Therapeutic Perspective

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CLINICAL INVESTIGATION

Use of pharmacogenomics in psoriasis

Clin. Invest. (2011) 1(3), 399–411

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Patients with moderate-to-severe psoriasis frequently require treatment with systemic or biologic therapies, but considerable interpatient variability is observed in both clinical responsiveness and toxicity relating to these agents. Thus, identifying patients with a greater risk of treatment toxicity or nonresponse prior to treatment initiation would allow targeting of therapies more precisely and safely to individual patients and minimize unnecessary expenditure. The discovery of predictive markers of treatment response would be a useful tool in the development of individually tailored treatment. The role of pharmacogenomics is becoming increasingly important as healthcare moves towards the ultimate goal of personalized medicine. This article reviews the pharmacogenomics of psoriasis treatments to date and explores the potential of this growing research field to provide safer, more effective psoriasis treatment. In particular, we describe pharmacogenomic studies of methotrexate, cyclosporine, TNF-α inhibitors, efalizumab, alefacept and narrowband-UVB phototherapy. As psoriasis is a complex polygenic disorder with environmental and clinical influences at play, the combination of both molecular and clinical profiling is necessary to achieve optimal personalized management. To this end, we propose the development of models to predict treatment response by combining pharmacogenomic approaches with comprehensive clinical characterization.

Keywords: adalimumab • alefacept • cyclosporine • efalizumab • etanercept • methotrexate • pharmacogenetics • pharmacogenomics • phototherapy • psoriasis • vitamin D-receptor polymorpism

Psoriasis is a chronic inflammatory polygenic skin disease that affects 1.5–3% of the population and typically follows a relapsing and remitting course [1]. The disease is associated with significant psychosocial disability and causes a reduction in health-related quality-of-life (HRQoL) comparable with other chronic diseases such as cancer, diabetes and depression [2,3]. Numerous studies have shown an increased incidence of cardiovascular events, obesity and metabolic syndrome in patients with moderate-to-severe psoriasis, suggesting that control of inflammation may be important for the reduction of cardiovascular morbidity [4–6]. Systemic and biologic treatments used for the treatment of moderate-to-severe psoriasis show significant variability in efficacy, and are associated with varying degrees of toxicity and cost. As a result, there is a great need for biomarkers to predict treatment outcomes and individualize care for psoriasis patients, particularly for drugs with significant side effects or a low rate of response. This would allow the identification of patients less likely to respond to particular treatments and those at increased risk of adverse drug reactions, reducing unnecessary exposure to treatment toxicity and resulting in significant health-related savings. The characterization of psoriasis patients according to common molecular mechanisms rather than by clinical phenotype may also allow the targeting of more selective therapeutic agents to genetically distinct groups of patients.

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While the pathogenesis of psoriasis is not fully understood, a complex interplay between genetic and environmental influences with upregulation of both the innate and specific immune responses appears to be paramount [1]. A genetic predisposition is supported by twin studies, family studies, a strong correlation with human leukocyte antigens (HLAs) and, more recently, data emerging from genome-wide association scans [7–13]. Psoriasis patients show significant genetic diversity, however, and although the *HLA-Cw*6* allele confers the most significant and consistently demonstrated risk for the development of psoriasis ($p < 10^{-100}$), in a recent genome-wide association scan, over half of psoriasis patients do not carry this gene [7–13]. There has been little research into the impact of this genetic heterogeneity on treatment response. There is also significant variation in the clinical presentation of psoriasis [14]. Chronic plaque psoriasis is generally divided into what are considered to be two genetically distinct types of disease, type 1 and type 2 psoriasis. The former have an earlier disease onset (before 40 years of age), more severe disease, a higher frequency of *HLA-Cw*6* positivity, and are more likely to have a positive family history. Those with type 2 disease develop psoriasis after the age of 40 years and are less likely to carry the *HLA-Cw*6* allele or to have a positive family history. Psoriasis lesions also vary in size, thickness and distribution and up to 30% of patients may develop an associated arthropathy [15]. Palmoplantar pustulosis is a less common, distinct clinical variant characterized by sterile pustules of the palms and soles [16]. Genetic analyses distinguish patients with palmoplantar pustulosis from those with chronic plaque psoriasis [17]. In addition, the drugs currently used to treat chronic plaque psoriasis frequently show less efficacy in this variant, supporting the suggestion that palmoplantar pustulosis is a separate disease entity with a distinct immunopathogenic basis [14].

Identification of pharmacogenomic markers

The International Conference on Harmonisation (ICH) E15 definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories defines pharmacogenomics as the study of variations of DNA and RNA characteristics as related to drug response. Pharmacogenetics is the study of the relationship between individual gene variation and drug response [18]. A polymorphism of a gene occurs when the variant allele occurs in 1% of the normal population or more [19]. The most frequent type of polymorphism is a single nucleotide polymorphism (SNP), which results from a one-nucleotide alteration in the sequence of the gene. Variation in genes encoding drug-metabolizing enzymes, transporters and drug targets may account for up to 95% of interpatient variation in treatment response, although it is generally to the order of 10–35% [20,21]. The most widely used example of pharmacogenetic testing in routine dermatology practice at present is the determination of thiopurine methyltransferase (TPMT) status prior to azathioprine administration [20,22]. Three loss-of-function allelic variants of this enzyme can significantly impair enzyme activity resulting in potentially critical bone marrow suppression after the initiation of azathioprine treatment. The use of pharmacogenetic markers and transcriptional profiling is now also being used to direct immunotherapy and chemotherapy in melanoma treatment [23]. To date, the most commonly used pharmacogenetic approach to assess variability in the efficacy and toxicity of psoriasis treatments has used a candidate gene approach, with evaluation of SNPs present in drug-metabolizing enzymes, drug transporters and psoriasis susceptibility genes.

Pharmacogenomics uses a whole-genome application of pharmacogenetics to examine the influence of genetic variation on drug response by correlating gene expression with the efficacy or toxicity of the drug. Response to psoriasis treatment is not constant over time, with patients frequently losing response to treatment over time or failing to respond to a second course of a treatment that was previously successful. This may be due to tachyphylaxis (a decrease in response to the drug with increasing exposure), development of antibodies to the drug or unknown antigenic factors. Using pharmacogenetic markers such as SNPs to predict treatment response over time does not allow for this intra-individual variability in response to treatments. The analysis of transcriptional profiles of the skin or blood using RNA microarray analysis or RNA sequencing provides a means to investigate the molecular pathways of immune-mediated conditions on a genome-wide scale and has the potential to play a significant role in the discovery of functionally relevant biomarkers of response to psoriasis treatment [24,25]. Comparison of the differential genetic expression between responders and nonresponders to individual drugs may identify baseline immunogenetic signatures that predict treatment response. Assessment of changes in genetic expression during treatment may give further insight into molecular mechanisms underlying the variable efficacy of these drugs and identify the immunogenetic pathways that lead to disease clearance. This approach may also facilitate the identification of more selective therapeutic targets in the future.

Changes in the transcriptome, including alterations in levels of noncoding RNAs (including miRNAs) may lead to altered epigenetic modifications in psoriasis [26]. These include CpG methylation status or

histone modifications. Hence, one might also expect that these would be correlated with the variability in response to psoriasis treatments over time. Studies of this type in psoriasis, however, are currently lacking. The study of small-molecule metabolite profiles, or 'metabolomics', allows the analysis and comparison of biochemical profiles in patients with varying response to treatment [27,28]. This may allow prediction of response to treatment at an early stage by showing specific profiles in patients who are responding differently to the drug in question. By using pharmacogenomic approaches such as pharmacogenetics, transcriptional profiling and epigenetics in combination with complementary techniques such as proteomics, flow cytometry analysis and metabolomics, we have a growing armentarium to facilitate global analysis of treatment response and to build predictive models using biostatistical methods.

■ Methotrexate

Methotrexate has been the first-line systemic agent for psoriasis for over 50 years [29]; however, its mechanism of action remains to be fully elucidated. Its anti-inflammatory and immunodulatory effects are thought to be mediated by inhibition of the purine pathway. The use of methotrexate as a treatment for psoriasis is limited by unpredictable response and toxicity. A 75% reduction in the Psoriasis Area and Severity Index (PASI-75) from baseline, is conventionally used to define a significant response in clinical trials of psoriasis treatment [30]. Approximately half the patients treated with methotrexate do not achieve a PASI-75 response by week 16 [31,32], while up to 30% experience adverse effects that necessitate discontinuation of therapy, including gastrointestinal side effects, bone marrow suppression, hepatotoxicity, pneumonitis, neuropathy and alopecia [31–33].

To date, the largest pharmacogenetic studies in psoriasis have evaluated the effect of SNPs on treatment response to methotrexate [34–36]. A cohort of 374 psoriasis patients currently or previously treated with methotrexate were recruited retrospectively, and classified as responders or nonresponders based on available data. The presence or absence of treatment toxicity was also recorded. The study used a haplotype-tagging method to assess variation in ten genes relevant to methotrexate metabolism. SNPs in two methotrexate efflux transporter genes, ATP-binding cassette, subfamily C, member 1 (*ABCC1*) and ATP-binding cassette, subfamily G, member 2 (*ABCG2*), were associated with both efficacy and toxicity of methotrexate. Two SNPs, rs35592 (intron 9, *ABCC1*) and rs6532049 (intron 1, *ABCG2*), were significantly associated with efficacy (χ^2 test for trend: p = 0.008 and 0.0003, respectively), giving odds ratios of 2.2 (95% CI: 1.2, 4.1; p = 0.004) and 2.3 (95% CI: 1.3, 4.2; p = 0.002) for responders to methotrexate, respectively. Only rs6532049 remained significant (empiric p-value 2 [EMP2] = 0.04) after correction for multiple markers that were assessed. Five SNPs in *ABCC1* were strongly associated with treatment toxicity. Interestingly, these five SNPs had a significant degree of linkage disequilibrium, suggesting they may reside on a haplotype with a common marker driving this association. No SNPs in the other eight genes that were studied had associations that remained significant following correction for the markers that were assessed.

A smaller study (n = 203), conducted by Campalani *et al.* that incorporated some of patients from the previously described study, found an association between an SNP in the reduced folate carrier, a transporter involved in intracellular folate transportation, and methotrexate-induced toxicity [36]. Polymorphisms of the promoter enhancer region of the thymidylate synthase (*TYMS*) gene were also examined, including two or three 28 base pair (bp) tandem repeat sequences (2R and 3R, respectively) and a G>C SNP in the second repeat of the 3R allele [37]. The 3R allele was significantly (p = 0.029) more frequent in patients who did not respond to methotrexate (64%) than in responders (50%), but frequency of the 3R/3R variant homozygous genotype did not vary significantly between these groups.

Although these pharmacogenetic studies of methotrexate treatment in psoriasis suggest that SNPs may play a role in the variability its efficacy and toxicity, there are significant limitations in studies to date. First, the data were collected in a retrospective manner, which did not allow reproducible or objective collection of phenotypic information, and second, although these were among some of the largest pharmacogenetic studies performed to date, the power of the studies to detect individual adverse events was limited.

No studies to date have used gene expression profiling to assess variability in methotrexate efficacy or toxicity in psoriasis. Transcriptional profiling in human chondrocytes and colon cancer cells has been used to assess the response of rheumatoid arthritis and colon cancer to methotrexate, respectively [38,39]. Pretreatment cytokine profiles of PBMCs have been shown to characterize a subset of rheumatoid arthritis patients who are more likely to respond to methotrexate treatment, but this has not been studied in psoriasis patients [40].

■ Cyclosporine

Cyclosporine is a calcineurin antagonist that has been successfully utilized for the treatment of moderate-to-severe psoriasis and other dermatoses since the 1980s [41,42]. At a dose of 3 mg/kg/day, cyclosporine

rapidly produces a PASI-75 response in up to 70% of patients, with increased response rates seen at higher doses [42]. Concern regarding its adverse-effect profile, however, has limited its use in dermatology. In particular, cyclosporine can cause chronic nephrotoxicity, hypertension, hyperlipidemia and neurologic adverse effects [43]. Moreover, cyclosporine has a narrow therapeutic index, with significant variability in its pharmacokinetic profile and poor correlation between its serum concentration and efficacy in psoriasis [43].

Pharmacogenetic studies of cyclosporine in psoriasis patients are lacking. Transplantation research has provided much of our knowledge regarding the effect of genetic polymorphisms on variation in the pharmacokinetics of cyclosporine. The oral bioavailability and systemic clearance of cyclosporine are controlled by the cytochrome P450 (CYP) isoenzymes CYP3A4 and CYP3A5, and by the efflux P-glycoprotein (P-gp) pump, a transmembrane transporter expressed in the gastrointestinal tract and liver that limits intestinal absorption and facilitates biliary excretion of lipophilic drugs and is encoded by the gene *ABCB1* (ATP-binding cassette B1; also known as multidrug resistance-1 [*MDR1*]) [44–60]. Many SNPs in the *CYP3A4*, *CYP3A5* and *ABCB1* genes have been identified and are thought, in part, to account for the variability in the pharmacokinetics of cyclosporine. There is significant ethnic variation in the prevalence of these polymorphisms [44,45].

When expressed, CYP3A5 may represent up to 50% of the total CYP3A content [46]. In one study, healthy volunteers carrying the *CYP3A5* 6986A>G wild-type allele (*CYP3A5**3C) showed a lower area under the concentration-time curve (AUC) and higher clearance of cyclosporine compared with those homozygous for the variant allele [47]. Aside from one isolated study that showed lower dose-corrected cyclosporine levels in 6986A carriers [48], other studies have failed to demonstrate any relationship between cyclosporine pharmacokinetics and *CYP3A5* polymorphisms [49–51]. In another study of the pharmacokinetics of cyclosporine in healthy subjects, patients who were homozygous for the *CYP3A4**18B allele (characterized by a G>A substitution at position 82266) showed significantly higher oral clearance and a lower AUC of cyclosporine compared with those who were homozygous for the wild-type *CYP3A4* allele [52]. In a study of 103 renal transplant patients, lower serum cyclosporine concentrations were also seen in patients who were homozygous for the *CYP3A4**18B allele [53].

Findings on the influence of SNPs of *ABCB1* on the pharmacokinetics of cyclosporine have also been conflicting. In a study of 106 renal transplant recipients, there was a small but significant decrease in the dose-corrected AUC in carriers of the *ABCB1* 1236C>T wild-type allele [51]. Patients who were homozygous for the variant T allele of the *ABCB1* 3435C>T polymorphism had higher dose-corrected cyclosporine levels and required only 50% of the dose required by wild-type patients in a study of liver transplant recipients [54], but again this was refuted in two other studies in renal transplant patients [55,56]. Fanta *et al.* reported 1.5-fold increased oral bioavailability of cyclosporine in pediatric renal transplant patients over the age of 8 years with the variant 1236T and 2677T alleles, suggesting that the effect of *ABCB1* polymorphisms on cyclosporine pharmacokinetics may be age-related [57].

Conflicting reports also exist regarding the impact of SNPs on cyclosporine-induced nephrotoxicty. In a study of cyclosporine-treated renal transplant patients, a lack of cyclosporine-induced upregulation of renal P-gp expression was associated with nephrotoxicity, suggesting that the *ABCB1* genotype may be a risk factor [58]. Donor kidneys bearing the homozygous variant *ABCB1* 3435 TT genotype were associated with a higher incidence of nephrotoxicity in transplant recipients [59]. Surprisingly, however, in a study of liver transplant patients, homozygosity for the ABCB1 2677T (S893) allele, which is strongly linked to the 3455TT genotype, was associated with reduced risk of chronic renal dysfunction post-transplantation [60].

A study examining genetic susceptibility to cyclosporine-induced gingival overgrowth in 52 renal transplant patients suggested that the presence of the *HLA-DR1* allele had a protective role against this adverse effect [61]. Of the 26 patients with gingival hypertrophy, one was positive for the *HLA-DR1* allele, compared with nine of the 26 without gingival hypertrophy. Although this was statistically significant ($p < 0.001$), the small numbers in each group and lack of validation in further studies makes routine use of this test in clinical practice for psoriasis patients unlikely.

There have been two studies of the effect of cyclosporine treatment on gene expression in moderate-to-severe psoriasis using RNA microarray analysis [24,25]. The first study analyzed the effect of cyclosporine treatment on genetic expression in the blood and skin of 11 responding patients using RNA microarray analysis and real-time PCR. Microarray analysis was performed in the blood of four responding patients at baseline and on day 14 of treatment, and in the lesional and nonlesional skin of nine and five patients, respectively, at baseline and at day 14 in eight patients. Cyclosporine downregulated the expression of 220 genes by at least 1.5-fold in skin, the vast majority of which were associated with proinflammatory cells, keratinocytes and fibroblasts. By contrast, there were no changes in genetic expression in peripheral blood at day 14. When expression of genes in the

skin was correlated with the overall clinical score (using epidermal thickness, PASI and K16 expression), IL-17 expression correlated best with activity at day 14, while inducible nitric oxide synthase (iNOS) correlated best with long-term response.

The second study examined the alteration of expression levels of genes that were upregulated in the skin of psoriasis patients following treatment with cyclosporine [25]. Microarray profiling was used to analyze genetic expression in lesional and nonlesional skin from eight patients compared with normal skin and showed 159 differentially expressed genes. Evaluation of the effect of cyclosporine treatment on the expression of these 159 genes in the skin of three psoriasis patients (two responding, one nonresponding), showed upregulation of genes encoding S100A12, ID4, MTX1 and HBP17 (FGFBP1) within 1 week of treatment, preceding clinical improvement in responders only.

Acitretin

Acitretin, a vitamin A derivative, has been used to treat psoriasis since the early 1980s. The mechanism of action of oral retinoids in psoriasis is not fully understood, but they are known to decrease epidermal proliferation and have anti-inflammatory properties. As a monotherapy, acitretin is less effective than other systemic agents with approximately 25% of patients achieving a PASI-75 response [62]. Higher doses give better responses, but are limited by toxicity factors, especially mucocutaneous adverse effects.

Polymorphisms of VEGF are associated with an increased susceptibility to psoriasis [63–65]. The *VEGF* gene is expressed on chromosome 6, close to *PSORS1*. The *VEGF*-460C>T polymorphism has been shown to play a role in predicting response or nonresponse of psoriasis to acitretin [66]. This polymorphism is associated with early-onset psoriasis and is situated close to the functional activator site through which retinoids block VEGF production.

Another study evaluated polymorphisms of the apolipoprotein E gene (*APOE*) as predictors of response to acitretin [67]. Although the frequency of the *APOE* e4 allele (+3937C/+4075C) was higher in patients with chronic plaque and guttate psoriasis than in controls, there was no significant difference in the frequency of alleles in acitretin responders and nonresponders.

TNF-α inhibitors

Anti-TNF-α therapies have revolutionized the treatment of psoriasis and psoriatic arthritis. However, TNF inhibitors are expensive and are associated with potentially serious adverse effects. While they are very effective, the response to treatment is variable, and 20 to 50% of patients achieve an inadequate response or lose response over time [68–71]. Likewise, they are expensive and associated with side effects, occasionally serious. Infliximab and adalimumab are monoclonal antibodies to TNF-α, while etanercept is a recombinant human TNF-α receptor fusion protein [72]. As there is little metabolism of biologic agents, drug pharmacodynamics are likely to play a greater role than pharmacokinetics in the variation in treatment response observed with these agents. Pharmacogenetic studies of anti-TNF treatments, however, are lacking.

Functional polymorphisms in the promoter region of the TNF gene at G>A238, G>A308 and -857 influence the binding of transcription factors and TNF-α production in psoriasis [73]. Many studies have examined polymorphisms associated with this gene as predictors of response to anti-TNF treatments for rheumatoid arthritis and have produced conflicting results [74–82]. One preliminary study has examined polymorphisms in the TNF promoter region in 220 psoriasis patients treated with etanercept and 29 patients treated with adalimumab [83]. The data were analyzed for an allelic association between drug response and genotypes for four SNPs in the promoter region of TNF. There was a moderate association between adalimumab responders and the -1031T/C polymorphism (OR = 4.43; p = 0.04). This study may be of limited benefit, however, as the assessment of response was subjectively determined by the patients using a visual analog scale.

Pharmacogenetic studies of the *HLA-Cw**6 allele, the most significant psoriasis susceptibility gene, have not shown an association with treatment response to TNF-α inhibitors. In a study of patients treated with etanercept (n = 78) or adalimumab (n = 50), the presence of the *HLA-Cw**0602 allele did not predict response to etanercept, although there was a nonsignificant trend suggesting that *HLA-C**0602-positive patients were more likely to respond to adalimumab (χ^2 = 2.77; df = 1; p = 0.09) [84]. In a study of 82 patients treated with etanercept (n = 48) or efalizumab (n = 34), the presence of the *HLA-Cw**6 allele was linked to treatment response to efalizumab but not etanercept [85].

A small study comparing the genomic expression profiles in the skin of 15 patients responding (n = 11) or not responding (n = 4) to etanercept showed suppression of IL-17 signaling genes rather than TNF-related genes with effective treatment [86]. Gene-expression profiling in lesional and nonlesional skin has been used to determine the changes in gene expression following 3 months of etanercept treatment in patients responding to treatment [87]. Interestingly, the expression of a subset of genes did not return to nonlesional levels despite apparent clearance of disease. A 'residual disease genomic profile' of 248 probe sets was identified that

failed to improve by more than 75%. This 'molecular scar' of psoriasis may explain the tendency of psoriasis to recur and provide new therapeutic targets for the treatment of psoriasis; however, no psoriasis study has as of yet used transcriptional profiling to predict response to anti-TNF treatments prior to initiation of therapy.

Genetic profiling of PBMCs before treatment has been used to predict response or nonresponse to infliximab in the treatment of rheumatoid arthritis [88]. The combined expression of 20 trancripts classified 16 out of 20 patients with a sensitivity of 90% and specificity of 70%. Another study in rheumatoid arthritis showed differential expression of 42 genes in PBMCs in responders and nonresponders to etanercept after 3 days of treatment [89]. Expression change of seven pairs and ten triplets within the 42 genes had a prediction accuracy of 89% at day 3. Although these gene sets could not predict treatment response before initiation of therapy, they predicted treatment response at a very early stage.

At present, as with rheumatoid arthritis, there are no good predictors of treatment response to TNF inhibitors in psoriasis, a class of biologic agents important for the treatment of severe psoriasis. TNF-induced protein (TNFAIP)3 and TNFAIP3-interacting protein (TNIP)1 are psoriasis susceptibility loci whose gene products work downstream of TNF [11]. These polymorphisms should be investigated as potential pharmacogenetic markers of treatment response to TNF inhibitors.

■ Alefacept

Alefacept, a fully human fusion protein consisting of the extracellular portion of lymphocyte-function-associated antigen type 3 and the Fc domain of IgG1, was the first biologic therapy approved for use in psoriasis in 2003 [90]. It binds to CD2 on T-lymphocytes and natural killer cells to inhibit secondary signaling and induce T-cell apoptosis. Although a PASI-75 response is achieved in less than 25% of patients by week 14, alefacept produces a significant and prolonged remission in a small subset of patients for a median duration of 7–8 months following a single 12-week course, a feature seldom seen with other biologic or systemic agents [90,91], making it an ideal candidate for pharmacogenomic studies.

In a study by Haider *et al.*, responders and nonresponders to alefacept had distinct signatures of gene expression [92]. Alefacept downregulated several genes related to T-cell or natural killer cell signaling at 6 h post-treatment in responders, including *CD3D*, *CD2*, *CD8A*, IL-2-inducible T-cell kinase (*ITK*), and KLR-subfamily C, member 3 (*KLRC3*), while nonresponders had increased expression of Toll-like receptor-5 (*TLR5*) and spleen tyrosine kinase (*SYK*). The gene expression of forkhead box P3 (*FOXP3*), a known marker of regulatory T cells, was increased in peripheral blood mononuclear cells (PBMCs) of responders only. At baseline, prior to initiation of treatment, 199 genes were differentially expressed in the pretreatment blood of responders compared with nonresponders. Genes that were overexpressed in nonresponders included T-cell activation genes such as *CD69*, integrin-α6 (*ITGA6*) and *CD3D*, while the expression of *CD2*, *CD8A*, *CD33*, *TLR5*, and myeloid differentiation primary response gene 88 (*MYD88*) was higher in responders. Alefacept also decreased circulating $CD3^+$, $CD4^+$ and $CD8^+$ T cells more significantly in responders than in nonresponders. These combined parameters would allow categorization of responders and nonresponders before treatment or at an early timepoint after commencing treatment.

A study of 20 patients using quantitative PCR to examine genetic markers of treatment response to alefacept showed a 2.4-fold upregulation of *TOAG1* in the PBMCs of responding patients by week 2 and a 5.5-fold upregulation of the receptor for hyaluronic acid mediated migration (*RHAMM*; also known as *HMMR*) in the PBMCs of nonresponding patients by week 3, before clinical improvement (mean week 9) was seen [93]. At week 2, a cut-off value of 115% *TOAG1* expression compared with 100% before therapy had high sensitivity (0.889) and specificity for predicting response, while similarly, at week 3 a cut-off value of 142% *RHAMM* expression compared with 100% before therapy also predicted nonresponse with high sensitivity (0.7) and specificity (1.0). A ratio of *TOAG1*/*RHAMM* gave enhanced discrimination between responders and nonresponders at any timepoint during treatment, with a cut-off of 1.36 predicting response with a sensitivity of 0.889 and a specificity of 0.909.

A further study used a genomic classifier to predict histological response to alefacept prior to treatment initiation [94]. Microarray data from PBMCs of 16 patients were analyzed using the 'nearest shrunken centroid' method of discriminant analysis to produce a disease response classifier of 23 genes that accurately predicted response to alefacept with a 12.3% error rate (S-F). Although small, this is the first study in psoriasis to use a treatment response classifier based on gene expression of PBMCS collected prior to treatment initiation and serves as a paradigm for future larger studies.

■ Efalizumab

Efalizumab, an anti-CD11a monoclonal antibody, has now been withdrawn from the market following four reported cases of fatal progressive multifocal leukoencephalopathy (PML) [95]. This drug achieved a marked and sustained improvement in approximately

25–30% of psoriasis patients, particularly in those with palmoplantar disease [96]. As with alafecept, it would have been very valuable to identify this patient subgroup using pharmacogenomic markers. As described previously, the presence of the *HLA-Cw**6 allele was associated with response to efalizumab [85]. Moreover, those negative for the allele were more likely to experience a rebound flare after discontinuation, suggesting that this single pharmacogenetic marker could predict both treatment response and treatment toxicity. Another smaller study also showed an association between the presence of the *HLA-Cw**6 allele and response to efalizumab [97,98]. In a larger study to identify genetic markers of treatment response to efalizumab, however, whole-genome scanning of a 542-patient subset from a multicenter, open-label, Phase IIIb/IV study failed to identify *HLA-Cw**0602 as being statistically associated with treatment response to efalizumab [99]. At present, studies are assessing gene-expression profiles of previously stored PBMCs of patients treated with efalizumab to identify predictive signatures of treatment response and of paradoxical disease flaring. The characterization of dysregulated immunogenetic pathways central to the development of PML in affected individuals may also allow identification of markers that predict susceptibility to this fatal infection with treatments such as efalizumab, rituximab and natalizumab (Tysabri).

Anti-IL-12/-23 antibodies

Antibodies to the common p40 subunit of IL-12 and IL-23 have shown significant efficacy in the treatment of chronic plaque psoriasis with maintenance of response in the vast majority of patients [100,101]. Genome-wide association scans have shown genetic polymorphisms of the IL-23 receptor (*IL-23R*), *IL-23A* and *IL-12B* to be significantly associated with psoriasis [11,102–105]. There is overexpression of IL-12 and IL-23 in lesional psoriatic skin [106–108]. Patients with the IL-12RB-associated risk haplotype show increased IL-23 and decreased IL-12 expression and secretion, providing a biologically plausible mechanism for the increased risk of psoriasis observed in these patients [109]. These polymorphisms may also influence response to anti-IL-12p40 treatments, but this has yet to be investigated.

Phototherapy

Narrowband UVB (NB-UVB) is very effective for the treatment of psoriasis, clearing up to 80% of patients using a three-times weekly regimen [110]. Attendance for phototherapy three times a week, however, is a significant time commitment in busy modern day living and leads to work-related difficulties. The identification of predictors of response to NB-UVB would allow better targeting of therapy to those psoriasis patients who would benefit most. There is considerable variability in the number of exposures of NB-UVB required to clear psoriasis and in the duration of remission. Studies have shown that NB-UVB affects vitamin D status while clearing psoriasis [111,112], which could partly explain its beneficial effect. Vitamin D3 exerts the majority of its effects by binding to the vitamin D receptor (VDR). In a prospective study of 119 patients with chronic plaque psoriasis treated with NB-UVB, the influence of genetic polymorphisms of the VDR (Fok1, Apa1, Bsm1, Taq1 and rs4516035) and clinical variables on the clearance rate and remission duration were assessed [113]. The Taq 1 VDR polymorphism (rs731236) significantly predicted remission duration ($p = 0.038$). This polymorphism results in a silent T to C transition in exon 9 at the 3′ region of the VDR gene, leading to decreased VDR activity [114]. The negative influence of carriage of the C allele on remission duration is highlighted by shorter remission duration in those homozygous for the C allele compared with those homozygous for the T allele ($p = 0.013$) or heterozygous for the C allele ($p = 0.026$). Patients homozygous for the T allele were only 48% as likely as those homozygous for the C allele to relapse. The only clinical factor influencing remission duration was the number of exposures ($p = 0.0009$) with a decreased remission duration in those who required a greater number of exposures to clear. This was the first prospective study to investigate both clinical and genetic parameters as predictors of response to psoriasis treatment in tandem and serves as a paradigm for future pharmacogenomic studies in psoriasis.

Topical treatments

Wonder why use analogs, rather than vitamin D itself?

■ Vitamin D analogs

Topical vitamin D analogs are known to improve psoriasis. However, the response is not dramatic and a significant proportion of patients show minimal improvement. This differential responsiveness was evaluated by Chen *et al.* who showed that clinical response correlated with induction of vitamin D receptor (VDR) messenger RNA (mRNA) expression in psoriatic plaques, with no increase in the receptor mRNA level in nonresponders [115]. This suggests that response of psoriasis to treatment with topical vitamin D_3 is determined by the ability to upregulate transcription. Polymorphisms of the *VDR* gene may influence this transcription. Studies of the association of V*DR* gene polymorphisms and response to topical vitamin D analogs, however, have shown conflicting results [114,116–120]. In a study by Halsall *et al.* (114 patient)s with the A, F and T alleles of the A-1012G, Fok1 and Taq1 VDR polymorphisms, respectively, were shown to have a positive response to topical calcipotriol. In a study of Turkish familial psoriasis, patients homozygous for the Taq1 T allele had a

higher rate of nonresponsiveness to calcipotriol treatment [116]. In a Japanese study, the frequency of the *Fok1* F allele was lower in patients who did not respond to calcipotriol [117]. There was no association between *VDR* genotype and response to calcipotriol in three other studies, most of which had small numbers of patients [118–120]. As response to topical vitamin D_3 analogs is reasonably quick and these drugs are relatively inexpensive and nontoxic in comparison with systemic medications, the evaluation of pharmacogenetic predictors of response in individual patients is neither practical nor necessary in clinical practice. Identification of genetic markers that account for variability in treatment response may, however, instruct us further as to the molecular mechanism of action of the numerous vitamin D analogs available for the treatment of psoriasis.

Coal tar preparations

Coal tar has been used for over 100 years in the topical treatment of psoriasis. Glutathione *S*-transferase is involved in the detoxification of carcinogenic derivatives of coal tar and is encoded by the glutathione *S*-transferase-Mu (*GSTM*) gene. Approximately half of Europeans carry the *GSTM1*-null allele, which results in low or absent activity of this enzyme. Those carrying the *GSTM1*-null allele showed a twofold increase in urinary 1-hydroxypyrene (a biomarker of polyaromatic hydrocarbon exposure) compared with those who had normal enzymatic activity [121]. Although there are no convincing data on an association between topical tar treatment and carcinogenicity in humans, there is a theoretical risk of higher mutagen exposure in those with the null allele.

Conclusion & future perspective

The science of individualizing treatment using molecular profiling and clinical phenotyping is gaining rapid momentum. Psoriasis results from a complex interplay between both genetic and environmental factors, and although clinical phenotype is likely most strongly influenced by genotype, it is also modulated by environmental influences and extraneous factors, including smoking status, alcohol intake, body mass index and comorbidites. These could affect the transcriptome through epigenetic modifications described above. As a result, predictive models or algorithms of treatment response must combine pharmacogenomic approaches with comprehensive clinical characterization for the development of truly 'personalized' medicine.

Until now, pharmacogenomic studies in psoriasis have been underpowered to produce reliable results and the majority have not recorded treatment response or toxicities prospectively in an objective and reproducible manner. Many of the published studies to date have adopted a candidate gene approach, focusing on single gene polymorphisms based on existing knowledge of the metabolic pathways of psoriasis treatments producing conflicting or nonsignificant results for the most part. Validation of results in distinct, adequately powered patient cohorts is therefore essential before pharmacogenomic markers can be used to predict treatment response in the clinical setting.

Psoriasis has been increasingly used as a paradigm for autoimmune diseases and for proof-of-principle studies of targeted biologic therapies due to easy accessibility to the skin and the ability to objectively measure disease severity and treatment response. The analysis of genetic variation and transcriptional profiling as part of large-scale Phase III or IV clinical drug trials could facilitate great advances in the field of pharmacogenomics of psoriasis and of autoimmune diseases in general. Alternatively, genome-wide association studies assessing response or toxicity to individual drugs may identify predictive markers of treatment response, but this would entail large numbers of patients to produce meaningful and statistically valid results. This could be achieved through the development of collaborations or large-scale meta-analyses in well-characterized patient populations that are uniformly treated and systemically evaluated. The genetic profiling of patients in registries for systemic and biologic treatments, which accrue comprehensive demographic and phenotypic information and prospectively record treatment response and toxicities over time in a standardized fashion could play a valuable role in advancing the field of pharmacogenomics of psoriasis. Data-modeling techniques could be employed to integrate longitudinal data collected from these patients, such as genetic polymorphisms, gene-expression profiling, epigenetic, proteomic and metabolomic studies, and flow cytometry analysis in association with comprehensive clinical phenotyping to construct models predictive of treatment response with more far-reaching applicability.

Financial & competing interests disclosure

Caitriona Ryan has acted as a speaker for Jansen-Cilag, an advisory board member for Galderma, and has received a travel fellowship from Abbott. Alan Menter has received research support and has acted as consultant or lecturer for Abbott, Amgen, Astellas, Asubio, Celgene, Centocor, DUSA, Eli Lilly, Galderma, Genentech, Novartis, Novo-Nordisk, Merck-Serono, Pfizer, Promius, Stiefel, Syntrix Biosystems, Warner Chilcott and Wyeth (now Pfizer). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- The discovery of predictive markers of treatment response may be useful in predicting clinical response to psoriasis therapies to allow individually tailored treatment.
- Pharmacogenomics is the study of variations of DNA and RNA characteristics as related to drug response.
- Polymorphisms of two methotrexate efflux transporter genes: adenosine triphosphate (ATP)-binding cassette, subfamily C, member 1 (*ABCC1*), and ATP-binding cassette, subfamily G, member 2 (*ABCG2*) are associated with both efficacy and toxicity of methotrexate.
- Polymorphisms in the promoter enhancer region of the thymidylate synthase (*TYMS*) gene may be associated with methotrexate response, although results have been conflicting.
- The VEGF–460C>T polymorphism is associated with response to acitretin.
- Functional polymorphisms in the promoter region of the TNF gene may be associated with response to TNF-α inhibitors.
- The *HLA-Cw**6 allele does not appear to predict response to TNF-α inhibitors.
- Responders and nonresponders to alefacept show differential gene expression prior to initiation of therapy and in the early stages of treatment. A genomic classifier based on gene expression profiles may predict response to alafecept.
- In a small study, presence of the *HLA-Cw**6 allele predicted favorable response to efalizumab, while its absence was associated with an increased risk of rebound flaring on discontinuation of the drug.
- The Taq 1 polymorphism (rs731236) of the vitamin D receptor gene predicts prolonged remission duration following narrowband-UVB therapy.
- Studies of the association of vitamin D receptor gene polymorphisms and response to topical vitamin D analogs show conflicting results.

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