Chapter 9

Pharmacogenetics of Psoriasis Treatment

Sara Redenšek and Vita Dolžan

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.68185

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]. Interindividual 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 folylpolyglutamate 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 methylentetrahydrofolate dehydrogenase (MTHFD1), methylentetrahydrofolate 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].

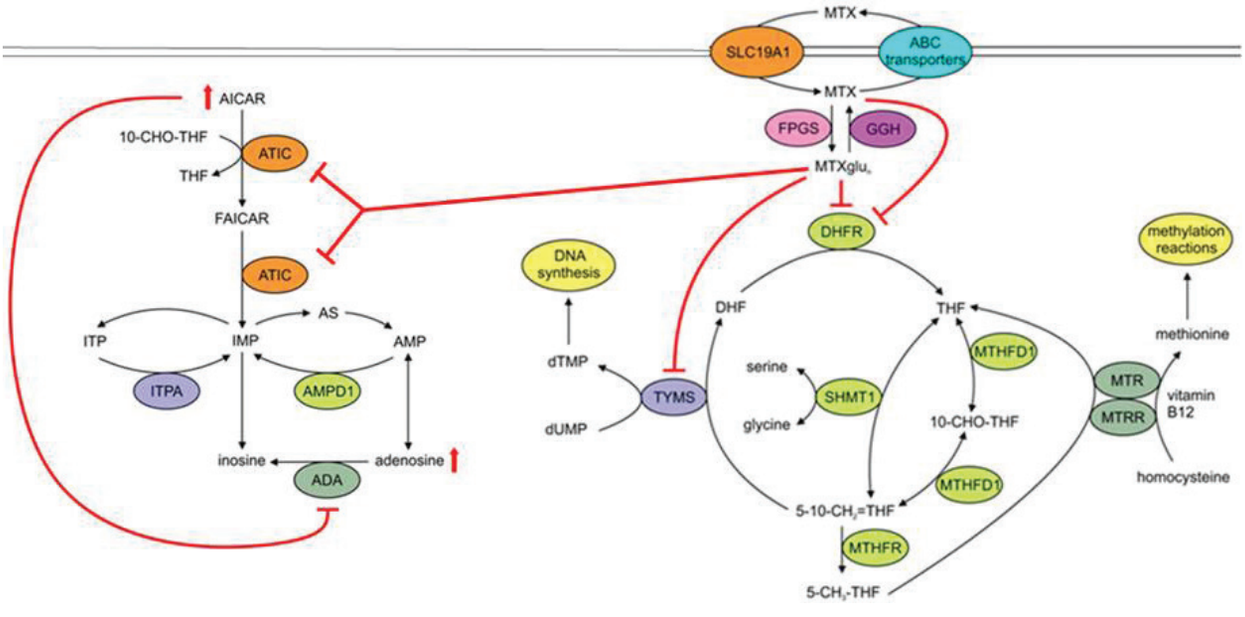

Figure 1. Schematic view of MTX mechanism of action on folate and adenosine pathway. SLC19A1—reduced folate carrier, MTX—methotrexate, ABC—ABC transporters (ATP dependent), FPGS—folypolyglutamate synthase, GGH—gamma-glutamyl hydrolase, MTXglu—methotrexate polyglutamate, DHFR—dihydrofolate reductase, THF—tetrahydrofolate, MTHFD1—methylentetrahydrofolate dehydrogenase, SHMT1—serine hydroxymethyltransferase, MTHFR—methylentetrahydrofolate reductase, MTR—methionine synthase, MTRR—methionine synthase reductase, TYMS—thymidylate synthase, DHF—dihydrofolate, dTMP—deoxythimidine monophosphate, dUMP—deoxyuridine monophosphate, AICAR—5-aminoimidazole-4-carboxamide ribonucleotide, ATIC—AICAR 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.

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]

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]
		0.01	Homozygotes for the major allele more susceptible to MTX toxicity	[22]
	rs4672768 c.1660-135G>A	0.02	Homozygotes for the major allele more susceptible to MTX toxicity	[22]
ABCC1	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	
ADORA2A	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

yet. However, a study that included 281 patients with PsA showed association between the minor allele of the rs1232027 polymorphism (35289G>A) and MTX efficacy ($p = 0.02$; OR = 2.99). Patients with rs1232027 A allele had a statistically significant better response to MTX [15].

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-methylentetrahydrofolate, 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 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.Asp8Asn) 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 ($p = 0.01$; 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 epidermal 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]. Beside 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
Efficacy				
ABCB1	rs1045642 c.3435C>T p.Ile1145=	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 p.Met196Arg	0.001	T allele associated with better response to etanercept	[49]
		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.2609009C>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-SLCO1C1	rs3794271 c.50+1078G>A	0.0031	AA genotype associated with better response to etanercept	[59]
		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]

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]. *IL-17F* 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 *ERAP1*gene, rs151823 and rs26653, and good response to ustekinumab was also reported [54].

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]
ERAP1	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.

Author details

Sara Redenšek and Vita Dolžan*

*Address all correspondence to: vita.dolzan@mf.uni-lj.si

Pharmacogenetics Laboratory, Institute of Biochemistry, Faculty of Medicine, University of Ljubljana, Slovenia

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