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Review Article

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

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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,[6] 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'.[7]

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.

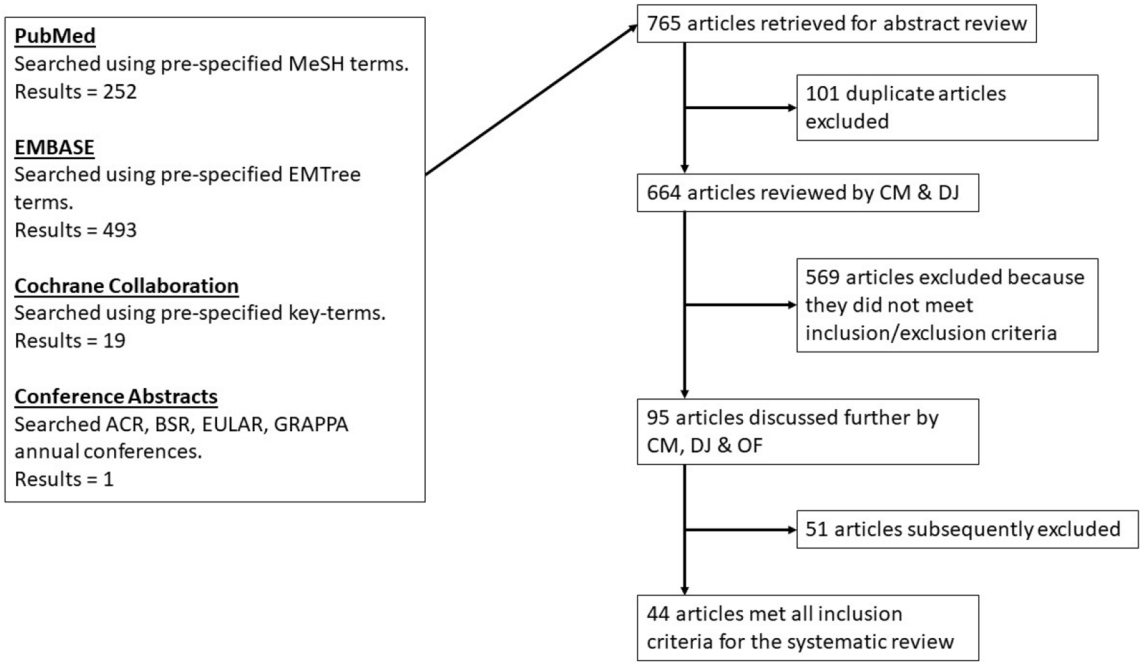

Figure 1. Systematic review search algorithm.
ACR, American College of Rheumatology; BSR, British Society for Rheumatology; EULAR, European League Against Rheumatism; GRAPPA, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis.

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.*[19]	PsV	Spain	33	Prospective, single centre
De Keyser *et al.*[11]	PsV	Belgium, the Netherlands	137	Prospective, multicentre
Dand *et al.*[8]	PsV	UK	1326	Retrospective, multicentre
Ovejero-Benito *et al.*[15]	PsV	Spain	95	Prospective, single centre
Prieto-Pérez *et al.*[10]	PsV	Spain	144	Prospective, single centre
Ovejero-Benito *et al.*[16]	PsV	Spain	78	Prospective, single centre
Lu *et al.*[26]	PsV	China	43	Prospective, single centre
Masouri *et al.*[9]	PsV	Greece	N/A	Retrospective, single centre
Nishikawa *et al.*[17]	PsV	Japan	65	Prospective, multicentre
Tan *et al.*[22]	PsV	US	N/A	Prospective, multicentre
Lima *et al.*[27]	PsV	Brazil	38	Prospective, single centre
Hoffman *et al.*[29]	PsV	Germany	146	Retrospective, single centre
Kivelevitch *et al.*[18]	PsV	US	35	Prospective, single centre
Lembo *et al.*[21]	PsV	Italy	16	Prospective, single centre
Ryan *et al.*[12]	PsV	US	138	Retrospective, multicentre
Strober *et al.*[24]	PsV	US	152	Prospective, multicentre
Gedebjerg *et al.*[20]	PsV	Denmark	18	Prospective, single centre
Jokai *et al.*[30]	PsV	Hungary	38	Prospective, single centre
Shimauchi *et al.*[28]	PsV	Japan	28	Retrospective, single centre
Chiu *et al.*[13]	PsV	Taiwan	102	Prospective, single centre
Gulliver *et al.*[14]	PsV	Canada	45	Retrospective, single centre
Kanelleas *et al.*[25]	PsV	Greece	41	Prospective, single centre
Alivernini *et al.*[36]	PsA	Italy	12	Prospective, single centre
David *et al.*[31]	PsA	UK	128	Prospective, multicentre
Hellman *et al.*[47]	PsA	Sweden	20	Prospective, multicentre
Mascia *et al.*[32]	PsA	Italy	70	Prospective, single centre
Ørnbjerg *et al.*[40]	PsA	Multinational	7975	Retrospective, multicentre
Siebert *et al.*[46]	PsA	UK, US	1069	Retrospective, multicentre
Song *et al.*[45]	PsA	US	142	Prospective, multicentre
Ovejero-Benito *et al.*[33]	PsA	Spain	20	Prospective, single centre
Scrivo *et al.*[41]	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, NFKBIA, ZNF816A and SLC9A8 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)

Table 2. (Continued)

Reference	Outcome measure	Treatment	Biomarker	Outcome
Nishikawa *et al.*[17]	PASI	ADA, IFX	Genetic polymorphisms (GWAS)	Reported on the 10 SNPs showing the strongest association with response to TNFi treatment
Tan *et al.*[22]	PASI75	TOF	CRP	Baseline CRP was not predictive of treatment response
Lima *et al.*[27]	NA	NA	Serum chemokines (CXCL9, CXCL10 and CXCL16)	Levels of serum chemokines do not predict treatment response
Hoffman *et al.*[29]	LOR, SSE	ADA, ETN	Anti-dsDNA concentration	Low baseline anti-dsDNA concentrations associated with better outcomes in ADA therapy
Kivelevitch *et al.*[18]	PASI	ADA, UST	DEGs	57 DEGs differentiated UST responders from non-responders
Lembo *et al.*[21]	PASI	ADA, ETN, EFZ	MCP-1 levels in plasma and skin	MCP-1 levels not found as a predictor of disease response
Ryan *et al.*[12]	PASI75	ADA, ETN	HLA-C, KIR, VDR genotypes	None of the genotypes examined were predictive of treatment response
Strober *et al.*[24]	PASI	ADA	CRP	Baseline CRP was not associated with change in PASI
Gedebjerg *et al.*[20]	PASI	UST	mRNA expression in skin	IL-20, IL-21 and p40 mRNA expression in lesional psoriatic skin were upregulated in non-responders compared to responders
Jokai *et al.*[30]	PASI	ADA, ETN, IFX	CLA	Responders showed (not significantly) lower initial CLA expression than relapsing patients
Shimauchi *et al.*[28]	PASI75	IFX, ADA, UST	Serum IL-22 & VEGF	Baseline levels of serum IL-22 and VEGF were not significantly different between responders and non-responders
Chiu *et al.*[13]	PASI50	ALC, EFZ, ETN, UST	HLA-B & HLA-C alleles	HLA-C*06 status did not affect PASI 50 response
Gulliver *et al.*[14]	PASI75	ALC	Genetic polymorphisms (GWAS)	HLA-C*06 did not predict response to alefacept
Kanelleas *et al.*[25]	PASI75	ETN	Inflammatory markers	No significant difference at baseline between responders and non-responders

ADA, adalimumab; ALC, alefacept; CLA, cutaneous lymphocyte-associated antigen; CRP, C-reactive protein; DEG, differentially expressed gene; dsDNA, double stranded DNA; EFZ, efalizumab; ETN, etanercept; GWAS, genome-wide association study; HLA, human leucocyte antigen; IFX, infliximab; IL, interleukin; KIR, killer immunoglobulin receptor; LOR, loss of response; MCP, monocyte chemoattractant protein; miRNA, microRNA; mRNA, messenger RNA; NA, not available; PASI, psoriasis area and severity index; PsV, psoriasis vulgaris; SNP, single nucleotide polymorphism; SSE, serious side effect; TNFi, TNF inhibitors; TOF, tofacitinib; UST, ustekinumab; VDR, vitamin D receptor; VEGF, vascular endothelial growth factor.

psoriasis who had been treated with alefacept.[14] 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.[15,16] 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.[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 *et al.* examined differentially expressed genes using microarray analysis in 35 patients treated with either adalimumab or ustekinumab.[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 *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 *et al.* reported on expression of miRNAs in psoriatic skin at baseline and their associations with subsequent response to biologic therapy.[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 *et al.*[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 *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.[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 *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.[22,23] Baseline C-reactive protein (CRP) was not associated with PASI75 response. Similarly, Strober *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.[24] Kanelleas *et al.* reported similar results.[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 *et al.* measured baseline levels of IL-6, IL-12, IL-17A, IL-23 and TNF-α in patients with moderate to severe psoriasis before commencing on etanercept therapy.[26] They reported that baseline IL-12 serum levels were significantly higher in responders compared with non-responders ($p=0.03$). Lima *et al.* measured serum levels of CXCL9, CXCL10 and CXCL16 and the frequencies of CD4+CXCR3+ T lymphocytes through ELISA and flow cytometry, respectively.[27] They found systemic levels of chemokine ligands unable to predict response to treatment. Shimauchi *et al.* examined serum levels of IL-22 and vascular endothelial growth factor (VEGF),[28] but found them unable to predict response to treatment with ustekinumab or TNFi. Hoffman *et al.* measured baseline anti-dsDNA antibody concentrations in patients undergoing treatment with adalimumab.[29] They found patients with lower baseline anti-dsDNA concentrations responded better. Lastly, a study by Jokai *et al.* examined a potential role for CLA as a predictor of response to TNFi therapy.[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.

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 *HLA* alleles and other genetic polymorphisms in responders and non-responders. David *et al.* examined whether the presence of *HLA-B*27* is a predictor of treatment response to biologics in PsA,[31] but concluded it was not associated with EULAR good response or DAS28 improvement. Mascia *et al.* aimed to

Table 3. Studies evaluating biomarkers predictive of treatment response in PsA.

Reference	Outcome measure	Treatment	Biomarker	Outcome
Alivernini *et al.*[36]	MDA	MTX	Synovial CD3+ cells	Patients who reached MDA status at 6 months had lower baseline CD3+ cell immunohistochemistry scores
David *et al.*[31]	DAS28	bDMARD	HLA-B*27 allele	HLA-B*27 status was not associated with treatment response
Hellman *et al.*[47]	MDA, DAPSA, ACR20/50/70	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.*[32]	PsARC, ACR20	TNFi	Genetic polymorphisms	SNP-29 predicts response to TNFi
Ørnbjerg *et al.*[40]	DAPSA28 remission	TNFi	CRP	Normal CRP at baseline decreased the probability of DAPSA28 remission at 6 months
Siebert *et al.*[46]	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.*[45]	ACR20, PASI75	GUS	CRP, SAA, slCAM1, svCAM1, IL-17A, IL-17F, IL-22	None of the baseline proteins measured were associated with treatment response
Ovejero-Benito *et al.*[33]	Improvement in Arthritis, EuroQol	ADA, ETN, IFX	Genetic polymorphisms	Association between polymorphisms in the TNFAIP3 gene and treatment response
Scrivo *et al.*[41]	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.*[48]	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.*[37]	DAS28-CRP	ADA	Synovial tissue proteins	Panel of 57 proteins predictive of response to treatment (AUC of 0.76)
Collins *et al.*[38]	DAS28	TNFi	Synovial tissue proteins	25 proteins differentially expressed between good and poor responders
Fabris *et al.*[34]	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.*[35]	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.*[49]	SJC, TJC, PASI	ADA, ETN, IFX, GOL	MMP-3	Baseline level of MMP-3 was independently associated with treatment response

(continued)

Table 3. (Continued)

Reference	Outcome measure	Treatment	Biomarker	Outcome
Wagner *et al.*[50]	ACR20; DAS28-CRP; PASI75	GOL	92 serum biomarkers	Pyridinoline, adiponectin, PAP and factor VII were identified as a panel of markers having the potential to be predictive of ACR20 response
Chimenti *et al.*[51]	DAS28	ETN, ADA	Complement C3	Higher baseline C3 levels were associated with non-response
Marotta *et al.*[52]	SJC68; PASI, CRP, ESR, DAS28, ACR50	ADA	14-3-3 eta serum protein	Baseline 14-3-3 eta titres were predictive of an ACR50 response
Pontifex *et al.*[39]	DAS28	ANR, ETN	CD3+ T cells (synovium & peripheral blood)	Baseline levels of CD3+ T cells were not predictive of treatment response
Pedersen *et al.*[42]	VAS-pain; PGA; 28 joint count	ADA, ETN, IFX	CRP, IL-6, VEGF, YKL-40, MMP-3, total aggrecan	Baseline levels of serum CRP and MMP3 and plasma IL-6 and VEGF were all higher in responders compared to non-responders
Gratacos *et al.*[43]	ACR50	IFX	ESR, CRP	High CRP values were independently associated with a good therapeutic response
Kristensen *et al.*[44]	TNFi survival	ADA, ETN, IFX	ESR, CRP	Higher baseline CRP levels associated with drug survival

ACR, American college of rheumatology; ADA, adalimumab; ANR, anakinra; AUC, area under the curve; bDMARD, biologic DMARD; CAM, cell adhesion molecule; CRP, C-reactive protein; DAPSA, disease activity in psoriatic arthritis; DAS, disease activity score; ESR, erythrocyte sedimentation rate; ETN, etanercept; GOL, golimumab; GUS, guselkumab; HA, hyaluronan; HAQ, health assessment questionnaire; HLA, human leucocyte antigen; hs-CRP, high sensitivity CRP; IFX, infliximab; IL, interleukin; MDA, minimal disease activity; MMP, matrix metalloprotease; MTX, methotrexate; PASI, psoriasis area and severity index; PGA, patient global assessment; PsA, psoriatic arthritis; PsARC, psoriatic arthritis response criteria; SAA, serum amyloid A; SJC, swollen joint count; SNP, single nucleotide polymorphism; TJC, tender joint count; TNFi, TNF inhibitor; UST, ustekinumab; VAS, visual analogue score; VEGF, vascular endothelial growth factor.

identify genetic variants in the TNF-α genomic region able to predict therapeutic response to TNFi therapy.[32] 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 in 20 PsA patients treated with TNFi therapy.[33] rs6920220 and rs610604 mapping the *TNFAIP3* gene showed a significant association with an improvement EuroQol score after 3 months of treatment. Fabris *et al.* 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,[34] some of whom had PsA. Murdaca *et al.*[35] 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).[36] 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.[37] Collins *et al.* reported 25 synovial tissue proteins that were differentially expressed between good responders and poor responders to

TNFi therapy.[38] Another study, by Pontifex *et al.*, quantified cellular markers including CD3+ T-cells but found baseline levels were not predictive of treatment response.[39]

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.[40] 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.[41] 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.[42] Similarly, Gratacos *et al.* found that high CRP levels at the start of treatment were independently associated with a good therapeutic response to infliximab.[43] In a study by Kristensen *et al.*, drug persistence was used as a surrogate of treatment response.[44] 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.[45] 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.[46] 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.[47] 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.[48] 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.[49] Notably, they found no association between hs-CRP and treatment response. In a prospectively planned biomarker substudy, 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.[50] Pyridinoline, adiponectin, prostatic 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.[51] 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.[52]

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.[36]

A significant limitation to the majority of studies in this review was the number of subjects enrolled. Only 14 of the 44 studies had at least 100 subjects, while only 4 had at least 200. In smaller studies, particularly where less stringent outcome measures were used, the numbers of non-responders

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 heterogenous 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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