

# Towards Personalized Medicine in Psoriasis: Current Progress

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**Abstract:** Although innovative targeted therapies have positively revolutionized psoriasis treatment shifting treatment goals to complete or almost complete skin clearance, primary or secondary lack of efficacy is still possible. Hence, identifying robust biomarkers that reflect the various clinical psoriasis phenotypes would allow stratify patients in subgroups or endotypes, and tailor treatments according to the characteristics of each individual (precision medicine). To sum up the current progress in personalized medicine for psoriasis, we performed a review on the available evidence on biomarkers predictive of response to psoriasis treatments, with focus on phototherapy and systemic agents. Relevant literature published in English was searched for using the following databases from the last five years up to March 20, 2022: PubMed, Embase, Google Scholar, EBSCO, MEDLINE, and the Cochrane library. Currently, more evidence exists towards biologicals, as justified by the huge health care costs as compared to phototherapy or conventional systemic drugs. Among them, most of the studies focused on anti-TNF and IL12/23, with still few on IL17 (mainly secukinumab). The most discussed biomarker gene is the HLA-C\*02:06 status that has been shown to be associated with psoriasis, and also differential response to biologicals. Although its positivity is associated with great response to MTX, debatable results were retrieved concerning both anti-TNF and IL12/23 while it seems not to affect secukinumab response. Personalized treatment in psoriasis would provide excellent outcome minimizing the risk of side effects. To date, although several candidates were proposed and assessed, the scarcity and heterogeneity of the results do not allow the identification of the gold-standard biomarker per each treatment. Anyway, the creation of a more comprehensive panel would be more reliable for the treatment decision process.

**Keywords:** precision medicine, stratification medicine, biomarkers, pharmacogenetics, pharmacogenomics, biologicals, small molecules, phototherapy, conventional systemic treatments, apremilast, acitretin, ciclosporin, methotrexate, dimethyl fumarate, MTX, DMF, SM

## Introduction

Psoriasis is a chronic inflammatory disease that affects up to 3% of the general population.<sup>1</sup> Although rarely life-threatening, it is associated with several comorbidities such as psoriatic arthritis, psychiatric disorders, metabolic syndrome, inflammatory bowel diseases and uveitis.<sup>2,3</sup> Hence, it represents a great burden not only for patients, that experience a reduced quality of life, but also for health care systems, that sustain the huge treatment costs of this impactful chronic systemic disease.<sup>3</sup> The current therapeutic armamentarium comprises topicals, phototherapy, conventional systemic treatments, biologicals and small molecules (SM). The therapeutic strategy is identified according to patients' characteristics (age, sex, comorbidities, preferences), disease's features (type, localization, severity, extension, symptoms) as well as health system drug availability.<sup>2,4</sup> The performance of each treatment modality is variable and seems to mirror the complex and multifactorial etiopathogenesis of the psoriatic disease.<sup>2</sup> Indeed, it results from the interplay between the individual's exposome (environmental, behavioral and lifestyle factors) and genome (genetic and epigenetic factors).<sup>2</sup> Understanding the pathophysiology of the psoriatic disease is fundamental for the development of target-treatments, highly precise and efficacious.<sup>2</sup> Moreover, investigating the molecular bases and mechanisms that

underly the extreme differential clinical expression of psoriasis in affected patients is crucial for treatment choice. In the current scenario, although innovative targeted therapies have positively revolutionized psoriasis treatment shifting treatment goals to complete or almost complete skin clearance, primary or secondary lack of efficacy is still possible with important consequent negative impact.<sup>5</sup> Hence, identifying robust biomarkers that reflect the various clinical psoriasis phenotypes would allow stratify patients in subgroups or *endotypes*, and tailor treatments according to the characteristics of each individual.<sup>6</sup> In other words, personalized medicine will embrace the role of new frontier in psoriasis management enabling treatment optimization, minimization of the risk of side effects as well as ensuring long-term remission, with important cost saving for health care systems and improvement in patients' quality of life.<sup>7,8</sup> To sum up the current progress in personalized medicine for psoriasis, we conducted a review on the available evidence on biomarkers predictive of response to psoriasis treatments, with focus on phototherapy and systemic agents.

## Materials and Methods

For the current review, relevant literature published in English was searched for using the following databases from the last five years up to March 20, 2022: PubMed, Embase, Google Scholar, EBSCO, MEDLINE, and the Cochrane library. For conventional systemic treatments, less recent articles were included. The search strategy was based on the following keywords: “personalized medicine”, “stratification medicine”, “precision medicine”, “individualized medicine”, “pharmacogenetics”, “pharmacogenomics”, “polymorphisms”, “microRNA”, “miRNA”, “proteomics”, “serum cytokines”, “psoriasis”, “treatment”, “phototherapy”, “biologics”, “small molecules”, “SM”, “acitretin”, “ciclosporin”, “methotrexate”, “MTX”, “dimethyl fumarate”, “DMF”, “apremilast”, “adalimumab”, “etanercept”, “certolizumab”, “infliximab”, “ustekinumab”, “guselkumab”, “risankizumab”, “tildrakizumab”, “ixekizumab”, “brodalumab”, “secukinumab”, and “bimekizumab.” References were reviewed in order to include studies that may have been missed. A flow-chart of literature review has been reported in Figure 1. A summary of the included articles is shown in Table 1.

## Phototherapy

Phototherapy is a valuable opportunity for moderate-to-severe psoriasis as first step or in case of contraindication to systemic agents. To date, studies that investigate the role of genetic factors in response to ultraviolet light therapy in psoriasis have been scarcely performed. Anyway, Ryan et al ran a prospective study on psoriasis patients under phototherapy for 1 year or until relapse, to assess the role of the Fok1, Apa1, Bsm1, Taq1 and the rs4516035 polymorphisms of the vitamin D receptor (VDR) gene on remission duration.<sup>9</sup> They discovered that the Taq1 VDR polymorphism significantly predicted the remission duration: in detail, those homozygous for the C allele (associated with lower VDR activity) had shorter remission as compared to those heterozygous for the same allele, or homozygous for the T allele.<sup>9</sup> Gallais Séréal et al conducted a study to assess the role of tissue resident memory (TRM) T-cells on active and resolved psoriatic lesions and their impact on clinical outcome and risk of relapse.<sup>10</sup> Indeed, TRM T-cells

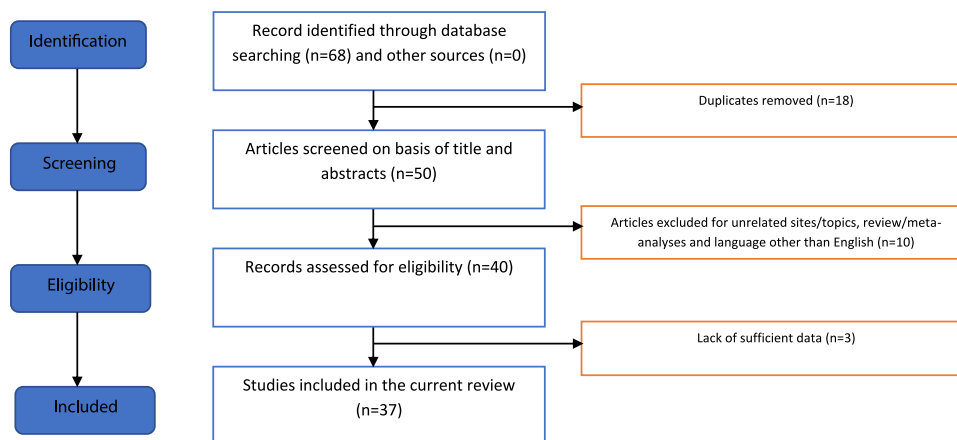


Figure 1 Flow-chart of literature review.

**Table I** Pharmacogenetics Studies on Systemic Treatments for Psoriasis Showing Type of Associations Between Polymorphisms and Response to Treatment

Drug	Authors, Year	Type of Study	Duration	No of Subjects	Biomarker	Association	Outcome Measure
Methotrexate	Campalani et al <sup>21</sup> 2007	Retrospective study	12 weeks	203	MTHFR	No association	PASI75
	Warren et al <sup>22</sup> 2008	Pharmacogenetic study	12 weeks	374	rs35592 (ABCC1)	Positive	/
					rs2238476 (ABCC1)	Positive	
					rs28364006 (ABCC1)	Positive	
					rs17731538 (ABCG2)	Positive	
	rs13120400 (ABCG2)	Positive					
	Warren et al <sup>20</sup> 2009	Pharmacogenetic study	12 weeks	374	MTHFR	No association	PASI75
	Ando et al <sup>17</sup> 2013	Prospective study	12 weeks	142	MTX-PG <sub>5</sub>	Positive	DAS28-3
	Indhumathi et al <sup>24</sup> 2017	Case-control study	12 weeks	189	HLA-C*06:02 POS	Positive	PASI75
					rs3761548 (FOXP3)	Positive	
West et al <sup>29</sup> 2017	Case-control study	1 year	70	HLA-Cw6 POS	Positive	Treatment duration beyond 12 months; number of topical drugs' prescription	
Grželj et al <sup>26</sup> 2021	Retrospective study	24 weeks	137	rs2306283 (SLCO1B1/OATP1B1)	Negative	PASI75	
				rs4149056 (SLCO1B1/OATP1B1)	Negative		
				rs717620 (ABCC2)	Negative		
				rs10948059 (GNMT)	Negative		
				rs2424913 (DNMT3b)	Negative		
Fan et al <sup>28</sup> 2021	Genetic study	12 weeks and 1 year	310	rs11960458 (ANXA6)	Positive	PASI75	
Acitretin	Young et al <sup>31</sup> 2006	Genetic study	12 weeks	124	rs833061 (VEGF) TT	Negative	/
					rs2010963 (VEGF)	No association	
	Campalani et al <sup>33</sup> 2006	Genetic study	12 weeks	208	ApoE	No association	PASI75
	Chen et al <sup>26</sup> 2018	Prospective study	8 weeks	151	rs4149056 (SLCO1B1) and rs2282143 (SLC22A1)	Positive association	PASI50
Chen et al <sup>32</sup> 2018	Prospective study	8 weeks	131	VEGF	No association	PASI 50	
Ciclosporin	Vasilopoulos et al <sup>37</sup> 2014	Genetic study	12 weeks	84	rs1045642 (ABCB1) 3435T genotype	Negative	/
Dimethyl Fumarate	Gambichler et al <sup>40</sup> 2016	Prospective study	12 weeks	84	Val/Val GSTP1	Negative	PASI
					GSTM1	No association	
Adalimumab	Gallo et al <sup>49</sup> 2013	Pharmacogenetic study	6 months	45	IL12B/IL23R	Positive	PASI75

(Continued)

Table I (Continued).

Drug	Authors, Year	Type of Study	Duration	No of Subjects	Biomarker	Association	Outcome Measure	
	Ana Batalla et al <sup>50</sup> 2015	Pharmacogenetic study	6 months	116	HLA-Cw6	Positive	PASI75	
	Linares-Pineda et al <sup>51</sup> 2016	Pharmacogenetic study	6 months	109	rs1800629 (TNF- $\alpha$ ) rs1799964 (TNF- $\alpha$ ) rs1799724 (TNF- $\alpha$ ) rs361520 (TNF- $\alpha$ )	Not relevant	PASI75	
	Linares-Pineda et al <sup>51</sup> 2016	Pharmacogenetic study	6 months	66	rs763780 (IL17F)	Not relevant	PASI75	
Etanercept	Gallo et al <sup>49</sup> 2013	Pharmacogenetic study	6 months	61	IL12B/IL23R	Positive	PASI75	
					HLA-Cw6	Negative	PASI75	
	De Simone et al <sup>72</sup> 2015	Pharmacogenetic study	3 months	97	(-238) rs36152 (TNF $\alpha$ )	Positive	PASI75	
					(-308) rs1800629 (TNF $\alpha$ )	Positive	PASI75	
Infliximab	Gallo et al <sup>49</sup> 2013	Pharmacogenetic study	6 months	33	IL12B/IL23R	Positive	PASI75	
					HLA-Cw6	Negative	PASI75	
	Linares-Pineda et al <sup>51</sup> 2016	Pharmacogenetic study	6 months	35	rs763780 (IL17F)	Not relevant	PASI75	
	Gallo et al <sup>49</sup> 2013	Pharmacogenetic study	6 months	33	rs11209026 (IL23R)	Positive	PASI90	
	Ustekinumab	Gallo et al <sup>47</sup> 2013	Pharmacogenetic study	6 months	27	(-1031) rs1799964 (TNF $\alpha$ )	Positive	PASI50
Raposo et al <sup>75</sup> 2017		Retrospective study	52 weeks	116	HLA-C*06:02 POS	Positive	PASI75	
					rs11209026 (IL-23R)	No association		
					rs6887695 (IL-12)	No association		
Ovejero-Benito et al <sup>23</sup> 2018		Review	/	/	/	rs763780 (IL-17F)	Positive	/
						rs151823 (ERAPI)	Positive	
						rs26653 (ERAPI)	Positive	
						rs2275913 (IL-17A)	No association	
						rs10484879 (IL-17A)	No association	
						rs610604 (TNFAIP3)	No association	
	rs10484554 (HLA-C)					No association		
	LCE3B/3C deletion					No association		
Prieto-Pérez et al <sup>79</sup> 2017	Prospective study	16 weeks	69	CHUK	Positive	PASI75		
				C17orf51	Positive			
				ZNF816A	Positive			
				STAT4,	Positive			
				SLC22A4	Positive			

(Continued)

Table I (Continued).

Drug	Authors, Year	Type of Study	Duration	No of Subjects	Biomarker	Association	Outcome Measure					
					Corf72	Positive						
					TNFRSF1A	Negative						
					HTR2A	Negative						
					NFKB1A	Negative						
					ADAM33	Negative						
					IL13	Negative						
	Loft et al <sup>80</sup> 2018	Prospective study	12 weeks	230	rs1143623 (IL1B)	Positive	PASI50, PASI75					
					rs1143627 (IL1B)	Positive						
					rs8177374 (TIRAP)	Positive						
					rs5744174 (TLR5)	Positive						
Connel et al <sup>81</sup> 2021	Genome-wide association study (GWAS)	40 weeks	439	rs35569429 (Chromosome 4) deletion	Negative	PASI50, PASI75 PASI90, PASI100						
Adalimumab and ustekinumab	Dand et al <sup>86</sup> 2019	Observational study	48 weeks	487	HLA-C	No association in case of HLA-C06 positivity. In case of HLA-C06 negativity association with adalimumab	PASI75, PASI90, PASI100					
Ustekinumab	Van Der Reek <sup>82</sup> 2017	Observational study	12 weeks	234	rs3213094 (IL12b)	Positive	PASI75					
rs610604 (TNFAIP3)					Positive							
rs6427528 (CD84)					Positive							
CD84 (the heterozygosity, GA)					Positive							
Etanercept	Costanzo et al <sup>89</sup> 2018	Phase III clinical trial (The SUPREME study)	24 weeks	434	HLA-C*06:02 POS	No association	PASI50, PASI75, PASI90, PASI100					
Adalimumab and ustekinumab					Anzengruber et al <sup>91</sup> 2018	Real-life retrospective study		12 weeks	18	HLA-C*06:02 POS	No association	PASI50, PASI75, PASI90
Secukinumab					Papini et al <sup>90</sup> 2019	An extension phase of the SUPREME study		72 weeks	434	HLA-C*06:02 POS	No association	PASI75, PASI90, PASI100
Secukinumab and ixekizumab	Vugt et al <sup>92</sup> 2020	Multicenter cohort study	24 weeks	134	IL-17	No association	PASI75, PASI90					

(Continued)

**Table I** (Continued).

Drug	Authors, Year	Type of Study	Duration	No of Subjects	Biomarker	Association	Outcome Measure
Apremilast	Verbenko et al <sup>112</sup> 2020	Genetic study	26 weeks	34	rs1143633 C/T (IL-1B)	Positive	PASI75
					rs20541 G/A (IL-4)	Positive	
					rs2201841 A/G/T (IL-23R)	Positive	
					rs1800629 A/G (TNF- $\alpha$ )	Positive	

**Abbreviations:** PASI, Psoriasis Area Severity Index; HLA, human leucocyte antigen; IL, interleukin; TNF, tumor necrosis factor; POS, positive; A, adenine; G, guanine; T, thiamine; C, cytosine; ERAP1, endoplasmic reticulum aminopeptidase 1; TNFAIP3, TNF alpha induced protein 3; TLR5, toll like receptor 5; DAS28-3, disease activity score in 28 joints; MTX-PG, MTX polyglutamate; TIRAP, TIR domain containing adaptor protein; SLCO1B1, solute carrier organic anion transporter family member 1B1; ABCC2, ATP-binding cassette transporters C2; DNMT3b, DNA (cytosine-5-)-methyltransferase 3B; GNMT, glycine N-methyltransferase; OATP1B1, organic anion transporter polypeptide 1B1; ApoE, apolipoprotein E; CHUK, component of inhibitor of nuclear factor kappa B kinase complex; STAT4, signal transducer and activator of transcription 4; ZNF816A, zinc finger protein 816 a; SLC22A4, solute carrier family 22 member 4; TNFRSF1A, TNF receptor superfamily member 1A; HTR2A, 5-hydroxytryptamine receptor 2A; NFKBIA nuclear factor kappa-b inhibitor, alpha; ADAM33, ADAM metallopeptidase domain 33; GSTP1, glutathione-S-transferase P1; GSTM1, glutathione-S-transferase M1.

producing IL-17 and IL-22 are highly represented both in active and inactive disease lesions; also, the delicate balance among different TRM subsets may influence tissue response after T-cell activation.<sup>10</sup> The authors found out that the relative ratio of tissue responses to interferon (INF), IL-10 and IL-17A is associated with time for disease relapse.<sup>10</sup> In detail, the epidermal upregulation of IL-17A was associated with early psoriasis relapse after a successfully complete cycle of narrowband ultraviolet B (UVB) phototherapy.<sup>10</sup> Hence, the stratification of tissue responses to T-cell activation in resolved psoriasis lesions may predict disease relapse after UVB phototherapy or other immunomodulating agents.<sup>10</sup> Further studies on the topic are warranted.

## Conventional Systemic Agents

Conventional systemic drugs are usually used as first-line agents for the management of moderate-to-severe psoriasis. They include MTX, acitretin, ciclosporin and DMF. Interindividual differences may lead to different therapeutic responses. Major knowledge on pharmacogenetics and pharmacogenomics may help clinicians in choosing a personalized treatment, preventing possible adverse events (AEs). However, pharmacogenetics data on acitretin, ciclosporin and DMF are scant.<sup>11</sup>

### Methotrexate

MTX is a folate antagonist employed in the management of patients affected by moderate-to-severe psoriasis at a dosage of 7.5–25 mg weekly.<sup>12</sup> It is also employed in the treatment of psoriatic arthritis.<sup>12</sup> For the treatment of psoriasis, MTX may be administered orally, intramuscularly (IM) or subcutaneously (SC).<sup>13,14</sup> Given the saturable intestinal absorption and nonlinear pharmacokinetics following the oral administration, the parental route is preferred.<sup>13,14</sup> Moreover, the comparability between the SC and IM administrations in terms of pharmacokinetics and pharmacodynamics, favored the first as a less painful and more convenient way to administer MTX.<sup>13,14</sup> In this context, the inter-individual genetic polymorphisms related to the pharmacodynamic and pharmacokinetic properties of MTX may affect its effectiveness and safety.<sup>15,16</sup> In detail, the cellular intake of MTX mainly depends on a carrier-mediated transport via the reduced folate carrier 1 (RFC1). It has been shown that polymorphisms in the RFC are associated with response to MTX as they correlate with the levels of MTX polyglutamate (MTX-PG), a more active metabolite, in red blood cells (RBC).<sup>17,18</sup> Moreover, long versus short chain MTX-PGs are associated with different cell retention and antifolate effects.<sup>17</sup> In a study by Ando et al the detectability of MTX-PG<sub>5</sub> in RBC resulted a possible biomarker for response to MTX; also, the low detectability of MTX-PG<sub>5</sub> was associated with the RFC1 80G>A mutation.<sup>17</sup> Moreover, since MTX undergoes a partial metabolization into an inactive isoform, the 7 hydroxy-MTX, through the aldehyde oxidase in the liver and then binds to albumin, differences in the enzymatic activity as well as the presence of competitive ligands (salicylates, tetracyclines, sulfonamides, oral contraceptives) may affect the toxicity and the effectiveness of MTX.<sup>19</sup> Another enzyme

involved in the MTX pathway is the methylenetetrahydrofolate reductase (MTHFR), that catalyzes the formation of 5-methyltetrahydrofolate, which in turn is involved in methionine synthesis. Studies on polymorphisms of MTHFR gene, failed to find association with response to MTX.<sup>20,21</sup> Finally, active efflux transporters, particularly ABCC1-5 (ATP-binding cassette, subfamily C, member 1–5) and ABCG-2MTX (ATP-binding cassette, subfamily G, member 2), are in charge of releasing MTX polyglutamates from the liver and the erythrocytes.<sup>22</sup> Genetic polymorphisms in these pumps seem not to affect MTX toxicity but its clinical effectiveness.<sup>22</sup> In detail, the SNPs of ABCC1 (rs35592, rs2238476, and rs28364006) and ABCG2 (rs17731538 and rs13120400) correlate with a positive response to MTX in psoriasis patients.<sup>22,23</sup> As regards MTX excretion, the renal (through both active secretion and glomerular filtration) and bile systems accounted for 85% and 15%, respectively.<sup>14</sup> Patients with renal dysfunction or taking drugs affecting renal excretion may develop toxic effect of MTX.<sup>14</sup> As regards safety, possible side effects can be reduced with the concomitant administration of folinic or folic acid.<sup>14</sup> Gastrointestinal intolerance is the most common AE when MTX is taken orally.<sup>14</sup> Another possible AE which can cause a life-threatening condition is the myelotoxicity.<sup>14</sup> Moreover, liver fibrosis can develop in up to 25% of patients receiving MTX for at least 5 years. Finally, MTX is teratogenic and mutagenic.<sup>14</sup> A recent study on the pharmacogenetics markers to predict the effectiveness of MTX in a South Indian Tamil population of 189 psoriasis patients (132 responders and 57 non-responders) showed significant differences between genotype frequencies of HLA-Cw6 and FOXP3 (rs3761548) among the responders compared to non-responders.<sup>24</sup> The presence of one 28-b triplet repeat (heterozygous 3R/2R allele, homozygous 3R/3R allele) in the thymidylate synthase (TYMS) 50-untranslated region (UTR) showed to be more common in non-responders' patients.<sup>24</sup> Moreover, a significant association was found between the TYMS 50-UTR 3R allele and AEs, symptomatic comorbidities, and hepatotoxicity.<sup>24</sup> Similarly, toxicity was more frequent in patients with SLC19A1 (80A allele) and the TYMS 30- nUTR 6 base-pair deletion.<sup>24</sup> Finally, a variant in ATIC (347G) was related with an increased risk of AEs, while a variant in MTHFR (1298C) seemed to be protective for hepatotoxicity.<sup>21</sup> As regards effectiveness, a reduction in mRNA expression of T-helper (Th) cell-related genes (ie, Th-1, Th17, and Th-22) was found in responders patients compared with non-responders after 4 months of treatment.<sup>25</sup> A recent study evaluating the effects of genetic predisposition on efficacy and toxicity of MTX in 137 psoriasis patients identified GNMT rs10948059 as a risk factor for inadequate efficacy showing a 7-fold increased risk of treatment failure in patients with at least one variant allele.<sup>26</sup> Also, DNMT3b rs2424913 was found as possible risk factor for inefficacy, with a 4-fold increased risk in patients carrying at least one variant allele.<sup>26</sup> Moreover, the BHMT rs3733890 variant allele was correlated to an increased risk of hepatotoxicity.<sup>26</sup> Variants in the genes for MTX transporters OATP1B1 (rs2306283/rs4149056 SLCO1B1 haplotypes) and ABCC2 (rs717620) were associated with increased risk of treatment failure.<sup>26</sup> A study analyzing the drug survival of MTX in 117 patients showed ABCC2 rs717620 genotype was significantly associated with drug survival, with variant T allele associated with longer drug survival.<sup>27</sup> Fan et al performed a study to assess if polymorphisms of the annexin A6 (ANxA6) gene, that confers psoriasis susceptibility, were associated with response to MTX.<sup>28</sup> They found out that the rs11960458 polymorphism was statistically significantly associated with response to MTX both in the short (12 weeks) and long-term (1 year).<sup>28</sup> In detail, the CC genotype was associated with a greater response (higher percentage of PASI75 at 12 weeks) as compared to TT/CT genotype.<sup>28</sup> Thus, this polymorphism may be a good candidate as predictive biomarker of response to MTX.<sup>28</sup> Finally, West et al investigated the role of the HLA-Cw6 status in influencing the efficacy and safety of MTX for psoriasis.<sup>29</sup> They reported that HLA-Cw6 positive patients responded better to MTX and had a lower incidence of AEs as compared to those negative for this allele.<sup>29</sup> Hence, the HLA-Cw6 is not only associated with psoriasis susceptibility but also to response to MTX.<sup>29</sup>

### Acitretin

Acitretin is a second-generation oral retinoid approved for the management of psoriasis, alone or in combination with other agents. Its efficacy is dose-dependent, requiring 3–6 months to achieve an optimal response.<sup>23</sup> Acitretin mechanism of action in psoriasis is not completely understood: anyway, it is involved in keratinocyte differentiation, reducing epidermal hyperplasia, and slowing cell proliferation.<sup>30</sup> It also regulates immune response through T-helper 1 and 17 cells.<sup>23</sup> The most important AE is teratogenicity, hence pregnancy is the main absolute contraindication.<sup>23</sup> To date, few studies have investigated the role of pharmacogenomics in influencing response to acitretin. In detail, Chen et al



investigated if polymorphisms in key transporter genes could influence acitretin effectiveness.<sup>30</sup> The genes in issue were the solute carrier organic anion transporter family member 1B1 (SLCO1B1) and solute carrier family 22 member 1 (SLC22A1).<sup>30</sup> They discovered the SLCO1B1 rs4149056 and SLC22A1 rs2282143 polymorphisms affect the clinical outcomes of acitretin for psoriasis.<sup>30</sup> In detail, those patients with the rs2282143CT-rs4149056TC haplotype displayed a higher response rate.<sup>30</sup> Also, since it is pumped into cells by the SLCO1B1 and SLC22A1 transporters, the rs4149056C and rs2282143T alleles have shown to reduce the its uptake, being then greatly associated with clinical efficacy.<sup>30</sup> Moreover, interindividual differences in vascular endothelial growth factor (VEGF) have been associated with susceptibility to psoriasis and variable response to acitretin.<sup>31,32</sup> While Chen et al found no statistically significant association between VEGF polymorphisms and clinical response to acitretin, Young et al identified the rs833061 (VEGF) variant to have a predictive role in treatment response since a significant increase of rs833061 (VEGF) TT genotype was reported in non-responder patients.<sup>31,32</sup> Finally, no association was found between rs2010963 (VEGF) and SNPs located on apolipoprotein E and response to acitretin.<sup>23,33</sup> Concerning side effects, the EGF rs2237051G allele displayed to be associated with the increased erythema during the combination therapy (acitretin + topical calcipotriol) for psoriasis.<sup>32</sup> Also, the serum frizzled-related proteins 4 (SFRP4) rs1802073 GG/GT genotypes were found to be associated with elevated serum lipid levels after acitretin treatment.<sup>34</sup>

### Ciclosporin

Ciclosporin A (CSA) is an effective systemic treatment approved for the management of psoriasis at a dosage of 2.5–5 mg/kg/day. CSA acts by the inhibition of the first phase of T-lymphocyte activation, resulting in lower levels of multiple inflammatory cytokines. However, the possibility of AEs, particularly nephrotoxicity and hypertension, limited the long-term use of CSA. Studies on pharmacogenomics and pharmacogenetics properties of CSA are scant.<sup>35</sup> CSA is primarily absorbed in the intestine.<sup>36</sup> The metabolizing CYP3A isozymes in the liver (ie, CYP3A4 and CYP3A5) and the multidrug efflux transporter P-glycoprotein (ABCB1) may explain the wide interindividual variability.<sup>36</sup> However, there are many contrasting results on the impact of SNPs on ciclosporin efficacy and nephrotoxicity.<sup>36</sup> A 3-month study on 84 psoriasis patients treated with CSA showed that the 3435T genotype in rs1045642 (ABCB1) was more frequent in non-responders compared with responders.<sup>37</sup> Another 56-week study enrolling 11 psoriasis patients undergoing treatment with CSA 4 mg/kg/day reported that CSA modulated several genes from activated T-lymphocytes, type 1 pathway (p-40, INF-g and STAT-1), Th17 pathway (IL-17, IL-22), dendritic cells and myeloid-derived cells.<sup>38</sup>

### Dimethyl Fumarate

DMF is an orally administered drug approved by the US FDA for the treatment of moderate-to-severe psoriasis in the adults.<sup>39</sup> It inhibits NF-kB translocation, lowers the level of pro-inflammatory cytokines and the inflammatory infiltrate in plaque psoriasis, halts the proliferation of keratinocytes, and also alters the expression of adhesion molecules, thus exerting anti-inflammatory effects.<sup>39</sup> At a molecular level, the immunomodulation derives from cellular glutathione depletion (and the induction of glutathione-S-transferase) and oxidative stress.<sup>40</sup> This drug showed a good efficacy and tolerable safety profile.<sup>39</sup> The most common AEs (flushing and gastrointestinal disorders) occurred mainly during the first few weeks of treatment and tended to improve or resolve over time.<sup>39</sup> Scarce pharmacogenetics data on biomarkers predictive of response to DMT for psoriasis are available. In detail, Gambichler et al investigated the role of glutathione-S-transferase (GST) M1 and GSTP1 polymorphisms in response to 3 month-treatment with DMF in 84 psoriasis patients.<sup>40</sup> They found out that the Val/Val GSTP1 polymorphism increased by 43 folds the risk of treatment failure (non-responders), while no association was reported for GSTM1.<sup>40</sup> Hence, the Val/Val GSTP1 polymorphism may be employed to screen for responders versus non-responders to DMT in the therapy decision process.<sup>40</sup>

### Biologicals

Biologicals are an innovative class of therapeutics with high efficacy and safety as compared to conventional systemic agents. They are engineered antibodies that specifically recognize a cytokine or its receptor, by competitively inhibiting the natural ligand or link and thus blocking the related inflammatory pathway. According to the inhibited cytokine, they are divided into anti-tumor necrosis factor (TNF), anti-IL12/23, anti-IL17, and anti-IL23. It is supposed that genetic



polymorphisms of cytokines and/or their receptor as well as major histocompatibility complex, may reflect the interindividual differential response to each class of inhibitors.<sup>39</sup> Indeed, it has been estimated that up to 50–70% of psoriatic patients may show different response degrees to anti-ILs drugs.<sup>41</sup>

### Anti-TNF

TNF inhibitors represent the first class of biological agents approved for the treatment of moderate-to-severe psoriasis.<sup>42</sup> This class includes etanercept, infliximab, adalimumab, certolizumab and their biosimilars.<sup>43</sup> To date, several studies have investigated the role of pharmacogenetics and pharmacogenomics markers as predictors of response to anti-TNF treatment. No data are available concerning certolizumab pegol. Etanercept is the soluble form of the p75 TNF $\alpha$  receptor, that acts by binding two molecules of TNF $\alpha$ , depleting them from the circulation.<sup>44</sup> Adalimumab is a fully human antibody, while infliximab is a chimeric mouse antibody, both drugs act by binding and inhibiting circulating TNF $\alpha$ .<sup>44,45</sup> Anti-TNF showed promising results in psoriasis management in terms of both efficacy and safety profiles. However, although their efficacy, it has been reported that up to 50% of patients treated with anti-TNF, do not show enough clinical improvement, with lower rates of both PASI90 and PASI100 responses.<sup>46</sup> With regards to pharmacogenetics studies, although the HLA-C:06:02 has been linked to a high risk of developing psoriasis, its ability to predict anti-TNF drug response is still debated.<sup>47</sup> Indeed, only few studies evaluated the association between the HLA-C:06:02 and response to TNF inhibitors, showing not significant and contrasting results.<sup>48</sup> However, a Spanish study reported that the HLA-C:06:02 allele patients may have a lower response rate to anti-TNF, including infliximab, etanercept, and adalimumab.<sup>49</sup> In contrast with these results, another interesting study showed HLA-C 06:02 allele patients were more likely to respond to TNF inhibitors.<sup>50</sup> These highly variable reports may be explained by the variable allele frequencies among different populations and ethnicities. Due to the central role played by TNF in psoriasis pathogenesis, several studies evaluated the correlation between TNF and its receptors, and anti-TNF response. Particularly, several SNPs located in TNF gene (such as rs1800629, rs1799964, rs1799724, rs361520) have been investigated as biomarkers of response to anti TNF.<sup>51</sup> However, further studies did not observe any significant correlation between these SNPs and response to TNF inhibitors.<sup>52,53</sup> On the other hand, a meta-analysis confirmed an association with rs1799724. However, only two of the 15 studies analyzed in this meta-analysis related to psoriasis. About pharmacogenomics studies, to date several data have been reported about pharmacogenetics of response to TNF inhibitors, with many reviews focusing on this biological classes.<sup>23,52,54,55</sup> Particularly, most of the published studies on this topic, followed a candidate-gene approach, focusing on the analysis of the reduction in the number of genes linked with psoriasis or with the positive response to biological treatment,<sup>23,53,56–65</sup> while only few studies have been conducted with a pharmacogenomics approach, hence, using GWAS.<sup>66,67</sup> However, data from the few reported GWAS studies did not identify any SNPs resulting significantly associated with a greater response to biological treatments, probably due to the relatively small sample size. More data have been reported in adalimumab treated patients. Particularly, a study evaluating mononuclear cells (both in peripheral blood and skin) showed in patients non responders to adalimumab a suppression in the gene expression of IL-22, TNF $\alpha$ , IL-17, IL-8, and IL-23A, while in adalimumab responders patients Th-17 pathway genes were suppressed (TGF- $\beta$ 1, IL-1 $\beta$ , IL-8, IFN- $\alpha$ , CCL20, S100A7, HBD-2).<sup>25</sup> Interestingly, in a recent published study, Ovejero-Benito et al reported a novel association of SNPs located on IL28RA, VEGFA, CYLD, LMO4, IL12B, and TNFAIP3 genes with overall and successful dose reduction for biological drugs in a relatively high number of patients (n=120).<sup>68</sup> Furthermore, the authors also reported an association between positive response to adalimumab and the polymorphisms in TLR10, IL28RA, MICA-A9, TRAF3IP2 and SDC4.<sup>68</sup> Another interesting correlation has been reported in patients treated with etanercept, who showed decreased levels of mRNA expression in the genes involved in notch and TLRs-2 and 9 pathways (such as NOTCH1, NOTCH2, and JAGGED1).<sup>69,70</sup> Among data available for etanercept treatment, a more recent study showed significant increased levels of microRNAs (miRNAs) (miR106b, miR223, miR126, and miR142-3p) in patients resulting unresponsive to etanercept, if compared to responders.<sup>71</sup> Contrasting results have been reported in patients carrying the T-allele of rs1799724 in the TNF $\alpha$  genes, associated to a better response to TNF inhibitors, including a subset of patients treated with infliximab,<sup>49</sup> while other studies showed that these patients may have a lower response rate to etanercept.<sup>53,72,73</sup>

## Anti-IL12/23

Ustekinumab is a human monoclonal antibody that targets the p40 subunit of IL-12 and IL-23 cytokines. It was approved by the US FDA for the treatment of moderate-to-severe psoriasis in 2009 and PsA in 2013.<sup>74</sup> Its mechanism of action results in the inhibition of the Th1 and Th17 cytokines and their respective inflammatory pathways. Several studies were performed to identify pharmacogenetics biomarkers of response to ustekinumab.<sup>23,75–83</sup> Anyway, results are conflicting, and more research is warranted on the topic. Overall, it appears to be more robust a panel of biomarkers instead of a single one in the prediction of treatment outcomes. The most discussed and studied genetic marker involved in response to ustekinumab is the HLA-C:06:02. Numerous studies have shown that carriers of the HLA-C:06:02 allele displayed a better and faster response to ustekinumab compared to the negative ones.<sup>75,76,84,85</sup> Such findings did not depend on ethnicity, being confirmed in Caucasian, Chinese and American patients.<sup>23,75</sup> In detail, a large cohort of European patients was screened for the HLA-C\*06 status in a retrospective multicentric study by Talamonti et al in order to confirm the role of this polymorphism as pharmacogenetics marker of response to ustekinumab, as previously reported.<sup>76,84</sup> Of the recruited patients, 127 were C\*06POS and 128 were C\*06NEG.<sup>76</sup> At week 4, PASI 50 was reached by a greater proportion of C\*06POS patients as compared to negative one, reaching statistical significance ( $p < 0.001$ ).<sup>76</sup> PASI 75 was reached by a statistically significant higher proportion of C\*06POS patients than C\*06NEG ones, at each follow-up visit (week 12, 28, and 52;  $p < 0.001$ ).<sup>76</sup> Such difference was even greater as for PASI 90 at week 12 and 52 ( $p < 0.001$  and  $p < 0.003$ , respectively).<sup>76</sup> Hence, the positivity of HLA-C\*06 has been shown to correlate not only to a great but also fast response to ustekinumab.<sup>76</sup> Similar findings were reported by Chiu et al in a study on Chinese population.<sup>85</sup> Moreover, Raposo et al conducted a retrospective study to evaluate the role of HLA-Cw\*0602 polymorphism as a predictor biomarker for response to ustekinumab.<sup>75</sup> On completion, the IL-23R (rs11209026) and IL-12 (rs6887695) polymorphisms were analyzed given the role of ustekinumab in the IL-12/23 axis.<sup>75</sup> Of the 116 enrolled patients, 47 patients (40.5%) were positive for HLA-Cw\*0602 (HLA-Cw\*06POS) and 69 (59.5%) were negative (HLA-Cw\*06NEG).<sup>75</sup> Response to treatment was higher in Cw06POS patients as compared to Cw06NEG patients at Week 12 and 24 ( $p < 0.05$ ), but not at Week 52 ( $p = 0.174$ ).<sup>75</sup> No statistically significant association was observed between the IL-23R (rs11209026) and IL-12 (rs6887695) polymorphisms and clinical response.<sup>75</sup> Hence, the HLA-Cw\*0602 may represent a biomarker for early response to ustekinumab.<sup>75</sup> Also, they speculate that, although the loss of statistical significance in the long term, HLA-Cw\*0602 positivity may reflect a specific subtype of psoriasis, mainly driven by the aberrant activation of the IL-12/23 pathway.<sup>75</sup> Anyway, the positive association between HLA-C:06:02 positivity and response to ustekinumab was questioned in more recent studies.<sup>77,78</sup> Indeed, a recent systematic review and meta-analysis of 8 studies involving 1048 psoriasis patients was run by van Vugt et al with the aim to investigate if the HLA-C\*06:02 status was associated with a differential response to ustekinumab in patients affected by psoriasis.<sup>77</sup> They showed that HLA-C\*06:02 positive patients had a median PASI75 response rate of 92% after 6 months of ustekinumab therapy compared to a median PASI75 response rate of 67% in the HLA-C\*06:02 negative patients.<sup>77</sup> Notwithstanding the difference, both genotype groups had a high PASI 75 response rates, so those HLA-C\*06:02 negative should not be denied treatment with ustekinumab.<sup>77</sup> These finding were further confirmed by a more recent retrospective study by Anzengruber et al.<sup>78</sup> Anyway, the great heterogeneity of the included studies does not allow a generalization,<sup>77</sup> for this reason, the authors suggest that a personalized therapy for psoriasis patients should rely on a set of biomarkers, rather than a single one.<sup>77</sup> Also, the same genotype may influence response to different biologics.<sup>86</sup> Dand et al performed an observational study to assess if the MHC class I allele HLA-C\*06:02, that confers psoriasis susceptibility, may determine patients' differential response to the two most prescribed biologicals for psoriasis: adalimumab and ustekinumab.<sup>86</sup> They found out that HLA-C\*06:02-negative psoriasis patients were significantly more likely to respond to adalimumab as compared to ustekinumab, especially in the presence of PsA as comorbidity.<sup>86</sup> Anyway, no statistically significant difference was found in case of HLA-C\*06:02-positivity for both drugs.<sup>86</sup> So, the authors recommend that in case of HLA-C\*06:02-positive psoriasis patients without PsA, ustekinumab should be preferred over adalimumab for the better posology (longer intervals) and drug survival.<sup>86</sup> They also speculate that the HLA-C\*06:02 status differentiates two biologically distinctive endotypes, hypothesizing that the TNF-alpha pathway constitutes the major driver of the psoriasis pathogenesis in case of negativity as compared to positivity.<sup>86</sup> Hence, HLA-C\*06:02 status should be ascertained for the

optimal selection of first-line therapy (adalimumab versus ustekinumab) in clinical practice given its straightforward determination, and so be employed as predictive biomarker of response to psoriasis treatment.<sup>86</sup> Further novel polymorphisms appear to be promising predictors of response to ustekinumab.<sup>23,79–82</sup> In a review by Ovejero-Benito et al, response to ustekinumab was associated with the following polymorphisms: rs763780 (IL-17F), rs151823 and rs26653 (ERAP1).<sup>23</sup> By contrast, rs2275913 and rs10484879 (IL-17A), rs610604 (TNFAIP3), rs10484554 (HLA-C), as well as LCE3B/3C gene deletions, were not associated with response to ustekinumab.<sup>23</sup> A study by Prieto-Pérez et al reported a good response to ustekinumab in the presence of SNPs in CHUK, C17orf51, ZNF816A, STAT4, SLC22A4, and Corf72 genes and a poor response in case of SNPs in TNFRSF1A, HTR2A, NFKBIA, ADAM33, and IL13 genes.<sup>79</sup> Other reported SNPs associated with response to ustekinumab in a Danish population were rs1143623, rs1143627 (IL1B), rs8177374 (TIRAP), and rs5744174 (TLR5).<sup>80</sup> Also, Connell et al recently performed a genome-wide association study (GWAS) to identify further biomarkers, other than the well-known HLA-C\*06:02, of response to ustekinumab. 439 European patients were included.<sup>81</sup> The genetic analysis was correlated to the phenotypic response to ustekinumab as measured by PASI in terms of percentage improvement at week 12 as compared to baseline.<sup>81</sup> The GWAS identified the Chromosome 4 SNP rs35569429 being highly associated with response to ustekinumab at week 12 at a genome-wide significant level.<sup>81</sup> In detail, at week 12, PASI75 was reached by 44% of those psoriasis patients harboring at least one copy of the deletion (Del+) allele of rs35569429 and by 75% of those without Del (Del-).<sup>81</sup> Treatment responses were boosted in case of co-expression of HLA-C\*06:02.<sup>81</sup> Indeed, those Del+ and HLA-C\*06:02- reached a week 12-PASI75 in 35% of cases, while those Del- and HLA-C\*06:02+ had a week 12-PASI75 response rate of 82%, with a more than 2-fold difference.<sup>81</sup> In conclusion, the absence of the minor allele (Del-) was associated with a statistically significant larger PASI improvement at 12 weeks from baseline and better PASI responses at each follow-up visits (week 2, 4, 24, 48) than those Del+.<sup>81</sup> Also, stratification of ustekinumab responses was greater when rs35569429 was considered in combination with HLA-C\*06:02.<sup>81</sup> Hence, the authors through GWAS identified a novel SNP potentially associated with response to ustekinumab in psoriasis patients.<sup>81</sup> Van Den Reek et al wanted to test biomarkers for treatment response towards biologicals commonly used in psoriasis (adalimumab, ustekinumab and etanercept) by collecting data from a prospective real-world BioCAPTURE cohort.<sup>82</sup> Genetic assessment included copy number variation in LCE3B and 3C genes and 8 SNPs in HLA -C\*06, CD84, IL12b, IL23R, TRAF3IP2, ERAP1, IFIH1 and TNFAIP3.<sup>82</sup> They found out that genetic variation in IL12b (rs3213094) and in TNFAIP3 (rs610604) were associated with ustekinumab response (variation in PASI score as compared to baseline).<sup>82</sup> Also, a variant in CD84 (rs6427528) was associated with etanercept treatment response.<sup>82</sup> For adalimumab and ustekinumab, the heterozygosity (GA) for the CD84 SNP also showed trends towards better treatment outcomes compared to homozygosity (GG).<sup>82</sup>

## Anti-IL17

The biologic class of anti-IL17 is involved in the downstream blockade of IL17/23 pathway that has been shown involved in psoriasis pathogenesis. It includes secukinumab, ixekizumab, brodalumab and the latest approved bimekizumab.<sup>87,88</sup> Overall, their performance in terms of efficacy and safety is high and onset time fast. However, there are few pharmacogenomics studies investigating if the presence of polymorphisms in key genes may influence response to anti-IL17 agents, given their recent approval.<sup>35</sup> In detail, more evidence exists concerning secukinumab, while no data are available for bimekizumab and brodalumab. The role of HLA-C\*06:02 on the efficacy and safety of secukinumab has been assessed in the SUPREME study, a phase III clinical trial on 434 patients with moderate-to-severe psoriasis.<sup>89</sup> No statistically significant difference in PASI90 has been found in those HLA-C\*06:02 positive and negative patients at week 16 (80.4% vs 79.7%),<sup>89</sup> similar results were recorded concerning PASI100 at week 24 (HLA-C\*06:02 positive and negative 62.0% vs 61.0%).<sup>89</sup> Hence, the HLA-C\*06:02 seems a poor candidate biomarker of response to secukinumab, given the high performance of this drug regardless of the HLA-C\*06:02 status.<sup>89</sup> This conclusion was further confirmed by an extension of the SUPREME study, where the response rate to the drug was comparable between those HLA-C\*06:02 positive and negative up to week 72.<sup>90</sup> Moreover, results from a real-life retrospective study by Anzengruber et al on 18 psoriasis patients under secukinumab were in line with the beforementioned studies, as no difference in PASI90 at 3 months of therapy was observed according to the HLA-C\*06:02 status; anyway, the authors recommend that a bigger sample size of at least 216 patients is needed to identify a difference in response ( $\alpha = 0.05$ ,

power= 90%).<sup>91</sup> As regards cytokines, several polymorphisms of the IL-17 gene have been related to different response degrees to its inhibitors. A multicenter study on 134 patients from 4 European hospitals under either secukinumab (118) or ixekizumab (16) performed the IL17A gene sequencing to assess if the presence of polymorphisms could explain the differential response to the drugs in issue.<sup>92</sup> They found out that the coding regions were invariable in the study population.<sup>92</sup> By contrast, they identified 5 SNPs in non-coding regions (rs3748067, C/T; rs2275913, C/G/T; rs3819025, A/G; rs7747909, A/G and rs8193037, A/C/T), that anyway did not affect the effectiveness of secukinumab and ixekizumab after 12 weeks of treatment.<sup>92</sup>

### Anti-IL23

The discovery of the central role of Th-17 pathway in psoriasis management, led to the development of highly effective biological drugs targeting the most important cytokines involved in the modulation of this pathway. Particularly, IL-23 has been showed to regulate T-cells production of high IL-17, resulting in a self-amplifying inflammatory response in keratinocytes, and finally in the development of typical psoriasis.<sup>93–96</sup> In this context, recent major research advancements resulted in the development of new biological drugs specifically inhibiting the key function played by IL23.<sup>97</sup> Anti-IL23 drugs (guselkumab, risankizumab, and tildrakizumab) represent the latest class of biologics approved in the treatment of moderate to severe psoriasis.<sup>98</sup> Guselkumab is a fully human monoclonal antibody that acts by binding the p19 subunit of IL-23, preventing its binding to IL23 receptor and the activation of the related inflammatory cascade.<sup>99</sup> Guselkumab represents the first IL-23 available in clinical practice, showing promising results in both clinical trials and real-life studies.<sup>98,100–105</sup> Risankizumab is a humanized Ig G1 monoclonal antibody specifically targeting IL23 by binding its p19 subunit. Its safety and efficacy profiles have been evaluated by several trials and real world evidence studies, which confirmed risankizumab promising results in the management of moderate to severe psoriasis.<sup>106–110</sup> Tildrakizumab represents the latest IL-23 inhibitor available in clinical practice in Italy. It is a fully humanized IgG1/k antibody selectively binding to the p19 subunit of the IL-23. Its safety and efficacy profiles were evaluated by clinical trials and fewer real-life studies than other IL-23 inhibitors, due to its more recent availability in daily clinical practice.<sup>97,98,111</sup> Even if few studies have investigated the molecular and clinical predictors of response to IL-23 inhibitors for other chronic inflammatory diseases, such as Crohn's disease and ulcerative colitis, to date no data have been published for a personalized medicine approach in psoriasis. Indeed, although the promising results in psoriasis management, data from pharmacogenomics and pharmacogenetics studies specifically evaluating and/or researching potential biomarkers to predict anti-IL-23 response are still lacking. However, due to their important role in the actual and future psoriasis management, certainly studies evaluating biomarkers and/or patients' characteristics linked to different rates of treatment response, may be useful to better choose and understand the exact role of this relatively new biologic class.

### Small Molecules

SM represent a valuable opportunity for patients with moderate-to-severe psoriasis: they are available in topical or oral formulations and have the advantage to easily reach the stratum corneum, have low prices and be not associated with immunogenicity reaction as compared to antibodies. The advent of numerous novel SM is the direct consequence of the discovery of new pharmacological targets. Anyway, their role in the armamentarium of the psoriasis treatment is yet to be determined: in fact, they can be positioned between conventional systemic treatments and biologicals, be an alternative to biologicals' non responders or used in combination with abovementioned treatments.

### Apremilast

Apremilast, is a phosphodiesterase-4 (PDE-4) inhibitor, approved by the FDA for the treatment of psoriasis and psoriatic arthritis of the adults in 2014. This SM acts by unbalancing the levels of pro- and anti-inflammatory molecules toward the latter, with consequent immunomodulating effects. The drug is administered orally, and it is metabolized by the CYP450 3A4. Side effects include headache, gastrointestinal symptoms (diarrhea, abdominal pain, nausea and vomit), weight loss, depression and nasopharyngitis. Response to apremilast is generally good, even if variable especially in the long term. Hence, studies to assess a possible association between genetic and response to apremilast were performed. In



detail, 4 SNPs (rs1143633, C/T; rs20541, G/A; rs2201841, A/G/T; rs1800629, A/G) of 4 genes (IL-1 $\beta$ , IL-4, IL-23R, and TNF- $\alpha$ ) involved in the immune response have been found.<sup>39</sup> Moreover, the presence of minor alleles was associated with good response to apremilast.<sup>39,112</sup>

## Miscellanea

### Serum Cytokines

Serum cytokines may represent a valuable biomarker in monitoring psoriasis activity and optimizing treatment strategies; in fact, they correlate with tissue or skin cytokines that may be inconvenient to assess given the invasiveness of biopsies.<sup>113</sup> Several studies tried to identify the correlation between serum cytokines and psoriasis, by comparing affected individuals with healthy controls, and to unveil a potential correlation between their levels, disease activity and response to treatments. Anyway, the path is still long towards the identification of reliable biomarkers in daily routine. A meta-analysis by Bai et al found out that TNF- $\alpha$ , IFN- $\gamma$ , sE-selectin, IL-2, IL-6, IL-8, IL-18, IL-22, fibrinogen and C3 were elevated in patients with psoriasis and could be employed as biomarkers for psoriasis occurrence.<sup>113</sup> Also, Khashaba et al reported a positive correlation between YKL-40, a mammalian chitinase 3- like protein associated with inflammatory diseases, and IL-17 levels as well as PASI score, making it a potential prognostic biomarker for psoriasis severity.<sup>114</sup> Serum cytokines may be monitored to evaluate response to treatment on the molecular basis, as complement to clinical assessment. In detail, Olejniczak-Staruch et al aimed at assessing the influence of biologicals on the levels of IL-6 and IL-22 measured before and during treatment with anti-TNF and IL-12/23 and at correlating them with PASI score changes.<sup>115</sup> They reported a statistically significant decrease in IL-6 levels in all study groups ( $p < 0.05$ ) and IL-22 in those treated with adalimumab and infliximab ( $p < 0.05$ ) but not etanercept or ustekinumab ( $p = 0.3642$  and  $p = 0.3362$ , respectively).<sup>115</sup> Moreover, no statistically significant correlation with PASI was observed.<sup>115</sup> Hence, they state that serum IL-6 and IL-22 may be accurate biomarkers for response to biologicals, although not correlated with PASI score.<sup>115</sup> Wang et al found out that levels of serum cytokines of the IL-17 pathway were lower in systemically well-treated patients as compared to untreated patients.<sup>116</sup> Moreover, there was a decrease in levels of IL-17C and PI3 in all treatment groups, i.e., anti-TNF, IL-12/23, IL-17 and IL-23 agents.<sup>116</sup> Also, there was a strong correlation between IL-17A levels and PASI as well as IL-17 C levels, PI3 levels and PASI.<sup>116</sup> Hence, circulating IL-17C and PI3 may be employed as biomarkers of response to treatment.<sup>116</sup> Likewise, Xu et al realized an in-depth serum proteomics platform through which they found out that PI3, along with CCL22 and IL-12B were highly associated with PASI score, while other two proteins, such as TNFRSF8 and CD14 were associated with the VAS scale.<sup>117</sup> Also, they reported that the number of neutrophils correlated positively with the serum levels of four proteins (SERPINE1, PI3, IL4, CX3CL1) and negatively with the serum level of other six proteins (CCL4, EGFR, CD8A, IFNG, IGLC2, MTRF1).<sup>117</sup> According with previous reports, the number of neutrophils correlated with PASI score.<sup>117</sup> Finally, PFN1, a protein responsible for the cytoskeleton structure, was identified as disease biomarker for psoriasis.<sup>117</sup> Elafin, or PI3, is a natural antimicrobial peptide (AMP) that exerts anti-inflammatory properties by halting neutrophil chemotaxis and inactivating neutrophil-derived serine proteases and elastase, responsible for tissue damage.<sup>118</sup> It has been shown that PI3 levels correlate with disease severity, as measured by PASI score, CRP (C-reactive protein) and ESR (erythrocyte sedimentation rate) levels but in a highly specific manner, and familial psoriasis since an increased expression of elafin gene was found in psoriasis-related gene mapping.<sup>118</sup> Hence, it can be used as a biomarker for monitoring psoriasis activity. Divyapriya et al reported an increased levels of Th1/Th17 cytokines (IFN- $\gamma$ , IL-17, IL-12 and IL-23) and decreased levels of Th2/Treg cytokines (IL-4 and TGF- $\beta$ ) in psoriasis patients at baseline as compared to healthy controls.<sup>119</sup> Moreover, an inverted trend in cytokines levels was observed after treatment with systemic MTX. Finally, serum Th1/Th17 cytokines correlated with disease severity.<sup>119</sup>

### MicroRNA (miRNA) and Long Non-Coding RNA (lncRNA)

Micro RNAs and long non-coding RNAs are molecules strongly involved in epigenetic regulation of gene expression. MicroRNA are small noncoding molecules of RNA involved in RNA-silencing and the post-transcriptional regulation of gene expression.<sup>120</sup> By contrast, lncRNAs are non-protein-coding RNAs of 200 nucleotides or more in length, that represent the most numerous group of non-coding RNA.<sup>121</sup> Several miRNAs and lncRNAs have been showed to be

involved in the maintenance and development of psoriasis. Concerning the first, miR-21, miR-31, miR-146a, miR-155, miR-203 and miR-125 are upregulated in psoriatic patients, while miR-197 and miR-520 are downregulated.<sup>120</sup> This concerto of miRNAs facilitates the proliferation and the abnormal differentiation of keratinocytes as well as the dysregulation of the CD4+ T cell subset balance.<sup>120</sup> Moreover, key psoriasis-associated transcription factors such as NF- $\kappa$ B and Signal transducer and activator of transcription 3 (STAT3) are regulated by these miRNAs.<sup>120</sup> El-Komy et al showed a statistically significant higher expression of miR-155 ( $p = 0.001$ ) and miR-210 ( $p = 0.001$ ) in 20 psoriatic patients compared with 20 controls.<sup>122</sup> Moreover, a statistically significant positive correlation was reported between serum miRNA-210 expression and serum levels of IL-17/IL-17A ( $P = 0.010$ ), suggesting a possible relationship between miRNA-210 and IL-17.<sup>122</sup> miRNAs seem to play a key role also in psoriatic arthritis (PsA) as suggested by Lättekivi et al who compared the miRNA in 12 psoriasis patients, 12 PsA patients and 12 healthy control subjects founding 212 different miRNAs in both psoriasis and PsA groups compared with healthy cohort.<sup>123</sup> A possible therapeutic approach using miRNAs was reported by Wu et al who showed that both miR-210 ablation in mice and inhibition of miR-210 by intradermal injection of antagomir-210 blocked the immune imbalance and the development of psoriasis-like inflammation in an imiquimod-induced or IL-23-induced psoriasis-like mouse model.<sup>124</sup> Thus, miRNAs seem to be promising biomarkers of prognosis, diagnosis and treatment response in psoriasis. Certainly, many others miRNAs are involved in psoriasis pathogenesis: in detail, Chen et al identified 246 differently expressed miRNAs (80 down-regulated and 146 up-regulated) among 14 psoriatic patients and 14 healthy controls.<sup>125</sup> As regards lncRNAs, Abdallah et al evaluated the role of lncRNA [Psoriasis-susceptibility-Related RNA Gene Induced by Stress (PRINS)] - miRNA (miRNA124-3p, miRNA203a-5p, miRNA129-5p, miRNA146a-5p, miRNA9-5p) - mRNA axis in 120 psoriatic patients compared with 120 healthy volunteers.<sup>126</sup> The lncRNAs PRINS (G1P3 and NPM) were reduced in psoriatic patients while all the investigated miRNAs resulted higher in the psoriasis cohort compared with the healthy group.<sup>126</sup> The authors showed an inverse correlation between lncRNA PRINS and miRNAs.<sup>126</sup> Also, G1P3 and NPM were significantly correlated with body mass index.<sup>126</sup> The authors suggested the PRINS-miRNA-mRNA as a possible target of personalized medicine in psoriasis management.<sup>126</sup> Moreover, Qiao et al showed that the upregulation of lncRNA-MSX2P1 was able to promote the growth of IL-22-stimulated keratinocytes through the inhibition of miR-6731-5p and the activation of S100A7.<sup>127</sup> Hence, the positive correlation between lncRNA-MSX2P1 and S100A7 expression as well as their association with miR-6731-5p suggested that the complex of MSX2P1-miR-6731-5p/S100A7 may be an innovative therapeutic target for psoriasis treatment.<sup>127</sup> Overall, further studies are needed to elucidate the role of epigenetic regulators such as miRNAs and lncRNAs in psoriasis.<sup>121</sup>

### Inflammasome

Inflammasomes are high-molecular-weight protein complexes that seem to contribute to psoriasis by the cleavage into active forms of two proinflammatory cytokines, pro-interleukin-1 $\beta$  and pro-interleukin-18. Various inflammasomes and inflammasome-related genes have been suggested as main actors in psoriasis pathogenesis. In particular, Nucleotide-binding oligomerization domain, Leucine rich Repeat and Pyrin domain containing 1 (NLRP1), NLRP3, and absent in melanoma 2 (AIM2) seem to be involved in pathogenesis of psoriasis.<sup>128</sup>

## Discussion

Personalized medicine consists in tailoring a medical treatment according to specific characteristics of an individual. The aim is to maximize outcomes, reducing the risks of side effects. To do that, it is important on the one hand, to investigate the pathogenetic mechanisms underlying a defined disease, and on the other hand, to test which is the driven force of the disease in a certain patient. In the case of psoriasis, to date several advances have been made in terms of pathogenesis, anyway, the differential distribution of driven pathways is known to differ per each phenotype and also within the same phenotype. Hence, the goal would be to identify biomarkers for drug response to be used in clinical practice through which stratify patients and prescribe the most appropriate genetic-based treatment. Of course, pharmacogenomics is the mainstay in treatment decision process but should be integrated in a holistic approach to the psoriatic patients since comorbidities as well as patients' preference should be taken into consideration when prescribing a drug. To date, several studies tried to identify robust biomarkers predictive of response to treatment to be adopted in daily routine but overall, no consensus has been reached and

further analyses are warranted. More evidence exists toward biologicals, as justified by the huge health care costs as compared to phototherapy or conventional systemic drugs. Among them, most of the studies focused on anti-TNF and IL12/23, with still few on IL17 (mainly secukinumab). The most discussed gene is the HLA-C\*02:06 status that has been shown to be associated with psoriasis, and also differential response to biologicals. Although its positivity is associated with great response to MTX, debatable results were retrieved concerning both anti-TNF and IL12/23. Indeed, while some authors found a better and faster response in the presence of the allele, others did not confirm those outcomes. By contrast, response to anti-IL17, in particular secukinumab, do not appear to be influenced by the HLA: Cw6 status. For conventional systemic agents, key genes involved in pharmacokinetics were mainly studied, as absorption, metabolization and excretion highly influence their half-life, bioavailability, efficacy and toxicity. Also, polymorphisms in cytokines genes and their receptor were under assessment. Anyway, the scarcity and the controversy of the results together with the great heterogeneity of the pharmacogenetics or genomic studies, targets, and sample size of enrolled populations, led to the impossibility to identify a robust biomarker predictive of response to a specific treatment. Instead, a panel of biomarkers could be more useful and reliable in guiding the treatment choice. Certainly, the controversial results may be partly justified also by the fact that genomics is only one of the “-omic” domains, that indeed encompass proteomics and metabolomics, which respectively analyze on a large-scale the proteins and metabolites of a cell or organism on a definite condition. Moreover, epigenetic modifications of key genes involved in psoriasis pathogenesis may have a strong role in differential phenotypical expression as well as response to treatment. These fields should work in parallel to provide a comprehensive view of psoriasis endotypes, that then can be combined with related phenotypes and fill in the existing gap. Hence, the future research should focus in creating an algorithm that combines and integrates data from the endotype and phenotype as well as other supporting information on patients’ comorbidities, preferences and lifestyle as well as health system opportunities. In this setting, the artificial intelligence (AI) and machine-learning approach would support clinicians’ daily practice, providing single patient’s identikit and guiding the therapeutic choice in an algorithm-based model. To conclude, personalized medicine in psoriasis is currently still under definition: small but growing steps ahead are being made every day and more efforts should be put worldwide given the common and shared benefits that can be derived. Also, to conceptualize and build more effective and reliable algorithms, data should be collected in a systematic and standardized manner and shared in international database with the same objective.

## Conclusion

Personalized treatment in psoriasis would provide excellent outcome minimizing the risk of side effects. To date, although several candidates were proposed and assessed, the scarcity and heterogeneity of the results do not allow the identification of the gold-standard biomarker per each treatment. Anyway, the creation of a more comprehensive panel would be more reliable for the treatment decision process. Finally, the integration of “-omics”-derived data with patients’ characteristics and health care system availability, would futuristically draw psoriasis patient’s identikit and guide the therapeutic choice in a machine-learning approach with the support of AI.

## Disclosure

The authors report no conflicts of interest in this work.

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