Biomarkers predictive of treatment response in psoriasis and psoriatic arthritis: a systematic review

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Abstract
Aims: The ability to predict response to treatment remains a key unmet need in psoriatic disease. We conducted a systematic review of studies relating to biomarkers associated with response to treatment in either psoriasis vulgaris (PsV) or psoriatic arthritis (PsA).
Methods: A search was conducted in PubMed, Embase and the Cochrane library from their inception to 2 September 2020, and conference proceedings from four major rheumatology conferences. Original research articles studying pre-treatment biomarker levels associated with subsequent response to pharmacologic treatment in either PsV or PsA were included.
Results: A total of 765 articles were retrieved and after review, 44 articles (22 relating to PsV and 22 to PsA) met the systematic review’s eligibility criteria. One study examined the response to methotrexate, one the response to tofacitinib and all the other studies to biologic disease-modifying antirheumatic drugs (DMARDs). Whilst several studies examined the HLA-C*06 allele in PsV, the results were conflicting. Interleukin (IL)-12 serum levels and polymorphisms in the IL-12B gene show promise as biomarkers of treatment response in PsV. Most, but not all, studies found that higher baseline levels of C-reactive protein (CRP) were associated with a better clinical response to treatment in patients with PsA.
Conclusion: Several studies have identified biomarkers associated with subsequent response to treatment in psoriatic disease. However, due to the different types of biomarkers, treatments and outcome measures used, firm conclusions cannot be drawn. Further validation is needed before any of these biomarkers translate to clinical practice.

Keywords: biological therapy, DMARD, drug response biomarkers, psoriatic arthritis, psoriasis, therapeutics

Introduction
Psoriasis is a common inflammatory skin disorder. The prevalence of psoriasis vulgaris (PsV), the most common form of psoriasis, is about 2%,1 and up to 30% of these patients develop psoriatic arthritis (PsA) – a chronic inflammatory condition that affects the joints, entheses and axial skeleton.

In the past 15 years, several effective biologic disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) have been licensed for the treatment of psoriatic disease. However, these treatments are either only partially or not effective for some patients. The best-designed, phase III randomised controlled trials (RCTs) in patients with PsA have been those conducted with bDMARDs and more recently with tsDMARDs. Less than 60% of patients achieve the primary outcome measure of an American College of Rheumatology 20% (ACR20) response, with approximately 40% and 20%, respectively, reaching harder targets of ACR50 or ACR70.2-5 The < 60% ACR20 response rate, which is a minimal disease response measure, means of course that > 40% do not
respond. Additionally, patients can exhibit discordant responses for their different manifestations of psoriatic disease with, for example, treatment targeting interleukin (IL)-17 resulting in sometimes dramatic improvements in skin psoriasis while features of peripheral arthritis may show little or no response. Trying to identify which drug to prescribe for which patient can be challenging and clinicians often use an individual’s clinical features and history of previous drug response as the best guide to treatment choice. This can result in patients cycling through several therapies before finding one that is effective for them, with this period of non-response contributing to disease progression and poor outcomes. bDMARDs are occasionally associated with serious adverse events, most commonly infection, and their high cost compared to conventional synthetic DMARDs (csDMARDs) must also be considered. The application of precision and stratified medicine is therefore needed, whereby psoriatic patients most likely to respond to different bDMARDs and tsDMARDs can be identified, thereby justifying their additional toxicity and cost.

The objectives of this systematic review were to identify studies of biomarkers associated with response to treatment in (i) PsV and (ii) PsA.

Methods
A protocol was developed in advance and contained eligibility criteria, information sources, search strategy and study selection. Our study aligns with ‘The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions’.

Inclusion criteria
We included cohort studies, case-control studies and RCTs that examined the relationship in patients with PsV or PsA between biomarker concentration prior to drug commencement and subsequent treatment response. The following types of biomarkers were included: genetic, serum, cellular, urine, synovial tissue and skin tissue.

Exclusion criteria
The following were exclusion criteria: studies with patients under 18 years of age; studies using clinical, radiological, or stool biomarkers; and studies examining response to non-pharmacologic treatments.

Searches
The initial search was performed on 18 June 2018 and was repeated on 2 September 2020 to capture the most up to date published information possible. The following medical literature electronic databases were searched: PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL). The following MeSH, EMTree or key terms were used: biomarkers; psoriatic arthritis; psoriasis; DMARD; biologic; antirheumatic agent. Conference proceedings were also searched for potential inclusion, including: American College of Rheumatology (ACR) annual meeting (2015–2019); European League Against Rheumatism (EULAR) annual congress (2015–2019); British Society for Rheumatology (BSR) annual conference (2015–2019); and Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) annual meeting (2015–2019).

Study selection
All search results were assessed independently by two reviewers (CM, DJ) for potential inclusion. Where there was a difference of opinion, the full article was discussed by the two reviewers with a third reviewer (OF) to reach a consensus. Figure 1 details the process of article selection.

Outcome measurements of treatment response accepted included objective measurements such as changes in psoriasis area severity index (PASI), disease activity score (DAS)28 and an ACR20 response, but also included patient reported outcomes such as EuroQol score and health assessment questionnaire (HAQ) score.

Results
The searches identified 765 articles; 101 duplicate articles were excluded, and of the 664 remaining unique articles, 569 were excluded because they did not meet the inclusion and exclusion criteria. Of the remaining 95 articles a further 51 were excluded, for example, if the citations failed to match the study design, outcome or population of interest. A total of 44 articles met all eligibility criteria (Table 1): 32 were full-length articles in peer-reviewed international journals and 12 were abstracts from peer-reviewed international conferences.
Biomarkers associated with treatment response in PsV

The 22 articles describing biomarkers associated with treatment response in PsV are shown in Table 2.

Ten articles examined the potential role of genetic polymorphisms and specific human leukocyte antigen (HLA) alleles as biomarkers of treatment response. Three of these studies reported associations between response and the HLA-C*06 haplotype. Using a national psoriasis registry, Dand et al. examined genotype data on 1326 patients.8 They reported that HLA-C*06:02-negative patients were significantly more likely to respond at all time points to the tumour necrosis factor-alpha inhibitor (TNFi), adalimumab, than to ustekinumab, which blocks the p40 subunit common to both IL-12 and IL-23 cytokines. They found no evidence that an interaction between the ERAP1 genotype and HLA-C*06:02 could provide a more effective predictive biomarker than HLA-C*06:02 alone. Masouri et al. found that rs10484554, a single nucleotide polymorphism (SNP) in the HLA-C gene, showed an association with a good response to TNF is but not to ustekinumab, while rs151823 and rs26653 SNPs in the ERAP1 gene showed associations with a good response to ustekinumab therapy.9 The study by Prieto-Pérez et al. studied 173 polymorphisms in an effort to establish an association with response to TNFi therapy.10 A multivariable analysis showed an association between polymorphisms in several genes including HLA-C.

Other studies have not found an association between the HLA-C gene and treatment response. De Keyser et al. examined the relationship between the presence of the HLA-C*06 haplotype and subsequent response to ustekinumab.11 They found no statistically significant difference in clinical response between HLA-C*06 positive and HLA-C*06 negative patients. Ryan et al. compared the frequencies of HLA-C, killer cell immunoglobulin like receptor (KIR) and vitamin D receptor (VDR) genes in responders and non-responders to etanercept or adalimumab in patients with severe chronic plaque psoriasis.12 None of the HLA-C, KIR or VDR genotypes examined were predictive of treatment response. A case-control study of 199 Chinese patients with PsV found that the presence of certain HLA-C*06 haplotypes was not predictive of treatment response to etanercept, ustekinumab, efalizumab or alefacept.13 Gulliver et al. conducted a retrospective study and identified 45 patients with...
### Table 1. Characteristics of studies included in the systematic review.

| References       | PsV/PsA | Country                          | No. of subjects | Study design                  |
|------------------|---------|----------------------------------|-----------------|------------------------------|
| Chicharro et al. | PsV     | Spain                            | 33              | Prospective, single centre    |
| De Keyser et al. | PsV     | Belgium, the Netherlands          | 137             | Prospective, multicentre      |
| Dand et al.      | PsV     | UK                               | 1326            | Retrospective, multicentre    |
| Ovejero-Benito et al. | PsV | Spain                           | 95              | Prospective, single centre    |
| Prieto-Pérez et al. | PsV | Spain                           | 144             | Prospective, single centre    |
| Ovejero-Benito et al. | PsV | Spain                           | 78              | Prospective, single centre    |
| Lu et al.        | PsV     | China                            | 43              | Prospective, single centre    |
| Masouri et al.   | PsV     | Greece                           | N/A             | Retrospective, single centre  |
| Nishikawa et al. | PsV     | Japan                            | 65              | Prospective, multicentre      |
| Tan et al.       | PsV     | US                               | N/A             | Prospective, multicentre      |
| Lima et al.      | PsV     | Brazil                           | 38              | Prospective, single centre    |
| Hoffman et al.   | PsV     | Germany                          | 146             | Retrospective, single centre  |
| Kivelevitch et al. | PsV | US                               | 35              | Prospective, single centre    |
| Lembo et al.     | PsV     | Italy                            | 16              | Prospective, single centre    |
| Ryan et al.      | PsV     | US                               | 138             | Retrospective, multicentre    |
| Strober et al.   | PsV     | US                               | 152             | Prospective, multicentre      |
| Gedebjerg et al. | PsV     | Denmark                          | 18              | Prospective, single centre    |
| Jokai et al.     | PsV     | Hungary                          | 38              | Prospective, single centre    |
| Shimauchi et al. | PsV     | Japan                            | 28              | Retrospective, single centre  |
| Chiu et al.      | PsV     | Taiwan                           | 102             | Prospective, single centre    |
| Gulliver et al.  | PsV     | Canada                           | 45              | Retrospective, single centre  |
| Kanelleas et al. | PsV     | Greece                           | 41              | Prospective, single centre    |
| Alivernini et al.| PsA     | Italy                            | 12              | Prospective, single centre    |
| David et al.     | PsA     | UK                               | 128             | Prospective, multicentre      |
| Hellman et al.   | PsA     | Sweden                           | 20              | Prospective, multicentre      |
| Mascia et al.    | PsA     | Italy                            | 70              | Prospective, single centre    |
| Ørnbjerg et al.  | PsA     | Multinational                     | 7975            | Retrospective, multicentre    |
| Siebert et al.   | PsA     | UK, US                           | 1069            | Retrospective, multicentre    |
| Song et al.      | PsA     | US                               | 142             | Prospective, multicentre      |
| Ovejero-Benito et al. | PsA | Spain                           | 20              | Prospective, single centre    |
| Scrivo et al.    | PsA     | Italy                            | 149             | Prospective, single centre    |

(continued)
Table 1. (Continued)

| References         | PsV/PsA | Country      | No. of subjects | Study design        |
|--------------------|---------|--------------|-----------------|---------------------|
| Muramatsu et al.48 | PsA     | Japan        | 29              | Prospective, single centre |
| Ademowo et al.37   | PsA     | Ireland      | 10              | Retrospective, single centre |
| Collins et al.38    | PsA     | Ireland      | 32              | Prospective, multicentre |
| Fabris et al.34     | PsA     | Italy        | 74              | Prospective, single centre |
| Murdaca et al.35    | PsA     | Italy        | 57              | Prospective, single centre |
| Chandran et al.49   | PsA     | Canada       | 40              | Prospective, single centre |
| Wagner et al.50     | PsA     | Multinational| 100             | Prospective, multicentre |
| Chimenti et al.51   | PsA     | Italy        | 55              | Prospective, single centre |
| Marotta et al.52    | PsA     | Canada       | 24              | Prospective, single centre |
| Pontifex et al.39   | PsA     | Ireland      | 25              | Prospective, single centre |
| Pedersen et al.42   | PsA     | Denmark      | 17              | Prospective, single centre |
| Gratacos et al.43   | PsA     | Spain        | 69              | Prospective, multicentre |
| Kristensen et al.44 | PsA     | Sweden       | 261             | Prospective, multicentre |

PsA, psoriatic arthritis; PsV, psoriasis vulgaris; UK, United Kingdom; US, United States.

Table 2. Studies evaluating biomarkers predictive of treatment response in PsV.

| Reference          | Outcome measure | Treatment | Biomarker                | Outcome |
|--------------------|-----------------|-----------|--------------------------|---------|
| Chicharro et al.19 | PASI            | TNFi, anti-IL-12/IL-23, anti-IL-17 miRNA in lesional and non-lesional psoriatic skin | Baseline expression of miRNA-146a in non-lesional skin and miRNA-135b in lesional skin were related to response to treatment |
| De Keyser et al.11 | PASI            | UST       | HLA-C*06 allele          | No statistically significant difference in clinical response between HLA-C*06 positive and HLA-C*06 negative patients |
| Dand et al.8       | PASI90          | ADA, UST  | HLA-C*06:02 allele       | HLA-C*06:02-negative patients were significantly more likely to respond to ADA than UST |
| Ovejero-Benito et al.15 | PASI75        | ADA, IFX  | Genetic polymorphisms   | Association between polymorphisms in IVL, IL-12B, NFKB1A, ZNF816A and SL9A8 genes and treatment response |
| Prieto-Perez et al.10 | PASI75       | TNFi      | Genetic polymorphisms   | Association between polymorphisms in PGLYR4, ZNF816A, CTNNA2, IL12B, MAP3K1 and HLA-C genes and treatment response |
| Ovejero-Benito et al.16 | PASI75      | ETN       | Genetic polymorphisms   | Association between polymorphisms in HLA-B/MICA, MAP3K1, PTTG1, ZNF816A genes and response to ETN |
| Lu et al.26        | PASI75         | ETN       | Serum cytokines         | Baseline IL-12 serum level was a significant factor affecting the clinical response to ETN |
| Masouri et al.9    | PASI            | TNFi, UST | Genetic polymorphisms   | Rs10484554, a genetic polymorphism in the HLA-C gene showed an association with a good response to TNFi agents but not to UST |

(continued)
psoriasis who had been treated with alefacept. They found that the presence of certain HLA-C*06 haplotypes was not predictive of response to treatment in PsV.

Three studies reported associations between other non-HLA polymorphisms and response to TNFi treatment. Ovejero-Benito et al. performed two studies investigating response to monoclonal antibody treatment and etanercept, respectively. Multivariable analyses showed five SNPs, in IVL, IL-12B, NFKBIA, ZNF816A and SLC9A8 genes, to be associated with achieving PASI75 response after 3 months of either adalimumab or infliximab. Multivariable analyses showed an association between polymorphisms in HLA-B/MICA, MAP3K1, PTTG1 and ZNF816A genes and the response to etanercept at 3 months. A genome-wide association study (GWAS) of 65 Japanese psoriasis patients reported on 10 SNPs, mapping to the SPEN, JAG2,
MACC1, GUCY1B3, PDE6A, CDH23, SHOC2, LOC728724, ADRA2A and KCNIP1 genes, showing association with TNFi treatment response.\textsuperscript{17} The authors also examined 68 SNPs that had previously been reported to be associated with response to TNFi treatment. Only one, rs11096957, mapping to the toll-like receptor (TLR) 10 gene was associated with treatment response.

Kivelevitch \textit{et al}. examined differentially expressed genes using microarray analysis in 35 patients treated with either adalimumab or ustekinumab.\textsuperscript{18} They found 57 differentially expressed genes, 14 upregulated and 43 downregulated, that differentiated ustekinumab responders from non-responders. The most significant differences in responders compared with non-responders were upregulation of \textit{HLA-DRB4} and carbohydrate metabolism pathways, and downregulation of tetrahydrobiopterin synthesis.

Three studies described either chemokine, microRNA (miRNA) or gene expression levels in lesional psoriatic skin. Chicharro \textit{et al}. reported on expression of miRNAs in psoriatic skin at baseline and their associations with subsequent response to biologic therapy.\textsuperscript{19} They found that expression of miRNA-146a in non-lesional skin and miRNA-135b in lesional skin were related to improvement after 3 months of treatment. Gedebjerg \textit{et al}.\textsuperscript{20} measured messenger RNA (mRNA) expression of various genes in skin biopsies by quantitative polymerase chain reaction. A total of 18 adult patients with moderate-to-severe chronic plaque psoriasis were included in the study and all patients were treated with ustekinumab. IL-20, IL-21 and p40 mRNA expression were significantly upregulated by factors of 2.7, 2.4 and 2.3, respectively, among non-responders compared with responders. Lembo \textit{et al}. studied monocyte chemoattractant protein-1 (MCP-1) plasma levels in psoriatic patients seeking an association between plasma and cutaneous MCP-1 expression and response to biological drugs.\textsuperscript{21} They also performed lesional skin biopsies in five patients treated with TNFi. They did not find an association between baseline MCP-1 levels and subsequent response to treatment.

The potential role of inflammatory markers as predictors of treatment response was examined in three studies. Tan \textit{et al}. examined data from the Oral-treatment Psoriasis Trial (OPT) Pivotal 1 phase 3 study on the use of tofacitinib, a Janus kinase (JAK) inhibitor, for the treatment of psoriasis.\textsuperscript{22,23} Baseline C-reactive protein (CRP) was not associated with PASI75 response. Similarly, Strober \textit{et al}. reported that baseline levels of CRP were not associated with subsequent change in PASI in patients treated with adalimumab who had a suboptimal response to previous therapies.\textsuperscript{24} Kanelleas \textit{et al}. reported similar results.\textsuperscript{25} They found that neither baseline levels of high sensitivity (hs) -CRP, nor ESR were associated with subsequently achieving a PASI75 response in patients treated with etanercept.

The remaining five studies on PsV examined levels of serum cytokines, chemokines, anti-double stranded (ds)DNA antibodies and cutaneous lymphocyte-associated antigen (CLA). Lu \textit{et al}. measured baseline levels of IL-6, IL-12, IL-17A, IL-23 and TNF-\alpha in patients with moderate to severe psoriasis before commencing on etanercept therapy.\textsuperscript{26} They reported that baseline IL-12 serum levels were significantly higher in responders compared with non-responders ($p = 0.03$). Lima \textit{et al}. measured serum levels of CXCL9, CXCL10 and CXCL16 and the frequencies of CD4+CXCR3+ T lymphocytes through ELISA and flow cytometry, respectively.\textsuperscript{27} They found systemic levels of chemokine ligands unable to predict response to treatment. Shimauchi \textit{et al}. examined serum levels of IL-22 and vascular endothelial growth factor (VEGF),\textsuperscript{28} but found them unable to predict response to treatment with ustekinumab or TNFi. Hoffman \textit{et al}. measured baseline anti-dsDNA antibody concentrations in patients undergoing treatment with adalimumab.\textsuperscript{29} They found patients with lower baseline anti-dsDNA concentrations responded better. Lastly, a study by Jokai \textit{et al}. examined a potential role for CLA as a predictor of response to TNFi therapy.\textsuperscript{30} They reported baseline CLA expression was not significantly different between those who responded to treatment and those who relapsed over a 24-week period.

\textit{Biomarkers associated with treatment response in PsA}

The 22 articles describing biomarkers predictive of treatment response in PsA are shown in Table 3.

Five studies investigated \textit{HLA} alleles and other genetic polymorphisms in responders and non-responders. David \textit{et al}. examined whether the presence of \textit{HLA-B*27} is a predictor of treatment response to biologics in PsA,\textsuperscript{31} but concluded it was not associated with EULAR good response or DAS28 improvement. Mascia \textit{et al}. aimed to
| Reference          | Outcome measure | Treatment | Biomarker | Outcome                                                                                                                                 |
|--------------------|-----------------|-----------|-----------|------------------------------------------------------------------------------------------------------------------------------------------|
| Alivernini et al.  | MDA             | MTX       | Synovial CD3+ cells | Patients who reached MDA status at 6 months had lower baseline CD3+ cell immunohistochemistry scores                                        |
| David et al.       | DAS28           | bDMARD    | HLA-B*27 allele | HLA-B*27 status was not associated with treatment response                                                                                 |
| Hellman et al.     | MDA, DAPSA,     | ADA       | HA in skin and serum | Higher levels of HA in serum associated with higher overall disease activity after 12 weeks of treatment                                      |
| Mascia et al.      | PsARC, ACR20    | TNFi      | Genetic polymorphisms | SNP-29 predicts response to TNFi                                                                                                           |
| Ørnbjerg et al.    | DAPSA28 remission | TNFi   | CRP      | Normal CRP at baseline decreased the probability of DAPSA28 remission at 6 months                                                          |
| Siebert et al.     | ACR20, PASI75   | GUS, UST  | IL-17A, IL-17F, CRP | Baseline levels of proteins measured not associated with treatment response to UST. Baseline IL-17F modestly associated with ACR20 response to GUS |
| Song et al.        | ACR20, PASI75   | GUS       | CRP, SAA, sICAM1, svCAM1, IL-17A, IL-17F, IL-22 | None of the baseline proteins measured were associated with treatment response                                                               |
| Ovejero-Benito et al. | Improvement in Arthritis, EuroQol | ADA, ETN, IFX | Genetic polymorphisms | Association between polymorphisms in the TNFAIP3 gene and treatment response                                                                   |
| Scrivo et al.      | Achievement of MDA | GOL      | hs-CRP   | A higher baseline hs-CRP value and the absence of comorbidities were predictive factors for achieving MDA at 6 months                          |
| Muramatsu et al.   | DAS28-CRP       | IFX, ADA, UST | Serum IL-6 levels | Baseline serum IL-6 levels not statistically different between good responders and poor responders to treatment                                  |
| Ademowo et al.     | DAS28-CRP       | ADA       | Synovial tissue proteins | Panel of 57 proteins predictive of response to treatment (AUC of 0.76)                                                                        |
| Collins et al.     | DAS28           | TNFi      | Synovial tissue proteins | 25 proteins differentially expressed between good and poor responders                                                                           |
| Fabris et al.      | Survival of first TNFi agent | TNFi      | Genetic polymorphisms | TNFα -308A allele and IL-6 -174GG homozygosis resulted as independent biomarkers predicting survival of the first TNFi therapy               |
| Murdaca et al.     | ACR 20/50/70; DAS28; HAQ | ADA, ETN, IFX | Genetic polymorphisms | TNFα gene polymorphisms at −308 and −238 not associated with response to TNFi treatment. SNP +489 A/A genotype associated with response to ADA |
| Chandran et al.    | SJC, TJC, PASI  | ADA, ETN, IFX, GOL | MMP-3 | Baseline level of MMP-3 was independently associated with treatment response                                                              |
identify genetic variants in the TNF-α genomic region able to predict therapeutic response to TNFi therapy. They found a significant association between SNP29, located between the lymphotoxin alpha (LTA) and TNF genes, with the response to TNFi treatment. Ovejero-Benito et al. examined 10 polymorphisms located in genes related to TNF, with the response to TNFi treatment. Ovejero-Benito et al. examined 10 polymorphisms located in genes related to TNF, with the response to TNFi treatment. They reported that the TNFα-308A allele as well as the presence of IL6-174GG homozygosity were independent biomarkers predicting survival of the first TNFi therapy in patients with spondyloarthritis, some of whom had PsA. Murdaca et al. investigated the role of SNPs in the TNFα gene in the response to TNFi therapy. The +489A allele showed a statistically non-significant trend for association with response to treatment with etanercept. Alleles −308 and −238 did not influence the clinical outcome of PsA patients treated with TNFi.

Four studies examined potential synovial tissue biomarkers for predicting response to treatment. Alivernini et al. examined synovial tissue biopsies using immunohistochemistry (IHC) in DMARD naive PsA patients prior to them commencing methotrexate (MTX). They reported a lower IHC score of CD3+ T-cells in patients reaching minimal disease activity (MDA) status at 6 months compared to those not achieving this outcome. Two of these studies utilised an unbiased proteomic analysis approach by using mass spectrometry to report levels of synovial tissue proteins. Ademowo et al. described a biomarker panel of 57 proteins confirmed to be predictive of treatment response with an area under the curve of 0.76. Collins et al. reported 25 synovial tissue proteins that were differentially expressed between good responders and poor responders to TNFi therapy.
TNFi therapy. Another study, by Pontifex et al., quantified cellular markers including CD3+ T-cells but found baseline levels were not predictive of treatment response.

A number of studies examined the association between inflammatory markers at baseline and subsequent response to treatment with bDMARDs. Five studies reported that a higher baseline level of CRP was associated with better treatment response or treatment continuation. Ørnbjerg et al. reported on data from nearly 8000 PsA patients in 13 European registries commencing on first TNFi. Using a multivariate model, they found a normal CRP at baseline decreased the probability of DAPSA28 remission at 6 months. Scrivo et al. reported higher levels of hs-CRP predicted MDA achievement after 6 months of treatment with golimumab. A study by Pedersen et al. of patients treated with TNFi therapy reported that compared with non-responders, responders had higher baseline CRP, IL-6, VEGF and MMP-3, whereas no difference was seen in YKL-40 or total aggrecan. Similarly, Gratacos et al. found that high CRP levels at the start of treatment were independently associated with a good therapeutic response to infliximab. In a study by Kristensen et al., drug persistence was used as a surrogate of treatment response. They reported that high CRP levels at TNFi initiation were associated with better overall drug survival. Conversely, other studies did not find an association between baseline levels of CRP and subsequent treatment response. Song et al. measured CRP, serum amyloid A (SAA), soluble cell adhesion molecules (sICAM1, sVCAM1) and Th17 effector cytokines (IL17A, IL17F and IL22) at baseline in patients subsequently treated with guselkumab. They did not identify an association between baseline protein levels and subsequent clinical response. Siebert et al. examined baseline levels of CRP, IL17A and IL17F in patients treated with either ustekinumab or guselkumab. While none of the baseline levels of evaluated cytokines were associated with clinical response to ustekinumab, baseline levels of IL17F in patients treated with guselkumab were modestly associated with ACR20 response at week 24.

The remaining six studies identified other candidate biomarkers of treatment response. In a prospective clinical study, Hellman et al. measured skin inflammation, serum hyaluronan (HA) and molecular mass of HA in patients subsequently treated with adalimumab. Patients with elevated HA values had more retained swollen joints and higher overall disease activity after 12 weeks of treatment. Muramatsu et al. found that baseline serum IL-6 levels were statistically not significantly different between good and poor responders to biologic treatment. Chandran et al. studied 10 soluble biomarkers in patients commencing TNFi treatment but found only baseline level of MMP-3 to be associated with responder status. Notably, they found no association between hs-CRP and treatment response. In a prospectively planned biomarker sub-study, Wagner et al. examined baseline levels of 92 biomarkers in 100 patients from the GO-REVEAL trial examining the response of patients with PsA to golimumab. Pyridinoline, adiponectin, prostaglandin acid phosphate and factor VII were identified as a panel of markers having the potential to be predictive of ACR20 response. As in the study by Chandran et al., baseline CRP levels were not associated with any of the clinical outcomes. Chimenti et al. examined baseline levels of complement, CRP and ESR. They found that higher baseline C3 levels were associated with non-response to TNFi therapy. Neither CRP nor ESR were associated with treatment response. Lastly, Marotta et al. reported baseline titres of 14-3-3 eta serum protein were predictive of an ACR50 response in patients with PsA treated with adalimumab.

Discussion

This review reports several different types of biomarkers that have been shown to be associated with treatment response in psoriatic disease. Of the 22 PsA studies, 21 involved bDMARD therapy; 13 were limited to TNFi therapy only, while two studies involved TNFi therapy as well as another agent, either ustekinumab or anakinra. One of the studies on PsV involved the use of a tsDMARD, tofacitinib. The other studies on PsV involved biologic therapy, predominantly TNFis, although six studies did involve ustekinumab treatment. The majority of the studies assessed outcomes after 12 to 28 weeks, which is a reasonable period of time after which to assess response to treatment. One limitation of the data is that only one of the studies reviewed included patients on a csDMARD and further studies exploring biomarkers following use of csDMARDs would be valuable.
tended to be low, making it difficult to identify statistically significant associations due to the higher standard error.

Another factor that made it more difficult to compare results from different studies was the number of different outcome measures used. All of the studies on PsV used change in PASI, most commonly PASI75, as an outcome measure. In contrast, a number of different measures were used to assess outcome in PsA, reflecting the heterogeneous nature of the disease. A DAS28 score was the most common outcome measure used, while ACR20/50/70, drug persistence, MDA and patient global assessment (PGA) were among the other measures used. Some of these outcome measures are more achievable than others. For example, MDA is a much stricter criteria for response to treatment than ACR20. The adoption of standardised, widely used outcome measures remains a challenge in PsA.

While some studies assessed response to one treatment only, a number of studies included patients treated with different therapies, sometimes acting on different molecular pathways, for example, TNFα inhibition and IL-12/23 inhibition. Mechanistically, it is likely that a biomarker is predictive of response to one specific class of treatment but not another, due to the immune axis being altered. Therefore, it is difficult to interpret analyses where pooling of patients treated with different classes of agents occurred.

These reasons may partially explain some of the seemingly inconsistent results reported. For example, of the six studies that investigated associations between the HLA-C gene and treatment response in PsV, three studies reported associations, while the other three did not. It must be noted that these studies included patients treated with different bDMARDs. Eight studies either focused primarily on, or included, CRP as a possible predictor of treatment response in PsA. Five studies reported higher baseline levels of CRP being associated with better response to treatment, whereas three studies did not. Notably, different outcome measures were used in all five studies where associations were shown. None of the three studies that examined the relationship between CRP and subsequent treatment response in PsV identified any association.

The most significant limitation of research in this field that has been identified by this systematic review is the lack of validation of results in independent cohorts. None of the potential biomarkers identified in this systematic review have been validated in larger independent cohorts. Validation of biomarkers in well defined, prospective cohorts is necessary before they can be developed into clinical tests that can be used on a routine basis.

In PsV, studies examining potential associations between genetic polymorphisms and treatment response gave some of the most promising results. This topic is a good candidate for prioritization for further research, with stratification of patients by type of bDMARD therapy received more likely to uncover meaningful associations.

In PsA, the relationship between CRP and subsequent response to bDMARD therapy is potentially of significant clinical use. The five studies that showed a positive relationship between higher levels of CRP at baseline and a good therapeutic response all related to the use of TNFis, while the more recent large study by Siebert et al. which did not show a similar association related to bDMARDs which block the IL12/23 pathway. Further study in this area is needed.

The ability to predict response to treatment remains a key unmet need in psoriatic disease. While many of the studies included in this review show promise, their results need to be validated before they can be developed into routine clinically useful tests.

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