| HLA-C   | rs10484554 g.260909C>T        | 0.007   | C allele associated with better response to adalimumab                            | [54]      |
| TRAF3IP2| rs13190932 c.220C>T p.Arg74Trp | 0.041   | G allele associated with better response to infliximab                             |           |
| HLA-A   | rs9260313 g.1428637T>C        | 0.05    | TT genotype associated with better response to adalimumab                         |           |
| FCGR2A  | rs1801274 c.497A>G p.His131Arg | 0.03    | Patients homozygous for high-affinity allele had a higher chance of achieving PASI75 after 3 months of therapy | [57]      |
|         |          | 0.034   | PsA patients with high-affinity genotype respond better to anti-TNFα drugs (etanercept) after 6 months of therapy | [64]      |
| FCGR3A  | rs396991 c.841T>C p.Val158Phe | 0.02    | Patients homozygous for high-affinity allele had a higher chance of achieving PASI75 after 3 months of therapy | [57]      |
|         |          | 0.018   | T allele associated with better response to etanercept                             | [58]      |
| PDE3A-   | rs3794271 c.50+1078G>A        | 0.0031  | AA genotype associated with better response to etanercept                         | [59]      |
| SLCO1C1  |          | 0.00034 | A gender-specific (males) association between G allele and poor response found in PsA patients | [65]      |
| CD84    | rs6427528 c.*1738A>G          | 0.025   | GA genotype associated with better response to etanercept                         | [60]      |
The most frequently investigated candidate gene is TNF and rs1800629 (c.-308G>A) within it. The polymorphism, which is located in the promoter region of TNF gene, gained attention because it was associated with TNFα secretion and circulating levels [21]. Many studies have reported the association of this polymorphism with different traits, such as increased susceptibility to psoriasis and PsA, earlier onset of the disease or poor prognosis of the

| Genes   | Variants                      | p-value | Predicted effect                                      | Reference |
|---------|-------------------------------|---------|------------------------------------------------------|-----------|
| SPEN    | rs6701290 c.84-10630G>A       | <0.05   | Associated with anti-TNFα drug response in a GWAS    | [62]      |
| JAG2    | rs3784240 c.475+782C>T        |         |                                                      |           |
| MACC1   | rs2390256 c.*2687G>A          |         |                                                      |           |
| GUCY1B3 | rs2219538 c.77+2269G>A        |         |                                                      |           |
| PDE6A   | rs10515637 c.2507-1067T>C     |         |                                                      |           |
| CDH23   | rs10823825 c.2290-538T>C      |         |                                                      |           |
| SHOC2   | rs1927159 c.704-13438A>C      |         |                                                      |           |
| LOC728724 | rs7820834 g.129238197T>C  |         |                                                      |           |
| ADRA2A  | rs553668 c.450+33966C>T       |         |                                                      |           |
| KCNIP1  | rs4867965 c.88+96839A>C        |         |                                                      |           |
| Toxicity|                               |         |                                                      |           |
| IL23R   | rs11209026 c.1142G>A p.Arg381Gln | 0.005   | AG genotype associated with development of paradoxical psoriasiform reactions | [61]      |
| FBXL19  | rs10782001 c.1361+720G>A      | 0.028   | GG genotype associated with development of paradoxical psoriasiform reactions |           |
| CTLA4   | rs3087243 c.*1421G>A          | 0.012   | AG/GG genotype associated with development of paradoxical psoriasiform reactions |           |
| SLC12A8 | rs651630 c.1706-272C>T        | 0.011   | TT genotype associated with development of paradoxical psoriasiform reactions |           |
| TAP1    | rs1800453 c.1307A>G           | 0.018   | AG genotype associated with development of paradoxical psoriasiform reactions |           |

Table 4. Genetic polymorphisms associated with response to anti-TNFα therapy in patients with psoriasis or psoriatic arthritis.

The most frequently investigated candidate gene is TNF and rs1800629 (c.-308G>A) within it. The polymorphism, which is located in the promoter region of TNF gene, gained attention because it was associated with TNFα secretion and circulating levels [21]. Many studies have reported the association of this polymorphism with different traits, such as increased susceptibility to psoriasis and PsA, earlier onset of the disease or poor prognosis of the
disease [41]. Zhu et al. performed a meta-analysis of 26 studies, which included 2159 psoriasis patients, 2360 patients with PsA and more than 2000 controls. They evaluated three SNPs in promoter region of TNFα, rs1800629 (c.-308G>A), rs361525 (c.-238A>G) and rs1799724 (c.-857T>C). They confirmed a protective influence of the polymorphic allele c.-308A. The polymorphic alleles of the other two frequently investigated polymorphisms also showed association with increased risk for psoriasis and PsA [42]. Another meta-analysis included nine studies with a total of 692 patients with RA. The main objective was to determine the influence of the TNF c.-308A allele on the response to TNFα inhibitors. The frequency of the TNF c.-308A allele was 22% in responders and 37% in patients not responding to treatment, irrespective of the choice of the TNFα inhibitor, which indicates that presence of c.-308A was associated with a poor response to the drug (p = 0.000245) [43]. This observation was in agreement with the findings of Mugnier et al. that showed better response to infliximab in RA patients with c.-308 GG genotype as compared to the patients with c.-308 AA/AG genotype [44]. Moreover, Guis et al. observed that RA patients homozygous for c.-308 G allele respond better to etanercept than heterozygous patients [45]. Seitz et al. evaluated response of RA, PsA and SA patients to infliximab, adalimumab and etanercept and came to the same conclusion as the above mentioned studies [46].

Other TNF promoter polymorphisms besides rs1800629 (c.-308G>A) were also investigated, among them were rs361525 (c.-238A>G), rs1799724 (c.-857T>C) and rs1799964 (c.-1031T>C). Better improvement in PASI score after 6 months of treatment with anti-TNFα drugs was achieved in psoriasis patients with TNF -238GG, -857CT/TT and -1031TT genotypes [47]. SNPs in TNF promoter were evaluated also by De Simone et al., and rs361525 (-238G allele; p = 0.03) and rs1800629 (-308GG genotype; p = 0.001) were found to be associated with good drug response [48].

Researchers expanded their interests also to polymorphisms in other genes in TNFα pathways. A study performed on 80 Greek patients with psoriasis investigated polymorphisms in TNF (c.-238G>A, c.-308G>A and c.-857C>T), tumour necrosis factor receptor superfamily 1A gene (TNFRSF1A rs7674559, c.36A>G) and tumour necrosis factor receptor superfamily 1B gene (TNFRSF1B rs1061622, c.676T>G). In total, 63 patients were responders and 17 non-responders. Carriers of TNF -857C (p = 0.002) and/or TNFRSF1B 676T (p = 0.001) alleles responded significantly better to etanercept treatment than non-carriers, while no SNPs were associated with response to infliximab or adalimumab [49]. Ongaro et al. reported poorer response to anti-TNFα therapy in RA patients with TNFRSF1 676TG genotype as compared to patients with 676TT genotype [50]. Recently, a meta-analysis investigated TNFRSF1B (rs1061622) and TNFRSF1A (rs7674559) polymorphisms in psoriasis patients. The investigated TNFRSF1A polymorphism showed no association with treatment response, but TNFRSF1B 676T allele was associated with better response [51]. Another recent study published in 2015 included 518 psoriasis patients and 480 healthy controls, but only 90 patients were treated with biologic drugs. In agreement with previous studies, they also observed higher frequency of TNFRSF1B 676G allele in non-responders, and rs1061622 polymorphism was shown to be associated with higher risk for the disease and poor response to anti-TNFα and anti-IL12/23 drugs [52].

Polymorphisms within gene coding for tumour necrosis factor alpha-induced protein 3 (TNFAIP3) were also associated with the response to biologics. A cohort of 433 patients with...
psoriasis and PsA was tested for two TNFAIP3 SNPs, rs2230926 and rs610604. The results showed that rs610604G allele was associated with better response to etanercept, infliximab and adalimumab, when patients treated with all these drugs were analysed together ($p = 0.05$; OR $= 1.50$), but only to etanercept, when each drug treatment was analysed separately ($p = 0.016$; OR $= 1.64$). In addition, rs2230926 T allele and rs610604 G allele were also predictors of a better outcome. Unfortunately, researchers were unable to reproduce these results in a smaller cohort [53].

Furthermore, polymorphisms in genes encoding several interleukins and their receptors were investigated in psoriasis patients treated with anti-TNFα drugs. A study that included 109 psoriasis patients investigated polymorphisms in IL12B (rs6887695 and rs3212227) and IL23R (rs7530511 and rs11209026). Carriers of the rs11209026 GG genotype showed better response at 6 months of anti-TNFα treatment compared to non-carriers. This study also showed the association of HLA-Cw6 haplotype with worse outcome [47]. Another association with HLA loci was observed by Masouri et al. who reported the association of HLA-C rs10484554 polymorphism with good response to adalimumab (CC or CT genotype, $p = 0.007$). In the same study, also TRAF3IP2 rs13190932, TNFAIP3 rs610604 and HLA-A rs9260313 were associated with good response to infliximab, etanercept and adalimumab, respectively [54]. In another small study of 60 psoriasis patients, a polymorphism in the IL6 promoter (rs1800795) was investigated. Homozygotes and heterozygotes for IL6 rs1800795 C allele responded better to therapy [55]. IL17F rs763780 was also investigated for the association with treatment outcome. This SNP was associated with no response to adalimumab after 6 months (TC genotype, $p = 0.0044$) and with better response to infliximab after 3 and 6 months (TC genotype; $p = 0.023$ and $p = 0.020$, respectively) [56]. IL17RA rs4819554 polymorphism was associated with better response after 12 weeks in carriers of AA genotype compared to AG and GG carriers ($p = 0.03$).

Genes for Fc gamma receptors were also investigated for their association with response of psoriasis patients to anti-TNFα drugs. Patients homozygous for high-affinity alleles of two variants FCGR2A-H131R (rs1801274) and FCGR3A-V158F (rs396991) had a higher chance of achieving PASI75 after 3 months of therapy [57]. FCGR3A rs396991 was also evaluated by Mendrinou et al. who showed that T allele could be a marker of better response to etanercept [58]. Moreover, a positive association was found between PDE3A-SLCO1C1 rs3794271AA genotype and PASI score in patients treated with etanercept [59]. Association between the CD84 genotypes and response to biologics was also evaluated. CD84 rs6427528 polymorphism with its heterozygous GA genotype ($p = 0.025$) was associated with better response to treatment with etanercept [60].

A study performed by Cabaleiro et al. revealed an association between certain polymorphisms and occurrence of paradoxical psoriasiform reactions after treatment with anti-TNFα therapy. Polymorphisms in five genes: IL23R rs11209026, FBXL19 rs10782001, CTLA4 rs3087243, SLC12A8 rs651630 and TAP1 rs1800453 were associated with the development of this adverse reaction to anti-TNFα treatment [61].

Another approach to identify novel loci and SNPs associated with response to anti-TNFα drugs included genome-wide association study (GWAS) approach. A small GWAS study was recently performed that included 65 psoriasis patients prospectively followed for 12 weeks. This study identified 10 SNPs in 10 different genes that could be associated with drug response: cadherin-related 23 (CDH2), soc-2 suppressor of clear homolog (SHOC2), adrenoceptor alpha
2A (ADRA2A), phosphodiesterase 6A (PDE6A), Kv channel interacting protein 1 (KCNIP1), spen family transcriptional repressor (SPEN), jagged 2 (JAG2), metastasis associated in colon cancer 1 (MACC1), guanylate cyclase 1, soluble, beta 3 (GUCY1B3) and long intergenic non-protein coding RNA 977 (LOC728724) gene [62]. However, all these SNPs still await to be replicated in independent patient cohorts.

Several studies have also investigated association of genetic polymorphisms with anti-TNFα treatment outcome in PsA cohorts. A study investigating the association of an intronic polymorphism at the position c.+489 of TNF gene (rs80267959) with response to treatment with etanercept reported better response in PsA patients carrying G allele compared to non-carriers (p = 0.0136) [63]. Furthermore, PsA patients with high-affinity FcgR2A His/His and His/Arg genotypes responded better to anti-TNFα drugs (etanercept) at 6 months of treatment compared to patients with low-affinity genotypes (p = 0.034) [64]. A gender-specific association between polymorphic rs3794271 G allele and poor response was reported at the PDE3A-SLCO1C1 locus (p = 0.00034) [65]. Other candidate genes for prediction of treatment response were suggested, including genes coding for death receptors, such as tumour necrosis factor-related apoptosis inducing ligand receptor 1 (TRAIL-R1). TRAIL-R1 (rs20575, 626G>C) and TNFR1A (rs767455, 36A>G) were investigated in a study of 55 PsA patients treated with TNFα blocker infliximab. This study concluded that TRAILR1 626CC (p = 0.048) and TNFR1A 36AA (p = 0.04) genotypes may be associated with better response after 3 months of infliximab treatment [66].

2.4.2. IL12/23 inhibitors

Ustekinumab is a human monoclonal antibody directed against interleukins IL12 and IL23. Studies of polymorphisms affecting patients’ response to these inhibitors are scarce, but some of them, listed in Table 5, pointed out positive associations. A cohort of 51 patients with psoriasis treated with ustekinumab was tested for three polymorphisms, including the HLA-Cw6 positivity, TNFAIP3 rs610604 polymorphism and LCE3B/3C gene deletions. Better and faster response to ustekinumab was observed in HLA-Cw6 positive patients, while no significant association with response was observed for the other two investigated genes [68]. Another larger study confirmed the role of HLA-Cw6 as Chui et al. reported that HLA-Cw6 positive patients were more likely to achieve PASI50, 75 and 90 after 28 weeks of treatment [69]. On the other hand, Galluzzo et al. suggested that a combination of genetic factors predicts response to ustekinumab better than a single factor. The presence of IL12B rs6887695 GG genotype in the absence of IL12B rs3212227 AA genotype in HLA Cw6 positive patients increased the chance of better treatment outcomes [70].

Another study found association between the TNFRSF1B rs1061622 G allele and poor response to anti-IL12/IL23 drugs (p = 0.05) [52]. Furthermore, study in a cohort of 70 psoriasis patients treated with ustekinumab reported an association between the IL-17F rs763780 TC genotype and no response to ustekinumab after 3 and 6 months of treatment (p = 0.022 and p = 0.016, respectively) [56]. IL12B rs3213094 polymorphism was also investigated for association with response to ustekinumab and CT genotype was recognized as a predictor of better response to the drug (p = 0.017) [60]. In the same study, TNFAIP3 rs610604 GG genotype was associated with poor response to ustekinumab (p = 0.031) [60]. Association between two polymorphisms in ERAP1gene, rs151823 and rs26653, and good response to ustekinumab was also reported [54].
Future perspectives

Large heterogeneity in patients’ response to therapy calls for new molecular predictors of treatment response. We have searched the current literature to compile a comprehensive review of today’s knowledge on genetic variants that may influence the outcome of psoriasis systemic treatment. A rather small number of studies were performed so far, and, although some of the results are encouraging, even larger number of studies shows inconsistent or even conflicting results. The investigated patient cohorts were with a few exceptions rather small and the number of evaluated polymorphisms limited. The future studies should expand the range of polymorphisms investigated by either looking into other pathways besides the ones directly involved in drug mechanisms, such as metabolism and transport, though they certainly are important in treatment response. Great interindividual variability in treatment outcome among patients could also be associated with heterogeneous pathology. Not all of the

| Genes     | Variants              | p-value | Predicted effect                                      | Reference |
|-----------|-----------------------|---------|------------------------------------------------------|-----------|
| **Efficacy** |                       |         |                                                      |           |
| IL-17F    | rs763780 c.482T>C p.His161Arg | 0.022   | TC genotype associated with no response at 3 months | [56]      |
|           |                       | 0.016   | TC genotype associated with no response at 6 months  |           |
| IL12B     | rs3213094 c.89-432G>A  | 0.017   | CT genotype associated with favourable response     | [60]      |
| TNFAIP3   | rs610604 c.987-152G>T  | 0.031   | GG genotype associated with poor response           |           |
| HLA-C     | Cw6POS/NEG            | 0.008   | Cw6POS patients respond better and faster            | [68]      |
|           |                       | 0.035   | Cw6POS patients respond better                       | [69]      |
| TNFRSF1B  | rs1061622 c.676T>G p.Met196Arg | 0.05    | G allele associated with poor response              | [52]      |
| ERAPI     | rs151823 c.-454-1169A>C| 0.026   | CC genotype associated with better response         | [54]      |
|           | rs26653 c.380G>C p.Arg127Pro | 0.016   | GG genotype associated with better response         |           |

Table 5. Genetic polymorphisms associated with response to ustekinumab in patients with psoriasis.

3. Future perspectives

Large heterogeneity in patients’ response to therapy calls for new molecular predictors of treatment response. We have searched the current literature to compile a comprehensive review of today’s knowledge on genetic variants that may influence the outcome of psoriasis systemic treatment. A rather small number of studies were performed so far, and, although some of the results are encouraging, even larger number of studies shows inconsistent or even conflicting results. The investigated patient cohorts were with a few exceptions rather small and the number of evaluated polymorphisms limited. The future studies should expand the range of polymorphisms investigated by either looking into other pathways besides the ones directly involved in drug mechanisms, such as metabolism and transport, though they certainly are important in treatment response. Great interindividual variability in treatment outcome among patients could also be associated with heterogeneous pathology. Not all of the
patients have the same pathogenesis, although they present with similar symptoms. Genetic defects in various pathways could be causative of the disease or support disease occurrence, and these defects in so-called susceptibility genes should also be checked regarding their influence on treatment outcome. The heterogeneity in pathogenesis could also be the reason for inconsistency in pharmacogenetic studies conducted so far. The hypothesis-free approach of the GWAS studies could help to overcome these obstacles and help to elucidate genetic factors associated with both disease pathways and treatment responses; however, such studies should include large number of well-characterized patients. Furthermore, the identified predictors of the course of the disease and of the treatment response should be validated in independent patient samples.

Such validated pharmacogenetic biomarkers would enable us to characterize patients with psoriasis by their genetic characteristics and not just their phenotype and would allow for a more targeted approach to pharmacotherapy. The patients could be stratified according to their genetic defects affecting the molecular mechanisms of the disease in combination with genetic defects in pathways of drug metabolism and transport as well as in drug targets and effector pathways. Pharmacogenetic factors should also be combined with clinical data to find the most suitable way of stratifying patients into groups eligible for certain treatment strategies. If a physician would be able to predict patient’s response based on pharmacogenetic polymorphisms, problems of inefficacy and toxicity could be overcome by choosing the right drug and dose for a particular patient. This would also help to lower the cost of the treatment and, what is more important, relieve some of the patient’s psychological burden, which is often overlooked in psoriasis. Methods for genotyping are fast, reliable, relatively cheap and suitable for use in diagnostic laboratories. Despite the costs that would be spent on implementation of new genetic analysis methods into everyday clinical practice, pharmacogenetics-based personalized treatment approach would probably lower the expenses of psoriasis treatment due to more rational pharmacotherapy.

4. Conclusions

Personalized medicine is emerging as the innovative approach also in psoriasis treatment. A general belief that every drug can help every patient is getting obsolete. However, to be able to properly tailor the patient’s treatment, consistent biomarkers of the treatment outcome must be identified and validated. In psoriasis treatment, the search for such biomarkers is still in its beginnings. In this chapter, we summarized the current knowledge on genetic predictors of response to MTX, cyclosporine, acitretin and biologic drugs. Several studies have already identified some of the genetic variants associated with response to a particular drug, but none of the genetic polymorphisms within these genes were recognized as specific enough to be used in clinical practice so far. However, some promising candidates for predictors of treatment response were identified that could be used in personalized treatment of psoriasis patients if validated in further studies.
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References

[1] Ryan C, Kirby B. Psoriasis is a systemic disease with multiple cardiovascular and metabolic comorbidities. Dermatol Clin. 2015;33(1):41–55. Epub 2014/11/22.

[2] Reich K. The concept of psoriasis as a systemic inflammation: implications for disease management. J Eur Acad Dermatol Venereol. 2012;2:3–11.

[3] Mease PJ, Armstrong AW. Managing patients with psoriatic disease: the diagnosis and pharmacologic treatment of psoriatic arthritis in patients with psoriasis. Drugs. 2014;74(4):423–41.

[4] Dauden E, Castaneda S, Suarez C, Garcia-Campayo J, Blasco AJ, Aguilar MD, et al. Clinical practice guideline for an integrated approach to comorbidity in patients with psoriasis. J Eur Acad Dermatol Venereol. 2013;27(11):1387–404.

[5] Voiculescu VM, Lupu M, Papagheorghe L, Giurcaneanu C, Micu E. Psoriasis and Metabolic Syndrome—scientific evidence and therapeutic implications. J Med Life. 2014;7(4):468–71. Epub 2015/02/26.

[6] Feldman SR, Zhao Y, Navaratnam P, Friedman HS, Lu J, Tran MH. Patterns of medication utilization and costs associated with the use of etanercept, adalimumab, and ustekinumab in the management of moderate-to-severe psoriasis. J Manag Care Spec Pharm. 2015;21(3):201–9.

[7] Nelson PA, Keyworth C, Chisholm A, Pearce CJ, Griffiths CE, Cordingley L, et al. ‘In someone’s clinic but not in mine’—clinicians’ views of supporting lifestyle behaviour change in patients with psoriasis: a qualitative interview study. Br J Dermatol. 2014;171(5):1116–22. Epub 2014/07/02.

[8] Levin AA, Gottlieb AB, Au SC. A comparison of psoriasis drug failure rates and reasons for discontinuation in biologics vs conventional systemic therapies. J Drugs Dermatol. 2014;13(7):848–53.

[9] Pathirana D, Ormerod AD, Saiag P, Smith C, Spuls PI, Nast A, et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris. J Eur Acad Dermatology Venereol. 2010;24(1):117–8.
[10] Sutherland A, Power RJ, Rahman P, O’Rielly DD. Pharmacogenetics and pharmacogenomics in psoriasis treatment: current challenges and future prospects. Expert Opin Drug Metab Toxicol. 2016;12(8):923–35.

[11] Ray-Jones H, Eyre S, Barton A, Warren RB. One SNP at a time: moving beyond GWAS in Psoriasis. J Invest Dermatol. 2016;136(3):567–73.

[12] Dolžan V. Genetic polymorphisms and drug metabolism. Zdravniški vestnik. 2007;76:II-5-II-12

[13] Venter JC, Adams MD, Myers EW, Li PW, Mural RJ, Sutton GG, et al. The sequence of the human genome. Science. 2001;291(5507):1304–51.

[14] Li A, Meyre D. Jumping on the train of personalized medicine: a primer for non-geneticist clinicians: Part 1. Fundamental concepts in molecular genetics. Curr Psychiatry Rev. 2014;10(2):91–100.

[15] Chandran V, Siannis F, Rahman P, Pellett FJ, Farewell VT, Gladman DD. Folate pathway enzyme gene polymorphisms and the efficacy and toxicity of methotrexate in psoriatic arthritis. J Rheumatol. 2010;37(7):1508–12.

[16] Foulkes AC, Warren RB. Pharmacogenomics and the resulting impact on psoriasis therapies. Dermatol Clin. 2015;33(1):149–60.

[17] Woolf RT, Smith CH. How genetic variation affects patient response and outcome to therapy for psoriasis. Expert Rev Clin Immunol. 2010;6(6):957–66.

[18] Cutolo M, Sulli A, Pizzorni C, Seriolo B, Straub RH. Anti-inflammatory mechanisms of methotrexate in rheumatoid arthritis. Ann Rheum Dis. 2001;60(8):729–35.

[19] Bohanec Grabar P, Logar D, Lestan B, Dolzan V. Genetic determinants of methotrexate toxicity in rheumatoid arthritis patients: a study of polymorphisms affecting methotrexate transport and folate metabolism. Eur J Clin Pharmacol. 2008;64(11):1057–68.

[20] Campalani E, Arenas M, Marinaki AM, Lewis CM, Barker JN, Smith CH. Polymorphisms in folate, pyrimidine, and purine metabolism are associated with efficacy and toxicity of methotrexate in psoriasis. J Invest Dermatol. 2007;127(8):1860–7.

[21] O’Rielly DD, Rahman P. Pharmacogenetics of psoriasis. Pharmacogenomics. 2011;12(1):87–101.

[22] Warren RB, Smith RL, Campalani E, Eyre S, Smith CH, Barker JN, et al. Outcomes of methotrexate therapy for psoriasis and relationship to genetic polymorphisms. Br J Dermatol. 2009;160(2):438–41.

[23] Wessels JA, van der Kooij SM, le Cessie S, Kievit W, Barerra P, Allaart CF, et al. A clinical pharmacogenetic model to predict the efficacy of methotrexate monotherapy in recent-onset rheumatoid arthritis. Arthritis Rheum. 2007;56(6):1765–75.
[24] Grabar PB, Rojko S, Logar D, Dolzan V. Genetic determinants of methotrexate treatment in rheumatoid arthritis patients: a study of polymorphisms in the adenosine pathway. Ann Rheum Dis. 2010;69(5):931–2. doi: 10.1136/ard.2009.111567.

[25] Warren RB, Smith RL, Campalani E, Eyre S, Smith CH, Barker JN, et al. Genetic variation in efflux transporters influences outcome to methotrexate therapy in patients with psoriasis. J Invest Dermatol. 2008;128(8):1925–9.

[26] Haider AS, Lowes MA, Suarez-Farinas M, Zaba LC, Cardinale I, Khatcherian A, et al. Identification of cellular pathways of “type 1,” Th17 T cells, and TNF- and inducible nitric oxide synthase-producing dendritic cells in autoimmune inflammation through pharmacogenomic study of cyclosporine A in psoriasis. J Immunol. 2008;180(3):1913–20.

[27] Keown P, Landsberg D, Halloran P, Shoker A, Rush D, Jeffery J, et al. A randomized, prospective multicenter pharmacoepidemiologic study of cyclosporine microemulsion in stable renal graft recipients. Report of the Canadian Neoral Renal Transplantation Study Group. Transplantation. 1996;62(12):1744–52.

[28] Zhang Y, Benet LZ. The gut as a barrier to drug absorption: combined role of cytochrome P450 3A and P-glycoprotein. Clin Pharmacokinet. 2001;40(3):159–68.

[29] Vasilopoulos Y, Sarri C, Zafiriou E, Patsatsi A, Stamatis C, Ntoumou E, et al. A pharmacogenetic study of ABCB1 polymorphisms and cyclosporine treatment response in patients with psoriasis in the Greek population. Pharmacogenomics J. 2014;14(6):523–5.

[30] Prieto-Perez R, Cabaleiro T, Dauden E, Ochoa D, Roman M, Abad-Santos F. Pharmacogenetics of topical and systemic treatment of psoriasis. Pharmacogenomics. 2013;14(13):1623–34.

[31] Young HS, Summers AM, Read IR, Fairhurst DA, Plant DJ, Campalani E, et al. Interaction between genetic control of vascular endothelial growth factor production and retinoid responsiveness in psoriasis. J Invest Dermatol. 2006;126(2):453–9.

[32] Barile S, Medda E, Nistico L, Bordignon V, Cordiali-Fei P, Carducci M, et al. Vascular endothelial growth factor gene polymorphisms increase the risk to develop psoriasis. Exp Dermatol. 2006;15(5):368–76.

[33] Young HS, Summers AM, Bhushan M, Brenchley PE, Griffiths CE. Single-nucleotide polymorphisms of vascular endothelial growth factor in psoriasis of early onset. J Invest Dermatol. 2004;122(1):209–15.

[34] Borghi A, Rizzo R, Corazza M, Bertoldi AM, Bortolotti D, Sturabotti G, et al. HLA-G 14-bp polymorphism: a possible marker of systemic treatment response in psoriasis vulgaris? Preliminary results of a retrospective study. Dermatol Ther. 2014;27(5):284–9.

[35] Campalani E, Allen MH, Fairhurst D, Young HS, Mendonca CO, Burden AD, et al. Apolipoprotein E gene polymorphisms are associated with psoriasis but do not determine disease response to acitretin. Br J Dermatol. 2006;154(2):345–52.
[36] Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. N Engl J Med. 2001;344(12):907–16.

[37] Horiuchi T, Mitoma H, Harashima S, Tsukamoto H, Shimoda T. Transmembrane TNF-alpha: structure, function and interaction with anti-TNF agents. Rheumatology. 2010;49(7):1215–28.

[38] Day R. Adverse reactions to TNF-alpha inhibitors in rheumatoid arthritis. Lancet. 2002;359(9306):540–1.

[39] O’Rielly DD, Rahman P. Pharmacogenetics of rheumatoid arthritis: Potential targets from susceptibility genes and present therapies. Pharmgenomics Pers Med. 2010;3:15–31.

[40] Mizutani H, Ohmoto Y, Mizutani T, Murata M, Shimizu M. Role of increased production of monocytes TNF-alpha, IL-1beta and IL-6 in psoriasis: relation to focal infection, disease activity and responses to treatments. J Dermatol Sci. 1997;14(2):145–53.

[41] Balding J, Kane D, Livingstone W, Mynett-Johnson L, Bresnihan B, Smith O, et al. Cytokine gene polymorphisms: association with psoriatic arthritis susceptibility and severity. Arthritis Rheum. 2003;48(5):1408–13.

[42] Zhu J, Qu H, Chen X, Wang H, Li J. Single nucleotide polymorphisms in the tumor necrosis factor-alpha gene promoter region alter the risk of psoriasis vulgaris and psoriatic arthritis: a meta-analysis. Plos One. 2013;8(5):e64376.

[43] O’Rielly DD, Roslin NM, Beyene J, Pope A, Rahman P. TNF-alpha-308 G/A polymorphism and responsiveness to TNF-alpha blockade therapy in moderate to severe rheumatoid arthritis: a systematic review and meta-analysis. Pharmacogenomics J. 2009;9(3):161–7.

[44] Mugnier B, Balandraud N, Darque A, Roudier C, Roudier J, Reviron D. Polymorphism at position -308 of the tumor necrosis factor alpha gene promoter region alter the risk of psoriasis vulgaris and psoriatic arthritis: a meta-analysis. Plos One. 2013;8(5):e64376.

[45] Guis S, Balandraud N, Bouvenot J, Auger I, Toussirot E, Wendling D, et al. Influence of -308 A/G polymorphism in the tumor necrosis factor alpha gene on etanercept treatment in rheumatoid arthritis. Arthritis Rheum. 2007;57(8):1426–30.

[46] Seitz M, Wirthmuller U, Moller B, Villiger PM. The -308 tumour necrosis factor-alpha gene polymorphism predicts therapeutic response to TNFalpha-blockers in rheumatoid arthritis and spondyloarthritis patients. Rheumatology. 2007;46(1):93–6.

[47] Gallo E, Cabaleiro T, Roman M, Solano-Lopez G, Abad-Santos F, Garcia-Diez A, et al. The relationship between tumour necrosis factor (TNF)-alpha promoter and IL12B/IL-23R genes polymorphisms and the efficacy of anti-TNF-alpha therapy in psoriasis: a case-control study. Br J Dermatol. 2013;169(4):819–29.

[48] De Simone C, Farina M, Maiorino A, Fanali C, Perino F, Flamini A, et al. TNF-alpha gene polymorphisms can help to predict response to etanercept in psoriatic patients. J Eur Acad Dermatol Venereol. 2015;29(9):1786–90.
[49] Vasilopoulos Y, Manolika M, Zafiriou E, Sarafidou T, Bagiatis V, Kruger-Krasagaki S, et al. Pharmacogenetic analysis of TNF, TNFRSF1A, and TNFRSF1B gene polymorphisms and prediction of response to anti-TNF therapy in psoriasis patients in the Greek population. Mol Diagn Ther. 2012;16(1):29–34.

[50] Ongaro A, De Mattei M, Pellati A, Caruso A, Ferretti S, Masieri FF, et al. Can tumor necrosis factor receptor II gene 676T>G polymorphism predict the response grading to anti-TNFalpha therapy in rheumatoid arthritis? Rheumatol Int. 2008;28(9):901–8.

[51] Chen W, Xu H, Wang X, Gu J, Xiong H, Shi Y. The tumor necrosis factor receptor superfamily member 1B polymorphisms predict response to anti-TNF therapy in patients with autoimmune disease: a meta-analysis. Int Immunopharmacol. 2015;30(5):405–12.

[52] Gonzalez-Lara L, Batalla A, Coto E, Gomez J, Eiris N, Santos-Juanes J, et al. The TNFRSF1B rs1061622 polymorphism (p.M196R) is associated with biological drug outcome in Psoriasis patients. Arch Dermatol Res. 2015;307(5):405–12.

[53] Tejasvi T, Stuart PE, Chandran V, Voorhees JJ, Gladman DD, Rahman P, et al. TNFAIP3 gene polymorphisms are associated with response to TNF blockade in psoriasis. J Invest Dermatol. 2012;132(3 Pt 1):593–600.

[54] Masouri S, Stefanaki I, Ntritsos G, Kypreou KP, Drakaki E, Evangelou E, et al. A pharmacogenetic study of psoriasis risk variants in a greek population and prediction of responses to anti-TNF-alpha and anti-IL-12/23 agents. Mol Diagn Ther. 2016;20(3):221–5.

[55] Di Renzo L, Bianchi A, Saraceno R, Calabrese V, Cornelius C, Iacopino L, et al. -174G/C IL-6 gene promoter polymorphism predicts therapeutic response to TNF-alpha blockers. Pharmacogenet Genomics. 2012;22(2):134–42.

[56] Prieto-Perez R, Solano-Lopez G, Cabaleiro T, Roman M, Ochoa D, Talegon M, et al. The polymorphism rs763780 in the IL-17F gene is associated with response to biological drugs in patients with psoriasis. Pharmacogenomics. 2015;16(15):1723–31.

[57] Julia M, Guilabert A, Lozano F, Suarez-Casasus B, Moreno N, Carrascosa JM, et al. The role of Fcgamma receptor polymorphisms in the response to anti-tumor necrosis factor therapy in psoriasis A pharmacogenetic study. JAMA Dermatol. 2013;149(9):1033–9.

[58] Mendrinou E, Patsatsi A, Zafiriou E, Papadopoulou D, Aggelou L, Sarri C, et al. FCGR3A-V158F polymorphism is a disease-specific pharmacogenetic marker for the treatment of psoriasis with Fc-containing TNFalpha inhibitors. Pharmacogenomics J. 2016;5(10):16.

[59] Julia A, Ferrandiz C, Dauden E, Fonseca E, Fernandez-Lopez E, Sanchez-Carazo JL, et al. Association of the PDE3A-SLCO1C1 locus with the response to anti-TNF agents in psoriasis. Pharmacogenomics J. 2015;5(4):322–5.

[60] van den Reek JM, Coenen MJ, van de L’isle Arias M, Zweegers J, Rodijk-Olthuis D, Schalkwijk J, et al. Polymorphisms in CD84, IL12B and TNFAIP3 are associated with response to biologics in patients with psoriasis. Br J Dermatol. 2016;26(10):15005.
[61] Cabaleiro T, Prieto-Perez R, Navarro R, Solano G, Roman M, Ochoa D, et al. Paradoxical psoriasiform reactions to anti-TNFalpha drugs are associated with genetic polymorphisms in patients with psoriasis. Pharmacogenomics J. 2016;16(4):336–40.

[62] Nishikawa R, Nagai H, Bito T, Ikeda T, Horikawa T, Adachi A, et al. Genetic prediction of the effectiveness of biologics for psoriasis treatment. J Dermatol. 2016;43(11):1273–7.

[63] Murdaca G, Gulli R, Spano F, Lantieri F, Burlando M, Parodi A, et al. TNF-alpha gene polymorphisms: association with disease susceptibility and response to anti-TNF-alpha treatment in psoriatic arthritis. J Invest Dermatol. 2014;134(10):2503–9.

[64] Ramirez J, Fernandez-Sueiro JL, Lopez-Meijas R, Montilla C, Arias M, Moll C, et al. FCGR2A/CD32A and FCGR3A/CD16A variants and EULAR response to tumor necrosis factor-alpha blockers in psoriatic arthritis: a longitudinal study with 6 months of followup. J Rheumatol. 2012;39(5):1035–41.

[65] Julia A, Rodriguez J, Fernandez-Sueiro JL, Gratacos J, Queiro R, Montilla C, et al. PDE3A-SLCO1C1 locus is associated with response to anti-tumor necrosis factor therapy in psoriatic arthritis. Pharmacogenomics. 2014;15(14):1763–9.

[66] Morales-Lara MJ, Canete JD, Torres-Moreno D, Hernandez MV, Pedrero F, Celis R, et al. Effects of polymorphisms in TRAILR1 and TNFR1A on the response to anti-TNF therapies in patients with rheumatoid and psoriatic arthritis. Joint Bone Spine. 2012;79(6):591–6.

[67] Batalla A, Coto E, Gomez J, Eiris N, Gonzalez-Fernandez D, Gomez-De Castro C, et al. IL17RA gene variants and anti-TNF response among psoriasis patients. Pharmacogenomics J. 2016;27(10):70.

[68] Talamonti M, Botti E, Galluzzo M, Teoli M, Spallone G, Bavetta M, et al. Pharmacogenetics of psoriasis: HLA-Cw6 but not LCE3B/3C deletion nor TNFAIP3 polymorphism predisposes to clinical response to interleukin 12/23 blocker ustekinumab. Br J Dermatol. 2013;169(2):458–63.

[69] Chiu HY, Wang TS, Chan CC, Cheng YP, Lin SJ, Tsai TF. Human leucocyte antigen-Cw6 as a predictor for clinical response to ustekinumab, an interleukin-12/23 blocker, in Chinese patients with psoriasis: a retrospective analysis. Br J Dermatol. 2014;171(5):1181–8.

[70] Galluzzo M, Boca AN, Botti E, Potenza C, Malara G, Malagoli P, et al. IL12B (p40) Gene Polymorphisms Contribute to Ustekinumab Response Prediction in Psoriasis. Dermatology. 2016;232(2):230–6.
