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Genetic Influences on Pharmacological Interventions in Psoriasis

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Abstract

Psoriasis is a common chronic inflammatory disease that affects 2% of the population. Therapeutic intervention for psoriasis mainly targets inflammatory cascade through the use of topical agents, phototherapy, systemic agents and the newer biologic agents. The efficacy of many treatments used in psoriasis varies from patient to patient, and some of this variance in response can presumably be attributed to genetic differences. While current research findings are still limited, the clinical utilization of pharmacogenetics allows for tailored treatment plans that have the potential for better response amongst patients as well as conserving expenditures and healthcare resources. In this review, we hope to focus and summarize the conclusions and findings of studies done on the topic of pharmacogenetics in the treatment of psoriasis.

Keywords: Psoriasis; Pharmacogenetics; HLA genes

Introduction

Psoriasis is a common chronic inflammatory dermatosis that affects 2% of the population. Psoriasis seems to have an autoimmune basis and its usual course contains periods of remission in between flares. The lesions of this condition present with well-demarcated, erythematous plaques that have loose silver scale. Although psoriasis is a skin disorder, it is associated with conditions such as arthropathy, myopathy, enteropathy and AIDS [1]. The pathogenesis of this disease seems to be that sensitized CD4 Th1 and Th17 cells and activated cytotoxic T cells enter and accumulate within the epidermis [1]. They then create an anomalous microenvironment by producing cytokines and growth factors. This environment encourages keratinocyte proliferation, which then leads to the psoriatic phenotype [1]. Therapy for psoriasis mainly targets different aspects of the inflammatory pathway through the use of topical agents, phototherapy, systemic agents and the newer biologic agents (Figure 1).

The clinical decision of which therapy to pursue relies mainly on the severity of illness, the patient preference and previous response to therapy. However, there is not uniform response to said therapies and the immunosuppressive nature of these drugs lead to some serious side effects [2]. The outcome and response to an individual has to a drug is due in part to many factors. These factors include the drug itself, the disease, and the individual, specifically his or her genes [3]. Psoriasis results from interactions of environmental and genetic factors, and as with many other autoimmune diseases, it is linked to polymorphisms within the HLA locus, particularly HLA-Cw0602 [1]. As of recently, many other loci and polymorphisms are beginning to emerge as imparting some susceptibility to psoriasis as well. Pharmacogenetics is a term used to describe the study of the association between genetic polymorphisms and response to a drug [3]. Pharmacogenetic findings have potential to greatly impact clinical decisions. The advantages of such findings would include minimizing cost of treatment and improving treatment safety by minimizing adverse events [3].

In this review, we hope to focus and summarize the conclusions and findings of studies done on the topic of pharmacogenetics in the treatment of psoriasis. The following cited studies and polymorphisms were chosen based on their relevance to the topic. If a study resulted in inconclusive results or strayed into the realm of other disorders or diseases, they were not included to maintain conciseness. Any psoriasis treatments or medications not mentioned are done so due to the lack of pharmacogenetic studies on them. While effort has been made to include all relevant studies, it is possible that we may have overlooked relevant research.

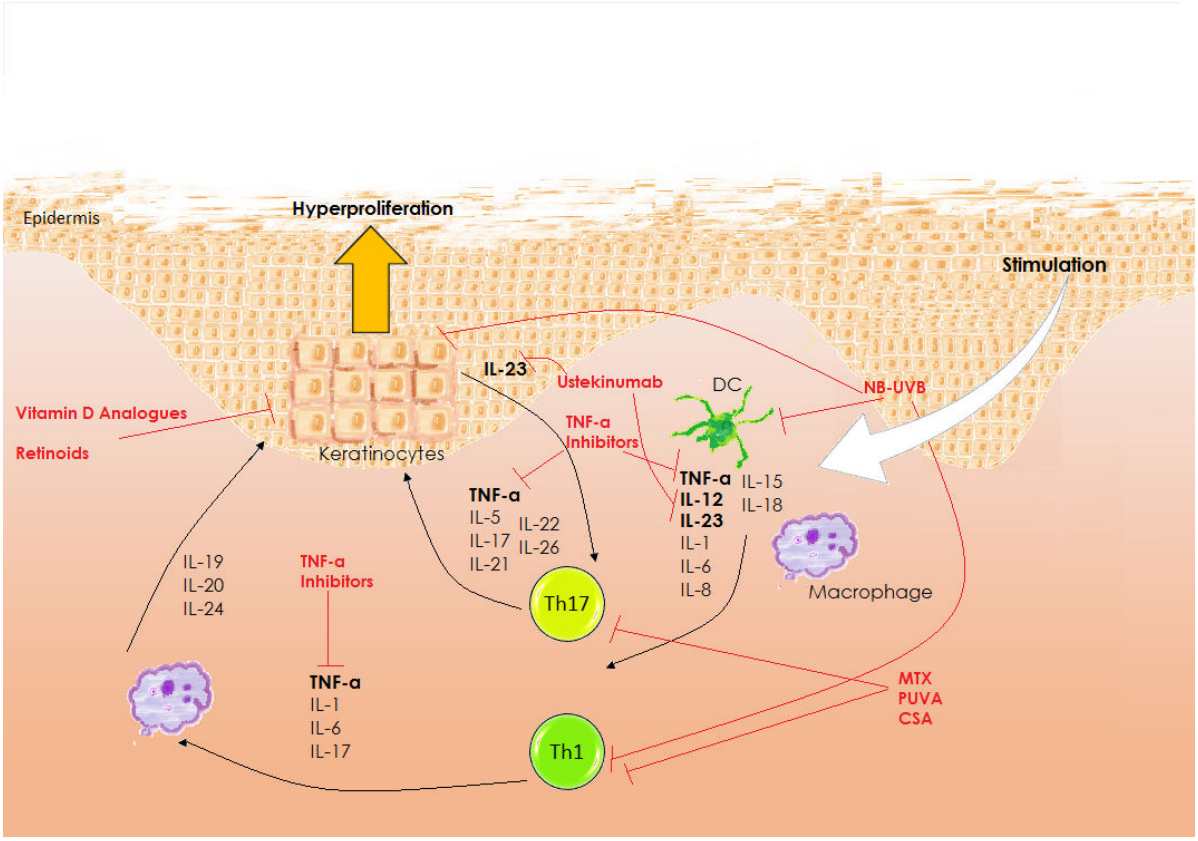

Figure 1: Schematic representation of the pathogenesis of psoriasis and current therapies that disrupt the mediators of this syndrome. The cytokines depicted in this schematic have an important role in promoting (→) the inflammatory process that leads to the characteristic lesions seen in psoriasis. Inflammation in psoriasis seems to be initiated by dendritic cells (DC) and macrophages, which stimulate Th1 lymphocytes (Th1) and Th17 lymphocytes (Th17). The ensuing inflammation leads to hyperproliferation of keratinocytes, amongst a host of other pathways. The therapies labelled in red are discussed in this paper and halt various aspects of this chain of events. Methotrexate (MTX) is a dihydrofolate reductase antagonist which is said to exert most of its action on the activated lymphocytes (Th1 and Th17). Psoralen and ultraviolet radiation A (PUVA) and cyclosporin A (CSA) are also said to effect these lymphocyte, albeit through different mechanisms elaborated further in this review. Vitamin analogues for vitamin D and A seem to enact anti-proliferative and pro-differentiation behavior on keratinocytes. Biologics such as the TNF-α inhibitors and the p40 antagonists inhibit TNF-α and IL-12/23, respectively. Narrow Band ultraviolet B radiation (NB-UVB) exerts effects on dendritic cells (DC), Th1 lymphocytes (Th1), and on keratinocytes [34,48].

Photochemotherapy

Phototherapy is an immunosuppressive agent utilized in psoriasis treatment. In particular, narrow-band ultraviolet B phototherapy (NB-UVB) is performed using TL01 lamps set at 311 nm. NB-UVB is directly cytotoxic against cells responsible for inflammation and immunity, including Th1 cells, dendritic cells, Langerhans cells, and keratinocytes. Its therapeutic effect is due in part to its ability to cause direct DNA damage [4] while also increasing regulatory T lymphocytes [5,6]. Clinical criteria help determine whether or not NB-UVB should be used on an individual [6], and although there are side effects such as pruritus and erythema, studies have supported that these side effects are minimal [4].

Another treatment for psoriasis that utilizes ultraviolet radiation is Psoralen-UVA (PUVA) photochemotherapy. Psoralen is a plant-based compound that is given to sensitize the skin prior to UV exposure [7]. 8-methoxypsoralen (8-MOP) is most commonly used clinically. The mechanism of action for PUVA's therapeutic effects in psoriasis is presumably through inducing lymphocyte apoptosis [8]. Some studies have shown PUVA's potential in inducing long term psoriasis remission [9]. However, there seems to be significant individuality in PUVA sensitivity amongst individuals [10].

A vital component of the innate immune system are Toll-like receptors (TLRs), which sense pathogen-associated molecular patterns (PAMPS) and damage associated molecular patterns (DAMPS). TLR downstream signalling pathways have been implicated in autoimmune diseases like psoriasis [6,11,12]. Toll-like receptor 9 (TLR9) single-nucleotide polymorphism (SNP) rs187084 was found to affect response to NB-UVB. Specifically, variant carrier showed a greater improvement in psoriasis area severity index, (PASI) after phototherapy in addition to achieving longer remissions (P=0.007, P=0.046) [6]. In this study, the role of SNPs TLR2, 5, 4, and 9 and response to NB-UVB was analyzed (n=39). Multivariate analysis showed differences in PASI improvement favoring TLR9 SNP variants (genotypes T/C and C/C), and these improvements were not dependent on other patient factors

such as age, gender, BMI, basal PASI, length of remission or disease evolution [6]. These findings require replication in a larger patient sample and a control population.

Cytochrome P450 enzymes are responsible for metabolizing drugs and endogenous compounds and work in conjunction with the NADPH cytochrome p450 reductase (CPR) [10]. Deeni et al. used *Escherichia coli* membranes co-expressing various p450s and CPR to study 8-MOP metabolism. In a Chinese hamster ovarian cell line expressing CYP1B1 and CPR, these cells were significantly more susceptible to PUVA cytotoxicity than control cell lines (P=0.002). This finding, according to the authors, suggests that this variant of cytochrome P450 may metabolize 8-MOP to products that are more phototoxic [10]. However, limitations to this study include lack of testing in human subjects.

The glutathione S-transferases (GSTs) are responsible for defence against oxidative damage and stress. Due to this role, GSTs become relevant biomarkers for PUVA sensitivity. There are several GSTs in humans that are polymorphic. Null polymorphisms have been linked to increased sensitivity to UVB damage as well as increased skin cancer risk [13]. The response to NB-UVB and the role of GST versus melanocortin 1 receptor (MC1R) was studied in patients with psoriasis [14]. Smith et al. were able to ascertain possible associations between genotype and minimum erythemal dose (MED) as well as treatment outcomes (n=256). The GST genotype GSTM1, but not GSTT1 or MC1R, had an influence on erythemal sensitivity to NB-UVB [14]. Significantly lower MED was observed in GSTM1 null patients (P=0.012). Of the genotypes studied, none were associated with treatment outcomes.

Ibbotson et al. also sought to investigate GST, but in regards to its effect on PUVA therapy sensitivity. They did this by studying the GST genotype in patients starting PUVA (n=111) and the effects of 8-MOP on antioxidant response element (ARE)-regulate gene expression. GSTM1 null allele homozygotes were found to have lower minimal phototoxic doses and high 8-MOP serum concentrations (P=0.022, 0=0.052) [13]. Further investigation should be done to examine the clinical relevance of these findings.

Vitamin D is a fat soluble vitamin that exerts its effects via the vitamin D receptor (VDR), which is a nuclear receptor responsible for mineral metabolism, immunity, and is even linked to carcinogenesis [15]. Vitamin D has been shown to have an anti-proliferative and pro-differentiation effect on keratinocytes, making it a target for study within the field of psoriasis [15]. One study looked at patients with VDR polymorphisms and the effect of NB-UVB (n=93). It was found that the VDR Taq1 polymorphism (SNP rs731236) homozygous C/C genotype was associated with diminished VDR activity with NB-UVB. Patients with this genotype also had shorter remission times than CT heterozygotes (P=0.026) and TT homozygotes (P=0.013) [15]. All results from the mentioned studies regarding phototherapy and pharmacogenetics are summarized in Table 1.

Gene	SNP	Gene function	Finding	References
TLR9	rs187084	Toll-like receptors are proteins that play a role in recognizing pathogen associated molecular patterns (PAMPS) and damage associated molecular patterns (DAMPS) and activating the innate immune system.	Individuals with the T/C genotype of this SNP showed better response to narrow-band ultraviolet B (NB-UVB) phototherapy. Patients with T/C and C/C genotype also showed a higher improvement of PASI than patients with T/T genotype.	[6]
Cytochrome p450	CYP1B1	Cytochrome P450 is a large family of enzymes responsible for metabolizing compounds such as drugs.	Data indicated that presence of this cytochrome may influence the reaction to psoralen and ultraviolet A (PUVA) treatment.	[10]
GSTs	GSTM1	The glutathione S-transferases react to and serve as cutaneous defence against ultraviolet radiation-induced oxidative stress.	In patients homozygous for the null allele, lower minimal phototoxic doses (MPD) and higher serum 8-MOP concentrations were observed.	[13]
GSTs	GSTM1	The glutathione S-transferases react to and serve as cutaneous defence against ultraviolet radiation-induced oxidative stress.	Individuals with this genotype showed significantly lower minimal erythemal doses (MED) and this gene is proposed to influence erythemal sensitivity to NB-UVB.	[14]
VDR	Taq1 (rs731236)	The vitamin D receptor is responsible for mediating the effects of the fat soluble vitamin D. The main actions of this receptor include mineral metabolism, immune response, but it may even exert influence on carcinogenesis and keratinocyte behavior.	CC genotype has been associated with diminished activity of VDR and shorter duration of remission than the CT or TT genotype in psoriasis patients treated with phototherapy (narrow-band UV light)	[15]

Table 1: Pharmacogenetic findings related to phototherapy in psoriasis treatment

Topical agents

Calcipotriol and other vitamin D analogues are effective topical treatments for psoriasis [16]. Vitamin D analogues have been shown to activate the VDR (as previously discussed in the photochemotherapy section) and lead to a series of positive events for psoriasis management. However, not all patients respond to vitamin D compounds. Patients who have better response to vitamin D analogues tend to have an upregulation of VDR messenger RNA (mRNA) expression within psoriatic plaques [16]. The upregulation of VDR mRNA was not seen in non-responders. Thus, the VDR gene and polymorphisms within this gene are candidates for psoriatic pharmacogenetic studies.

As previously mentioned, the VDR Taq1 SNP was significant for NB-UVB [15]. This SNP was also associated with response to Calcipotriol treatment [17]. In this study by Halsall et al., the aim was to test the hypothesis that the A allele of A-1012G, a polymorphism in VDR, is protective for the occurrence and severity of psoriasis. They also studied the effects of calcipotriol with VDR polymorphisms A-1012G, Fok1, and Taq1. The study group consisted of psoriasis patients (n=206) who received calcipotriol treatment and controls (n=80) [17]. This study claims that psoriasis patients with Fok1 F allele, Taq1 T allele, and A-1012G A allele VDR polymorphisms were associated with response to calcipotriol treatment (odds ratio (OR): 1.47 (95% CI: 0.77-2.81), 1.97 (1.04-3.76), and 2.18 (1.00-4.71)) [17]. All results from the mentioned studies regarding topical agents and pharmacogenetics are summarized in Table 2.

Gene	SNP	Gene function	Finding	References
VDR	A-1012G	The vitamin D receptor is responsible for mediating the effects of the fat soluble vitamin D. The main actions of this receptor include mineral metabolism, immune response, but it may even exert influence on carcinogenesis and keratinocyte behavior.	Presence of this polymorphism is associated with response to topical calcipotriol.	[17]
VDR	Fok1	The vitamin D receptor is responsible for mediating the effects of the fat soluble vitamin D. The main actions of this receptor include mineral metabolism, immune response, but it may even exert influence on carcinogenesis and keratinocyte behavior.	Presence of this polymorphism is associated with response to topical calcipotriol.	[17]
VDR	Taq1	The vitamin D receptor is responsible for mediating the effects of the fat soluble vitamin D. The main actions of this receptor include mineral metabolism, immune response, but it may even exert influence on carcinogenesis and keratinocyte behavior.	Presence of this polymorphism is associated with response to topical calcipotriol.	[17]

Table 2: Pharmacogenetic findings related to topical agents in psoriasis treatment

Systemic Agents

Systemic therapies for psoriasis are usually used on patients who have moderate-to-severe disease. The commonly used systemics (that have also been studied pharmacogenetically) include methotrexate (MTX; folic acid antagonist), cyclosporin (T lymphocyte suppressor) and acitretin (a retinoid).

Methotrexate

Methotrexate is a systemic treatment used for a variety of other diseases and has been proven to be a safe and effective option for psoriasis therapy [18]. MTX inhibits dihydrofolate reductase, thus halting dividing cells within the S phase. The anti-proliferative effects of MTX make it useful in situations of unwanted rapidly proliferating cells, such as neoplasm. It is also suggested that active circulating T lymphocytes and monocytes are more susceptible to the effects of MTX, which may attribute to its anti-inflammatory effects [18]. MTX can be administered orally, intramuscularly or subcutaneously. Recently, however, MTX has increased in importance due to its combination use with biologics. The biologics used in psoriasis therapy are usually monoclonal antibodies or foreign proteins that target specific mediators in the inflammatory response. Due to their protein structure, they are the target of host immunity and the generation of anti-drug antibodies [18]. The concomitant use of an immunosuppressive, like MTX, along with a biologic, can extend the use and response time while minimizing the production of ADAs [18]. However, MTX has its fair share of undesirable side effects, such as gastrointestinal irritation, hepatotoxicity, and hematopoietic suppression [9,18]. Up to 30% of individuals discontinue therapy due to these very serious side effects [19]. Pharmacogenetic studies can therefore be of help in deciding which patients may benefit the most from MTX therapy and which patients may be at most risk for negative side effects.

In a study done by Warren et al., the effect of methotrexate on patients with chronic plaque psoriasis (n=374) was investigated. DNA was collected and SNPs in genes of interest were analyzed. The ATP-binding cassette transporters family C (ABCC1, ABCG2) polymorphisms were associated with response to methotrexate. Specifically to ABCC1, rs25591 (P=0.008), rs2238476 (P=0.02), rs28364006 (P=0.02) [20]. In ABCG2, rs17731538 (P=0.007), rs13120400 (P=0.03) [20]. In this same study, certain polymorphisms in ABCC1, solute carrier family 19 member 1 (SLC19A1) and adenosine A2a (ADORA2a) were associated with adverse events following MTX treatment [20]. These genes all play a proposed role in the transport of MTX [20]. Six SNPs in ABCC1 had a significant association with the onset of adverse events following MTX. They included rs11075291 (P=0.008), rs1967120 (P=0.01), rs3784862 (P=0.002), rs246240 (P=0.0006), rs3784864 (P=0.03), and rs2238476 (P=0.01). SLC19A1 plays a role in transporting MTX into cells, and the SNP rs1051266 was also associated with adverse events after MTX treatment (P=0.03). ADORA2a SNP rs5760410 was found to be related to adverse events following MTX (P=0.03) [20]. A drawback to this study was that data was collected retrospectively, thus objective assessment clinical progress could not be done [20].

The target of investigation in a study by Campalani et al. was on polymorphisms within the folate, pyrimidine, and purine metabolic enzymes and their associated MTX efficacy and toxicity in psoriatic patients [21]. They collected DNA from recruited psoriasis patients treated with MTX not receiving folic acid supplementation (n=203) and genotyped them. They were able to conclude that specific polymorphisms are associated with toxicity or discontinuation of MTX. The gene reduced folate carrier (RFC) is a bidirectional anion transporter which participates in the uptake of reduced folates. Campalani et al. were able to determine that the RFC 80A allele was associated with MTX induced toxicity (P=0.025) and MTX discontinuation (P=0.048). The gene thymidylate synthase (TS) is involved in nucleotide synthesis, which relies on folate. TS 3' untranslated region (URT) 6bp deletion was linked to MTX induced toxicity (P=0.025). The 3R allele of the TS gene was significantly more frequent in patients who did not respond to MTX (P=0.029). 5-aminoimidazole-4-carboxamide ribonucleotide transformylase (ATIC)

encodes a gene that catalyzes the final steps of de novo purine biosynthesis. The 347G polymorphism was associated with MTX discontinuation (P=0.038) [21]. A limitation of this study is that it was a retrospective study. All results from the mentioned studies regarding methotrexate therapy and pharmacogenetics are summarized in Table 3.

Gene	SNP	Gene function	Finding	References
ABCC1	rs25591	ATP Binding Cassette Subfamily C Member 1 is a membrane associated protein responsible for transport of molecules across the cell membrane. This gene is implicated in multidrug resistant.	Presence of this SNP is associated with response to methotrexate.	[20]
ABCC1	rs2238476	ATP Binding Cassette Subfamily C Member 1 is a membrane associated protein responsible for transport of molecules across the cell membrane. This gene is implicated in multidrug resistant.	Presence of this SNP is associated with response to methotrexate.	[20]
ABCC1	rs28364006	ATP Binding Cassette Subfamily C Member 1 is a membrane associated protein responsible for transport of molecules across the cell membrane. This gene is implicated in multidrug resistant.	Presence of this SNP is associated with response to methotrexate.	[20]
ABCC1	rs2238476	ATP Binding Cassette Subfamily C Member 1 is a membrane associated protein responsible for transport of molecules across the cell membrane. This gene is implicated in multidrug resistant.	Presence of this SNP is associated with adverse events to methotrexate therapy.	[20]
ABCC1	rs3784864	ATP Binding Cassette Subfamily C Member 1 is a membrane associated protein responsible for transport of molecules across the cell membrane. This gene is implicated in multidrug resistant.	Presence of this SNP is associated with adverse events to methotrexate therapy.	[20]
ABCC1	rs246240	ATP Binding Cassette Subfamily C Member 1 is a membrane associated protein responsible for transport of molecules across the cell membrane. This gene is implicated in multidrug resistant.	Presence of this SNP is associated with adverse events to methotrexate therapy.	[20]
ABCC1	rs3784862	ATP Binding Cassette Subfamily C Member 1 is a membrane associated protein responsible for transport of molecules across the cell membrane. This gene is implicated in multidrug resistant.	Presence of this SNP is associated with adverse events to methotrexate therapy.	[20]
ABCC1	rs1967120	ATP Binding Cassette Subfamily C Member 1 is a membrane associated protein responsible for transport of molecules across the cell membrane. This gene is implicated in multidrug resistant.	Presence of this SNP is associated with adverse events to methotrexate therapy.	[20]
ABCC1	rs11075291	ATP Binding Cassette Subfamily C Member 1 is a membrane associated protein responsible for transport of molecules across the cell membrane. This gene is implicated in multidrug resistant.	Presence of this SNP is associated with adverse events to methotrexate therapy.	[20]
ABCG2	rs17731538	ATP Binding Cassette Subfamily G Member 2 is a membrane associated protein responsible for transport of molecules across the cell membrane. This gene is implicated in multidrug resistant.	Presence of this SNP is associated with response to methotrexate.	[20]
ABCG2	rs13120400	ATP Binding Cassette Subfamily G Member 2 is a membrane associated protein responsible for transport of molecules across the cell membrane. This gene is implicated in multidrug resistant.	Presence of this SNP is associated with response to methotrexate.	[20]
ADORA2a	rs5760410	Adenosine A2a receptor is a G-protein coupled receptor whose ligand is adenosine. It plays an important role in many biological functions, such as cardiac rhythm, blood flow to the cardiac and renal systems, immunity, pain perception, and sleep.	Presence of this SNP is associated with adverse events to methotrexate therapy.	[20]
SLC19A1	rs1051266	Solute carrier family 19 member 1, also known as RFC1, is a folate transporter. It functions to control the levels of intracellular folate.	Presence of this SNP is associated with adverse events to methotrexate therapy.	[20]
SLC19A1	80A allele	Solute carrier family 19 member 1, also known as RFC1, is a folate transporter. It functions to control the levels of intracellular folate.	Presence of this allele is associated with adverse events to methotrexate therapy.	[21]

SLC19A1	80A allele	Solute carrier family 19 member 1, also known as RFC1, is a folate transporter. It functions to control the levels of intracellular folate.	Presence of this allele is associated with discontinuation of methotrexate therapy.	[21]
TSMS	3R allele	Thymidylate synthase, an enzyme that catalyzes the conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP).	Presence of this SNP was significantly more frequent in non-responders to methotrexate therapy.	[21]
TSMS	3' untranslated region 6bp deletion	Thymidylate synthase, an enzyme that catalyzes the conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP).	Presence of this SNP is associated with adverse events to methotrexate therapy.	[21]
ATIC	347G	5 aminoimidazole-4-carboxamide ribonucleotide transformylase, encodes for an enzyme that participates in the last two reactions of de novo purine synthesis.	Presence of this SNP is associated with discontinuation of methotrexate therapy.	[21]

Table 3: Pharmacogenetic findings related to methotrexate in psoriasis treatment

Cyclosporine A

Cyclosporine A (CSA) is an immunosuppressive agent that has been successfully utilized for the management of psoriasis. CSA blocks the action of calcineurin, which is a calcium-dependent serine/threonine phosphatase responsible for activating T cells as well as other proinflammatory events [22]. In a study by Vasilopoulos et al., the ATP-binding cassette subfamily B (ABCB1) SNPs T-129C, G1199A, C1236T, G2677T, and C3435T were investigated for their association with response to CSA treatment in psoriasis patients (n=84) [23]. ABCB1 is an efflux transporter that encodes for P-glycoprotein which is responsible for removing certain compounds from the cell, like drugs [23]. This study found that C3435T (rs1045642) was found to be associated with negative response to cyclosporine (Pc=0.0075) [23]. The frequency of this allele was significantly increased in non-responders than responders. All results from the mentioned studies regarding CSA and pharmacogenetics are summarized in Table 4.

Gene	SNP	Gene function	Finding	References
ABCB1	rs1045642	ATP Binding Cassette Subfamily B Member 1 is a membrane associated protein responsible for transport of molecules across the cell membrane. This gene is implicated in multidrug resistant.	The presence of this SNP is associated with negative response to cyclosporine therapy. The frequency of this allele was found to be significantly increased in nonresponders compared with responders.	[23]

Table 4: Pharmacogenetic findings related to cyclosporine A in psoriasis treatment

Synthetic retinoids

Synthetic retinoids are accepted and effective forms of treatment for psoriasis. Retinoids are synthetic analogues of vitamin A, a fat soluble vitamin that reacts with the nuclear retinoic acid receptor (RARs) [24]. Retinoids affect keratonocyte behavior and differentiation, and help prevent hyperproliferation and inflammation [24]. In pustular psoriasis, retinoids are considered the drug of choice [24], but with plaque psoriasis, the most common form, response is variable to retinoids [24]. Vitamin A analogues can cause side effects such as hepatotoxicity and are contraindicated in pregnancy due to their teratogenicity [24].

In a study by Borghi et al., the effect of various systemic treatments was found to be associated with polymorphisms in the human leukocyte antigen-G (HLA-G) gene, which is a nonclassical HLA class I molecule that has an immunosuppressive function. They retrospectively analyzed the HLA-G 14-bp INS/DEL polymorphism in patients with moderate-to-severe plaque psoriasis treated with acitretin (n=21), cyclosporine (n=16), and anti-TNF alpha therapy (n=11) [25]. A significant association was found between HLA-G 14-bp DEL allele and the 14-bp DEL/DEL genotype and acitretin response and clinical outcome (P=0.008, p=0.05) [25]. Limitations to this study include a small patient population and the retrospective nature of the study.

Vascular endothelial growth factor (VEGF) promotes angiogenesis, and increased levels of VEGF are often found within the plaques of psoriasis. Retinoids can prevent the production of VEGF. In a study by Young et al., VEGF polymorphisms and various factors of psoriasis pathogenesis and response to acitretin were examined. Patients with type 1 early onset plaque psoriasis (which is defined as an onset of disease prior to the age of 40) and acitretin use were recruited (n=106) [26]. Patients with VEGF polymorphism genotype -460 TT were almost two times more likely to fail acitretin therapy than to respond [26]. There was also a significant amount of responders to acitretin therapy who were a -460 TC genotype (P=0.01) [26]. This study requires a larger cohort of patients to confirm these conclusions. All results from the mentioned studies regarding retinoids and pharmacogenetics are summarized in Table 5.

Gene	SNP	Gene function	Finding	References

HLA-G	14 bp deletion	Human leukocyte antigen G is a nonclassical major histocompatibility complex class I molecule. The HLA-G plays a role in immune regulation, specifically in providing negative feedback on inflammation and lymphoid cells.	Strong association between HLA-G 14 bp deletion/deletion genotype and acitretin clinical outcome.	[25]
VEGF	rs833061	Vascular endothelial growth factor is a growth factor that promotes angiogenesis.	The T/C genotype of this SNP is associated with clinical response to acitretin. The T/T genotype of this SNP is associated with no response to acitretin.	[26]

Table 5: Pharmacogenetic findings related to retinoids in psoriasis treatment

Biological Agents

TNF inhibitors

Biologic agents are relatively newer therapy options compared to the medications mentioned previously. The targets for biologic agents are key mediators in the inflammatory pathway, such as T lymphocytes, cytokines and cytokine receptors, all of which play a large role in the pathogenesis of psoriasis. These therapy falls into three broad types: monoclonal antibodies, fusion proteins, and recombinant cytokines [27].

TNF-alpha plays a significant role in psoriasis, although this is not entirely understood. TNF-alpha is a proinflammatory cytokine that is produced by various cells in the body and skin. It can induce a signalling cascade that favors the production of interleukins, like IL-1, IL-6, and IL-8 [27]. These interleukins are known to promote pathogenic changes seen in psoriasis, some of which are lymphocyte proliferation and differentiation, acute phase reactant proliferation and keratinocyte growth. TNF-alpha has been known to stimulate production of VEGF and angiogenesis, also. As we have previously mentioned, VEGF polymorphisms have been studied for their link to psoriasis.

The main TNF-alpha inhibitors include Etanercept, Infliximab, and Adalimumab. Etanercept is a TNF-receptor Ig fusion protein, which binds to soluble and membrane bound TNF-alpha. Infliximab is a chimeric anti-TNF-alpha monoclonal antibody that binds to TNF-alpha and prevents its activity. Adalimumab is a human anti-TNF monoclonal antibody that binds to membrane-bound and soluble TNF-alpha, and inhibits its activity by preventing interaction with cell surface TNF-alpha receptors (TNFRSF1A and TNFRSF1B) [28].

Although TNF-alpha inhibitors allow for targeted therapy and have been shown to be effective for psoriasis treatment, there are some negative aspects to this mode of therapy. For example not all patients respond to these drugs [29]. Furthermore, blocking the effects of TNF-alpha can also leave an individual immuno-suppressed, leaving them at risk for infection. Lastly, biologics cost substantially more than some of the more traditional psoriasis treatments [29]. Thus, pharmacogenetics could play a central role in increasing efficacy, decreasing unnecessary side effects, and determining who would best benefit from this class of drugs.

TNF-alpha genetic related findings

An understandable area of study in regards to TNF-alpha inhibitors would be polymorphisms within the TNF-alpha promoter. It was found that patients with the G/G genotype of the TNF-alpha promoter polymorphism -308 may predict a better response to etanercept, whereas the A/A genotype was associated with a poorer response to etanercept [29]. This particular SNP seems to influence the binding of transcription factors and control the amount of TNF alpha that is produced [29]. When investigating the TNF-alpha promoter polymorphism -238 (rs361525), it was found that patients with the G/G genotype had a better response to TNF-alpha inhibiters after 6 months of treatment (P=0.049) [30]. Patients with the G/G or G/A genotype of the TNF-alpha promoter polymorphism +489 had better response to etanercept treatment [29]. Several studies cited findings in the TNF-alpha promoter polymorphism -857 (rs1799724). This specific polymorphism is associated with higher circulating levels of TNF-alpha, and etanercept has been shown to bind soluble TNF-alpha more than adalimumab and infliximab [31]. Thus, polymorphisms associated with increased levels of soluble TNF-alpha may be good predictors of patient response to etanercept treatment [31]. Patients with the C allele of this polymorphism had a favorable response to etanercept after 6 months of treatment (P=0.002) [31]. Patients with the C/T and T/T genotype had a better response to TNF-alpha inhibitors after 6 months (P=0.004, P=0.009) [30]. Murdaca et al. also reported the C/T genotype of this polymorphism increases response to etanercept. The last reported TNF-alpha promoter polymorphism related to pharmacogenetic studies was the -1031 (rs1799964) polymorphism. The presence of the T/T genotype in psoriasis patients was associated with improved anti-TNF-alpha response after 3 and 6 months of treatment (P=0.047, P=0.038) [30].

The TNF-alpha receptor and associated polymorphisms were also extensively studied for their pharmacogenetic contributions. Individuals with polymorphisms -676 and -196 were reported to favor response to etanercept [29]. In a study on psoriatic arthritis (PsA), it was found that the TNFR1A, a member of the TNF-receptor superfamily, contributed to response to anti-TNF-alpha treatment, specifically, SNP rs767455 [32]. Individuals homozygous A/A for the SNP rs767455 and PsA were associated with better response to anti-TNF-alpha therapy after 3 months (A/A=88% versus A/G and G/G= 58.9%; P=0.04). TNFRSF10A, also known as TRAIL1, is a receptor that mediates the signaling cascade for cellular apoptosis. The CC genotype of TNFRSF10A SNP rs20575 was associated with European League Against Rheumatism (EULAR) response to infliximab at 6 months in patients with PsA (C/C= 71.4% versus C/G and G/G=50%; P=0.048). (Morales-Lara, 2012). Murdaca et al. reported that the A/A genotype of this SNP was also associated with a decreased response to etanercept [29]. TNFRSF1B encodes for the TNF receptor II. The polymorphism 676 T>G is associated with higher whole blood TNF-alpha production and was associated with positive response to etanercept (P=0.001) [31]. The TNFRSF1B rs1061622 G allele was increased in frequency among HLA-Cw6 positive psoriasis patients [33]. There was also an increased risk for negative response to biological therapy in individuals with this

allele [33]. This finding seems to conflict the results in another study, which stated that the TNFRSF1B SNP rs1061622 can predict good response to etanercept, but not to infliximab or adalimumab [34].

TNF Alpha Induced Protein 3 (TNFAIP3) is a zinc finger protein that has been shown to inhibit NF-kappa B activation and TNF-mediated apoptosis. It functions as negative feedback to TNF-alpha signaling. Individuals with the G allele of TNFAIP3 SNP rs610604 were associated with good response to therapy with all TNF-alpha inhibitors (P=0.05) and etanercept (P=0.016) [34,35]. The T allele of TNFAIP3 SNP rs2230926 was associated with good response to therapy of all TNF-alpha inhibitors [34,35].

HLA related findings

HLA genes encode the major histocompatibility complex (MHC) proteins which serve an important function in immune surveillance. HLA-Cw6 is widely attributed as an associated gene with Type 1 psoriasis [36]. Polymorphisms in this gene have been linked to varying responses to psoriasis treatments. HLA-Cw6 positive patients were found to have poor response to TNF-alpha inhibitors [30] and HLA-Cw6 negative patients were reported as having a higher (but not statistically significant) response to TNF-alpha inhibitors [37]. However, a more recent study conflicts these findings and showed a trend toward better response amongst HLA-Cw6 positive patients and TNF-alpha inhibitors [38]. Patients with HLA-C*05 were linked to achieving PASI 75 response when treated with etanercept [29]. HLA-C SNP rs10484554 was associated with good response to anti-TNF alpha agents, especially adalimumab [39]. And lastly, HLA-DRB1 encoding SE alleles *0101 and *0404 were both associated with good response to etanercept [29].

Other genes related to TNF-alpha inhibitor therapy

An assortment of other genes and polymorphisms were found to have pharmacogenetic trends with TNF-alpha inhibitors. F-box and leucine-rich repeat protein 19 (FBXL19) affects IL-33 activity, which can alter the innate immune response. Following TNF-alpha therapy, patients with FBXL19 SNP rs10782001 were associated with developing paradoxical psoriasiform reactions consisting of a change in morphology [40]. CTLA4 is a gene that is expressed during T cell activation. It delivers a signal to downregulate cell function and it also inhibits excessive expansions of activated T cells. Patients with CTLA4 SNP rs3087243 were also more likely to develop paradoxical psoriasiform following TNF-alpha inhibitor therapy [40]. SLC12A8 plays a role in controlling skin keratinocyte proliferation, and patients with SNP rs651630 were more likely to develop paradoxical psoriasiform reactions following TNF-alpha inhibitor therapy [40]. Transporter associated with Antigen Processing (TAP) genes are involved in class I antigen presentation, and the TAP1 SNP rs1800453 was associated with paradoxical psoriasiform reactions following TNF-alpha inhibitor therapy [40]. Most reactions occurred with etanercept (21.4%), although they were also observed with adalimumab (9.8%) and infliximab (7.7%) [40].

Phosphodiesterase 3A-Solute carrier organic anion transporter family member 1c1 (PDE3A-SCLO1C1) and related proteins are associated with active transport of different organic molecule, drugs and toxins out of cells. Some members of this family have also been shown to be constitutively expressed in human keratinocytes. The SNP rs3794271 was significantly associated with higher TNF-alpha inhibitor efficacy and response to treatment in patients with psoriasis (P=0.0031) [41].

Myeloid differentiation primary response gene 88 (MyD88) is a gene that encodes for an adaptor protein that has a central role in the immune response, both innate and adaptive. Patients with the MyD88 SNP rs7744 were associated with response to etanercept [29].

Conservative helix-loop-helix ubiquitous kinase (CHUK) is a protein kinase has many cellular targets and also plays a role in NF-kappa B transcription. NF-kappa B is a key mediator in immunity. The CHUK SNP rs11591741 was also associated with response to etanercept [29].

The Fc receptor is a receptor for the Fc portion of immunoglobulins. This receptor is found on the surface of mainly immune cells. They have a protective function and bind to antibodies attached to infected cells or invading pathogens. They can stimulate phagocytotic or cytotoxic cells. Fcγ receptor polymorphisms FcγIIIA-V158F and FcγIIA-H131R are significantly associated with lower body surface area (BSA) of psoriasiform plaques in the intermediate point of treatment with TNF-alpha inhibitors (P=0.02, P=0.03) [42].

Late cornified envelope (LCE) encodes for stratum corneum related proteins. Patients with the LCE DD genotype had a high frequency of not reaching PASI 75 with TNF-alpha inhibitors (P=0.028) [38].

All results from the mentioned studies regarding anti-TNF-alpha therapy and pharmacogenetics are summarized in Table 6.

Gene	SNP	Gene Function	Findings	References
IL23R	rs11209026	IL-23 is a proinflammatory cytokine which drives the local Th17 effector response via interaction with its receptor, IL-23R. Th17 cells are a key component of the pathogenesis of psoriasis. This SNP negatively affects IL-23 signal transduction, decreasing amount of IL-17.	Patients with the GG genotype achieved PASI-90 at 6 months more frequently. These individuals also had higher improvement of their PASI score.	[30]
IL23R	rs11209026	IL-23 is a proinflammatory cytokine which drives the local Th17 effector response via interaction with its receptor, IL-23R. Th17 cells are a key component of the pathogenesis	Amongst patients with plaque type psoriasis, this SNP was associated with a paradoxical psoriaform reaction leading to a change in morphology on 20% of individuals.	[40]

		of psoriasis. This SNP negatively affects IL-23 signal transduction, decreasing amount of IL-17.		
FBXL19	rs10782001	This gene encodes the F-box and leucine-rich repeat protein 19. This protein helps attenuate IL-33 activity and alters innate immunity. It may also activate nuclear factor-kB.	Amongst patients with plaque type psoriasis, this SNP was associated with a paradoxical psoriaform reaction leading to a change in morphology in 28% of individuals.	[40]
CTLA4	rs3087243	Cytotoxic T-lymphocyte-associated protein 4 is a receptor associated with downregulation of immune response and reduced expansion of T cells. This SNP is related to protection against psoriasiform lesions.	Amongst patients with plaque type psoriasis, this SNP was associated with a paradoxical psoriaform reaction leading to a change in morphology in 56% of individuals.	[40]
SLC12A8	rs651630	Solute carrier family 12 member 8 is a candidate gene for susceptibility to psoriasis. It is hypothesized that SLC12A8 may affect keratinocyte proliferation.	Amongst patients with plaque type psoriasis, this SNP was associated with a paradoxical psoriaform reaction leading to a change in morphology in 8% of individuals.	[40]
TAP1	rs1800453	Transporter 1, ATP-bending cassette subfamily. These genes are associated with multidrug resistance.	Amongst patients with plaque type psoriasis, this SNP was associated with a paradoxical psoriaform reaction leading to a change in morphology in 12% of individuals.	[40]
PDE3A-SCLO1C1	rs3794271	Phosphodiesterase 3A-SoLute carrier organic anion transported family member 1c1 is associated with immune and inflammatory activity. Members of this family have been shown to be constitutively active in keratinocytes.	Association between this SNP and higher anti-TNF-α therapy efficacy and response.	[41]
TNF-α promoter	-308	This particular SNP seems to influence the binding of transcription factors and control the level of transcription of TNF-α.	The G/G genotype of this SNP may predict a better response to etanercept. However, the A/A genotype of this SNP was associated with a poorer response to etanercept.	[29]
TNF-α promoter	rs361525 / -238GG	This particular SNP seems to influence the binding of transcription factors and control the level of transcription of TNF-α.	After 6 months of treatment, subjects with G/G genotype had a better response to anti TNF-α treatment.	[30]
TNF-α promoter	489	This particular SNP seems to influence the binding of transcription factors and control the level of transcription of TNF-α.	The genotypes G/G and G/A of this SNP favor response to etanercept treatment	[29]
TNF-α promoter	rs1799724 / 857	This particular SNP seems to influence the binding of transcription factors and control the level of transcription of TNF-α.	There is an association with C allele and favorable response to etanercept after 6 months of anti-TNF-α therapy.	[31]
TNF-α promoter	rs1799724 / 857 CT TT	This particular SNP seems to influence the binding of transcription factors and control the level of transcription of TNF-α.	The C/T and T/T genotype of this allele had better response to anti-TNF-α drugs after 6 months of therapy.	[30]

TNF-α promoter	-857	This particular SNP seems to influence the binding of transcription factors and control the level of transcription of TNF-α.	The C/T and T/T genotype of this allele had better response to anti-TNF-α drugs after 6 months of therapy.	[30]
TNF-α promoter	-857	This polymorphism is associated with higher circulating levels of TNFα.	The C/T genotype of this SNP was associated with increased response to etanercept.	[29]
TNF-α promoter	rs1799964 / -1031TT	This SNP seems to influence the binding of transcription factors and control the level of transcription of TNF-α.	After 3 and 6 months of treatment, individuals with the T/T genotype of this SNP were associated with an improved anti-TNF-α response.	[30]
TNF-α promoter	-676	The tumor necrosis factor receptor is involved in inflammation and apoptosis, amongst a host of other pathways.	Individuals with this polymorphism favor response to etanercept.	[29]
TNF receptor	-196	The tumor necrosis factor receptor is involved in inflammation and apoptosis, amongst a host of other pathways.	Individuals with this polymorphism favor response to etanercept.	[29]
HLA-DRB1 encoding SE	Allele *0404	Human Leukocyte Antigen encodes for the major histocompatibility (MHC) class II complex responsible for immune reactions.	Individuals with this polymorphism favor response to etanercept.	[29]
HLA-DRB1 encoding SE	Allele *0101	Human Leukocyte Antigen encodes for the major histocompatibility (MHC) class II complex responsible for immune reactions.	Individuals with this polymorphism favor response to etanercept.	[29]
TNFR1A	rs767455	The tumor necrosis factor receptor is involved in inflammation and apoptosis, amongst a host of other pathways.	This SNP was associated with better response to anti-TNF-α therapy at 3 months (A/A 88% vs A/G and G/G 58.9%)	[32]
TNFR1A	AA	The tumor necrosis factor receptor is involved in inflammation and apoptosis, amongst a host of other pathways.	This polymorphism was associated with decreased response to etanercept.	[29]
TNFRSF1B	676 T>G	This polymorphism in tumor necrosis factor receptor II is associated with higher whole blood TNF-α production.	Individuals with polymorphism are associated with positive response to drug treatment with etanercept.	[31]
TNFRSF1B	rs1061622 G allele (p.M196R polymorphism)	This polymorphism in tumor necrosis factor receptor II is associated with higher whole blood TNF-α production.	There is an increased frequency of this SNP among HLA-Cw6-positive psoriasis individuals, as well as an increased risk for negative response to biological therapy.	[33]
TNFRSF1B	rs1061622	This polymorphism in tumor necrosis factor receptor II is associated with higher whole blood TNF-α production.	This SNP can predict a good response to etanercept but not to infliximab or adalimumab.	[34]
TNFAIP3	rs610604	The protein encoded by this gene is a zinc finger protein and ubiquitin-editing enzyme. It has been shown to inhibit NF-κB and TNF-α mediated events.	The G allele of this SNP was associated with good response to therapy with all anti-TNF-α agents.	[34]

TNFAIP3	rs610604	The protein encoded by this gene is a zinc finger protein and ubiquitin-editing enzyme. It has been shown to inhibit NF-κB and TNF-α mediated events.	The G allele of this SNP was associated with good response to therapy with all anti-TNF-α agents.	[35]
TNFAIP3	rs2230926	The protein encoded by this gene is a zinc finger protein and ubiquitin-editing enzyme. It has been shown to inhibit NF-κB and TNF-α mediated events.	The T allele of this SNP was associated with good response to therapy with all anti-TNF-α agents.	[34]
TNFAIP3	rs2230926	The protein encoded by this gene is a zinc finger protein and ubiquitin-editing enzyme. It has been shown to inhibit NF-κB and TNF-α mediated events.	The T allele of this SNP was associated with good response to therapy with all anti-TNF-α agents.	[35]
HLA-Cw6		Human Leukocyte Antigen encodes for the major histocompatibility (MHC) complex responsible for immune reactions. Individuals carrying the HLA-Cw6 allele have a strong susceptibility to acquiring psoriasis.	Individual's positive for the HLA-Cw6 allele had a poor response to anti-TNF-α drugs.	[30]
HLA-Cw6		Human Leukocyte Antigen encodes for the major histocompatibility (MHC) complex responsible for immune reactions. Individuals carrying the HLA-Cw6 allele have a strong susceptibility to acquiring psoriasis.	HLA-Cw6 negative patients have a higher (but not statistically significant) response rate to anti-TNF-α therapy.	[37]
HLA-C	*05	Human Leukocyte Antigen encodes for the major histocompatibility (MHC) complex responsible for immune reactions.	Individuals with this polymorphism favor achieving PASI-75 response to etanercept.	[29]
IL-10	1087	Interleukin 10 is an anti-inflammatory cytokine.	Individuals with the G/G genotype of this polymorphism favor the response with etanercept.	[29]
IL-10 promoter	microsatellite allele IL-10.R3 and haplotype R3-G9	The interleukin 10 promoter affects transcription and production of IL-10.	Individuals with this SNP have increased response to etanercept.	[29]
MyD88	rs7744	Myeloid differentiation primary response 88 gene encodes for an adaptor protein involved in innate and adaptive immunity, particularly in IL-1 and Toll-like receptor pathways.	Individuals with this SNP were associated with response to etanercept.	[29]
CHUK	rs11591741	Conserved Helix-Loop-Helix Ubiquitous Kinase. This enzyme is involved in inhibiting the actions of NF-κB.	Individuals with this SNP were associated with response to etanercept.	[43]
IL-17F	rs763780	Pro-inflammatory cytokine	The T/C genotype of this SNP is associated with no response to adalimumab at weeks 24-28. This genotype was also associated with a better	[42]

			response to infliximab at weeks 12-16 and 24-28.	
IL-6 promoter	rs1800795 (-174)	Interleukin 6 plays a role in mediating the inflammatory response. The IL-6 promoter can affect transcription and production of this cytokine.	The G/C genotype of this polymorphism along with obesity predicted poor response to TNF-α blockers.	[42]
TRAILR1 (TNFRSF10A)	rs20575	Receptor for the cytotoxic ligand TNFSF10/TRAIL, which, when activated, leads to a subsequent cascade of caspases leading to apoptosis.	The G/C genotype of this polymorphism along with obesity predicted poor response to TNF-α blockers.	[39]
Fcy Receptor	FcyIIA-H131R	The FC receptor is a protein found on the surface of cells related to immunity. Their activity stimulates immune cells to destroy microbes and infected cells by antibody mediated phagocytosis.	This polymorphism is associated with lower body surface area (BSA) in the intermediate point of treatment.	[38]
Fcy Receptor	FcyIIIA-V158F	The FC receptor is a protein found on the surface of cells related to immunity. Their activity stimulates immune cells to destroy microbes and infected cells by antibody mediated phagocytosis.	This polymorphism is associated with lower body surface area (BSA) in the intermediate point of treatment.	[38]
HLA-C	rs10484554	Human Leukocyte Antigen encodes for the major histocompatibility (MHC) complex responsible for immune reactions.	This SNP was associated with good response to anti-TNF-α therapy (especially Adalimumab) but not with Ustekinumab.	
HLA-Cw6		Human Leukocyte Antigen encodes for the major histocompatibility (MHC) complex responsible for immune reactions. Individuals carrying the HLA-cw6 allele have a strong susceptibility to acquiring psoriasis.	There is a trend toward better response among HLA-Cw6 positive patients. Patients who were HLA-Cw6 POS and late cornified envelope (LCE-I) carriers were significantly more likely to reach PASI75 than those who were HLA-Cw6 negative and LCE-D/D.	
LCE	DD	Late cornified envelope, encodes for stratum corneum proteins.	The frequency of patients who did not reach PASI75 was higher among LCE D/D individuals.	

Table 6: Pharmacogenetic findings related to TNF-alpha antagonists in psoriasis treatment

IL-12 and IL-23 antagonists

IL-23 is a proinflammatory cytokine that drives the local Th17 effector response, which leads to the expression of various IL-23 dependent genes, including IL-17A. Th17 cells have been linked to the pathogenesis of psoriasis. Polymorphisms in genes related to IL-12 have been linked to efficacy with anti-TNF-alpha treatment. Patients with the IL-23 receptor SNP rs11209026 GG genotype who were treated with TNF-alpha inhibitors achieved PASI90 at 6 months more frequently than patients without this genotype (P=0.006) [30]. Furthermore, the improvement of the PASI score was also greater in these patients (P=0.013) [30]. This same SNP, rs11209026 was observed in another study to be associated with a paradoxical psoriasiform reaction with TNF-alpha inhibitor therapy. These patients originally had plaque type. The most reactions occurred with etanercept (21.4%), however reactions were also observed in patients taking adalimumab (9.8%) and infliximab (7.7%) [40]. Patients with the G/G genotype of a polymorphism within the IL-10 gene, -1087, favored response to etanercept therapy [29]. Within the IL-10 promoter gene, the microsatellite allele 1L-10.R3 as well as the haplotype R3-R9 showed an increase response to etanercept [29]. IL-17, a previously mentioned interleukin involved in the Th17 pathways, was also studied for relevant polymorphisms. The IL-17F SNP rs763780 was associated with no response to adalimumab at weeks 24-28 (T/C genotype, P=0.0044) and a better response to infliximab at weeks 12-16 and 24-28 (T/C genotype, P=0.023 and P=0.020) [43]. Allele mutant C of SNP rs763680 was also associated with lower expression and activity of IL-17F, which may have influenced the interaction of IL-17F and its receptor [43]. IL-6 is a multifunctional cytokine which plays a vital role in signaling acute phase reactants and inflammation. It is also linked to body fat and energy expenditure [44]. Patients with obesity and the G/C genotype of

IL-6 promoter polymorphism -174 (rs1800795) predicted poor response to TNF-alpha blockers [44]. This study concluded that patients with the G allele of this polymorphism, along with obesity, can be considered risk factors for the prognosis and management of psoriasis [44].

Ustekinumab is an IgG1kappa monoclonal antibody directed against the common p40 subunit of IL-12 and IL-23, which are both proteins that play a role in regulating components of the immune system [9]. This drug was developed to inhibit the inflammatory cascade of Th1 and Th17 lymphocytes, since dysregulation in these pathways in keratinocytes is linked to the pathogenesis of psoriasis [34]. Far less pharmacogenetic studies have been performed in regards to Ustekinumab in comparison to TNF-alpha blockers. However, a few studies found associations with different HLA-C genes. HLA-C SNP rs10484554 was associated with good response to anti-TNF therapy but not with ustekinumab [39]. This study looked at the use of biologics and response for 6 months of therapy, and genotype frequency was analyzed after. A possible limitation in these results was that this study (n=250) had very few patients on ustekinumab (n=22) in comparison to the TNF-alpha inhibitors. Another conclusion of this study (although unrelated to HLA-C genes) was that SNPs rs151823 and rs26653 of the endoplasmic reticulum aminopeptidase 1 (ERAP1) gene were found to be associated with good response to ustekinumab. ERAP1 is responsible for removing proteins that are displayed by the MHC complex on the surface of cells [39]. Two studies found a correlation between HLA-Cw6 positive individuals and positive results with ustekinumab [45,46]. Li et al. also reported a differential response to ustekinumab in HLA-Cw6 positive individuals in comparison to HLA-Cw6 negative individuals, however this difference was modest, especially at the higher response rate thresholds (PASI90/100) and later time points (weeks 24 and 28) [47]. There was a noteworthy association of the TNFRSF1B SNP rs1061622 G allele and HLA-Cw6. Psoriasis patients with both HLA-Cw6 and rs1061622 G allele were at an increased risk for negative response to biologics, including ustekinumab [33]. Lastly, a study looked at SNPS in IL-17A and IL17F in regards to response to ustekinumab [43]. This study included controls (n=197) and individuals with moderate-to-severe psoriasis (n=194) and results of univariate analysis showed an association between IL-17F SNP rs763780 and response to ustekinumab (n=70) and 3 and 6 months [43]. All results from the mentioned studies regarding anti-IL12/23 therapy and pharmacogenetics are summarized in Table 7.

Gene	SNP	Gene function	Finding	References
IL-17F	rs763780	Pro-inflammatory cytokine	The T/C genotype showed no response with Ustekinumab at 3 and 6 months.	[43]
HLA-Cw6		Human Leukocyte Antigen encodes for the major histocompatibility (MHC) complex responsible for immune reactions. Individuals carrying the HLA-cw6 allele have a strong susceptibility to acquiring psoriasis.	Increased response to Ustekinumab in HLA-Cw6 positive patient's vs HLA-Cw6 negative patients.	[46]
HLA-Cw6		Human Leukocyte Antigen encodes for the major histocompatibility (MHC) complex responsible for immune reactions. Individuals carrying the HLA-cw6 allele have a strong susceptibility to acquiring psoriasis.	Increased and faster response to Ustekinumab in HLA-Cw6 positive patient's vs HLA-Cw6 negative patients.	[37]
HLA-C	*06:02	Human Leukocyte Antigen encodes for the major histocompatibility (MHC) complex responsible for immune reactions.	A differential response to ustekinumab was confirmed in HLA-C*06:02 positive versus negative patients, but this difference was modest, especially at the higher response rate thresholds (PASI-90 and PASI-100).	[47]
TNFRSF1B	rs1061622 G allele (p.M196R polymorphism)	This SNP is associated with higher whole-blood TNF-α production.	Increased frequency of this SNP among HLA-Cw6-positive psoriasis patients; increased risk for negative response to biological therapy, both anti-TNF-α and anti-p40 therapy.	[33]
ERAP1	rs151823	Endoplasmic reticulum aminopeptidase 1 cleaves cytokine receptors on cell surfaces, which leads to a dampened signaling into the cell, thereby altering inflammation. These enzyme is also involved in protein cleaving for attachment to major histocompatibility complex (MHC) class 1 proteins.	Presence of this SNP was associated with positive response to anti-IL-12/23 therapy.	[39]
ERAP1	rs26653	Endoplasmic reticulum aminopeptidase 1 cleaves cytokine receptors on cell surfaces, which leads to a dampened signaling into the cell, thereby altering inflammation. These enzyme is also involved in protein cleaving for attachment	Presence of this SNP was associated with positive response to anti-IL-12/23 therapy.	[39]

		to major histocompatibility complex (MHC) class 1 proteins.		
HLA-C	rs10484554	Human Leukocyte Antigen encodes for the major histocompatibility (MHC) complex responsible for immune reactions.	This SNP was associated with good response to anti-TNF-α therapy (especially Adalimumab) but not with Ustekinumab.	[39]

Table 7: Pharmacogenetic findings related to IL-12/23 antagonists in psoriasis treatment

Conclusion

Current psoriasis treatment relies largely on targeting various aspects of the inflammatory cascade. The efficacy of many treatments used in psoriasis varies from patient to patient, and the side effect profile of these medications is numerous, due in part to their immunosuppressive nature. Some of this variance in response can presumably be attributed to genetic differences, as this review has discussed. While current research findings are still limited, the clinical utilization of pharmacogenetics in patient treatment is the ultimate goal of such research. Pharmacogenetics will allow for tailored treatment plans that have the potential for better response amongst patients as well as conserving expenditures and healthcare resources.

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