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REVIEW

Towards Personalized Medicine in Rheumatoid Arthritis

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Abstract: Rheumatoid arthritis (RA) is a chronic, incurable, multisystem, inflammatory disease characterized by synovitis and extra-articular features. Although several advanced therapies targeting inflammatory mechanisms underlying the disease are available, no advanced therapy is universally effective. Therefore, a ceiling of treatment response is currently accepted where no advanced therapy is superior to another. The current challenge for medical research is the discovery and integration of predictive markers of drug response that can be used to personalize medicine so that the patient is started on "the right drug at the right time". This review article summarizes our current understanding of predicting response to anti-rheumatic drugs in RA, obstacles impeding the development of personalized medicine approaches and future research priorities to overcome these barriers.

Keywords: genetics, omics, biomarkers, machine learning, precision medicine

Introduction

Rheumatoid arthritis (RA) is a chronic multisystem inflammatory disease affecting up to 1% of the adult population.[1] The disease is characterized by synovitis, which leads to joint erosions and disability, and is associated with a reduced life expectancy of 5 years.[2] Treatment is based upon a treat-to-target approach, with rapid escalation of therapy when the target is not achieved.[3] Therapies that target the underlying pathogenic mechanism of disease, such as the TNF inhibitor (TNFi) adalimumab, have been available since 2002. Since the introduction of the first biologic disease modifying anti-rheumatic drug (bDMARD) targeting TNFα, there has been an exponential growth in the number of targeted RA therapies. Despite the incredible technological progress made in drug development in RA, no disease modifying anti-rheumatic drug (DMARD) is universally effective and TNFi fail to attain remission in up to 70% of patients.[4] Current RA management is therefore based on a "trial and error" approach where time on an ineffective medication leads to pain, increased healthcare costs and disease progression.[5]

RA is a heterogenous disease, but its current management assumes that there are common pathogenic pathways that can be targeted and treated in all patients. There now exists an armamentarium of drugs targeting different aspects of the immune system and, with such a vast choice of treatment, personalized medicine approaches are required to guide therapeutic decisions. Rather than a "one size fits all", personalized medicine is the targeted treatment of disease based on the individual characteristics of the patient.[6] Personalized medicine recognizes that RA is heterogenous and that patients are individuals with a unique biomarker signature that, combined with lifestyle and clinical factors, may be a predictive biomarker for treatment response to enable management of patients according to the "right drug, right patient, right time".[7]

RA is a disease that is ideal for personalized medicine discovery research. As a common disease that affects 1% of the population, it is amenable to the recruitment of large cohorts of patients for biomarker discovery studies. RA has a heritability of ~60%,[8] with >120 single nucleotide polymorphisms (SNPs)[9] associated with disease susceptibility. Progress in understanding the genetics of RA has improved our knowledge of its hetero-geneity and the underlying disease mechanisms. For example, HLA is responsible for 18% of the genetic variance

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of heritability of anti-citrullinated protein antibodies (ACPA)-positive disease but only 2% for ACPA-negative disease.[10] This greater understanding of the genetic architecture of RA may assist with pharmacogenomic biomarker discovery.

It is likely that, rather than one RA biomarker that can predict response, and thus aide personalized medicine approaches, a panel of biomarkers exists, with data that is integrated from different sources, eg, genomic, clinical and lifestyle, which can predict drug response. The discovery of predictive biomarkers or a biomarker signature of a drug response would lead to the use of the most effective therapy, a treatment strategy that is more cost-effective compared to time on an ineffective drug. In the future it is hoped that a patient's unique biomarker signature would be measured and the most clinically effective treatment targeting the underlying pathogenesis would be started early in the course of the disease to prevent joint damage and disability (Figure 1).

The aim of this review article is to summarize the current understanding of predictors of response to anti-rheumatic drugs in RA, obstacles impeding the development of personalized medicine approaches and future research priorities that may overcome these barriers.

Clinical Factors Predicting Drug Response
Age
The incidence of RA increases with age, with a peak incidence of 75–84 years.[11,12] Older age has been associated with a reduced response to combination conventional disease-modifying anti-rheumatic drugs (csDMARDs)[13] and TNFis[14–17] in several studies. One of the largest of the studies was a prospective observational cohort study by Atzeni et al,[15] which sought to investigate predictors of response to TNFi therapy in established RA patients (n=1300) with at least moderate disease activity (DAS-28 >3.2). The study analyzed patients starting TNFis available at the time and showed that, whilst younger age was associated with a higher probability of a good EULAR response, its effect was, however, modest (OR=0.98, p=0.002).

Biological Sex
Several observational and clinical trials have consistently demonstrated sex differences that predict drug response, with female sex associated with reduced response to combination csDMARDs[13] and TNFi.[13,15–21] The prospective observational British Society for Rheumatology Biologics Register analyzed 2879 RA patients commencing etanercept or
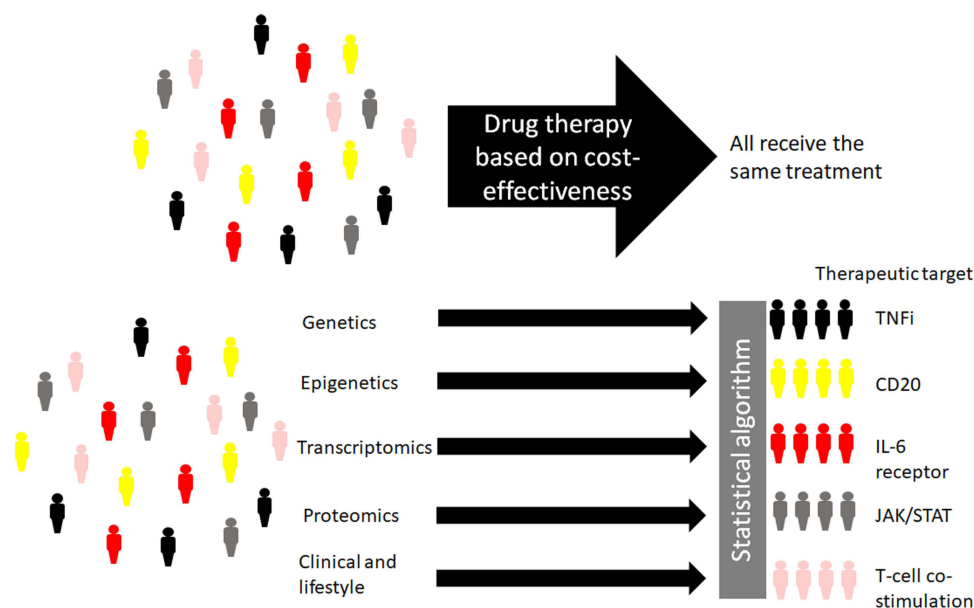
Figure 1 Illustration of how personalized medicine approaches using biomarkers and clinical predictors of treatment outcome can be applied to select a therapeutic target with an increased likelihood of response for the individual patient.
Abbreviations: TNFi, Tumor Necrosis Factor inhibitor; IL-6, Interleukin-6; JAK/STAT, Janus kinase/signal transducer and activator of transcription proteins.

infliximab and showed that females were 42% less likely to experience EULAR remission by six months compared to males (OR=0.58; 95% CI: 0.39–0.87).

Smoking

Smoking is associated with a two-times increase in the risk of developing RA in people who have a 20-pack per year history compared with non-smokers.[22] Several studies have shown that smokers experience worse outcomes compared to non-smokers to methotrexate,[23] infliximab[19] and combination therapy[18] but, interestingly, not rituximab.[24] The reason for worse clinical outcomes in smokers is not fully understood but smoking is associated with increased levels of pro-inflammatory cytokines such as TNFα[25] that may, in part, explain why TNFi therapy is less effective in smokers compared to non-smokers whilst there appears to be no modifying effect to B-cell depletion therapy.

Disease Activity

High disease activity is associated with poor clinical outcomes, including radiographic progression.[26] High baseline disease activity is associated with improved response to bDMARDs, including tocilizumab.[14,27,28] It has been hypothesized that the improved response in patients with high disease activity is due to the significant degree of biological inflammation that is amenable to pro-inflammatory cytokine inhibition.

BMI

Obesity has been shown to worsen clinical outcomes in patients commencing DMARD therapy.[18,29] The results of the Swedish pharmacotherapy trial (SWEFOT) of early RA patients (n=260) showed that obesity was associated with worse disease activity, functional impairment and pain following DMARD therapy at 24 months compared with non-obese patients. Additionally, obese patients were five times less likely to be in remission at 24 months (OR_{adj}=5.2; 95% CI: 1.8–15.2). There are several potential mechanisms underlying poor clinical outcomes in this patient group. Adipose tissue is biologically active and obesity is associated with an increase in pro-inflammatory cytokines, including TNFα and IL-6,[30] as well as an increase in load of weight-bearing joints. Additionally, raised BMI has been associated with reduced bDMARD drug levels through reduced absorption and increased drug clearance.[31–33] It may be postulated, therefore, that switching obese patients to weight-based therapies such as intravenous (IV) TOC to personalize therapy may lead to improved disease control. The MUSASHI study by Ogata et al analyzed the efficacy of tocilizumab in patients who switched from weight-adjusted IV tocilizumab to subcutaneous tocilizumab and showed that, whilst serum tocilizumab levels decreased, clinical remission, measured by DAS(ESR)-28, was maintained for the majority of patients; only 9% experienced a recurrence.[33] It is not known, however, if this is true for other bDMARDs.

Non-Adherence

Non-adherence is a health behavior that is more common than previously thought, with approximately 1 in 4 patients being non-adherent to methotrexate[34] and subcutaneous bDMARDs,[35] which is associated with poor treatment response. Clinicians are often unaware of adherence behavior, which can be associated with psychological factors. Directly observed therapy is an intervention whereby a healthcare worker observes medication administration. Whilst typically used for patients with tuberculosis,[36] several bDMARDs are available as IV preparations that require healthcare worker administration and can be a treatment strategy that guarantees therapy has been administered.

Summary of Clinical Prediction Guiding Personalized Medicine Approaches

Overall, clinical characteristics remain a modest predictor of response, at best. There are, however, some consistent findings but many are inherent to poor prognostic predictors of RA progression rather than treatment response per se. Additionally, it remains unclear if clinical predictors of a particular therapeutic agent would be similar to an alternative drug with a different mechanism of action that could help to guide personalized therapy. Further real-world studies are required to develop clinical risk prediction tools to individual drugs that can help guide personalized therapy in the future.

Omics

Considerable efforts made to elucidate the molecular pathways that underpin a large spectrum of complex human diseases have led to a rapid explosion of various "omics" technologies. These include genomics, epigenomics, transcriptomics, proteomics, metabolomics and other areas. New methodologies have produced unprecedented resolution and cost-efficient technologies allowing for the generation of large-scale data. We discuss the current landscape in RA for the omics fields and how they have been applied to try and identify indicators of treatment response to pave the way to personalized medicine approaches. The most prominent findings from the literature are summarized in Figure 2.

Pharmacogenomics

Pharmacogenomics is the study of genomic variation and drug response.[53] The use of pharmacogenomics to personalize therapeutic drug decisions offers great potential. Our genetics are fixed from birth and can therefore be measured at any time whilst remaining unique, thus offering the potential to truly personalize therapy. Since the human genome was first sequenced in 2003 by the Human Genome Project the cost of sequencing has significantly reduced.

Massey et al explored the heritability of TNFi response from a large (n=1752) UK RA patient cohort enrolled on an observational cohort study.[54] The study showed that change in swollen joint count (SJC) and erythrocyte sedimentation rate (ESR) were heritable (restricted maxiumum likelihood [REML] estimates of 0.48 and 0.39, respectively); however, the more subjective measures of tender joint count (TJC) and patient global assessment (visual analog scale [VAS]) that can be inflated by non-inflammatory conditions[55] were not (REML estimates of 0.00 and 0.00, respectively). Following the Massey et al study, a two-component DAS-28 was developed which excluded the TJC and VAS and could better
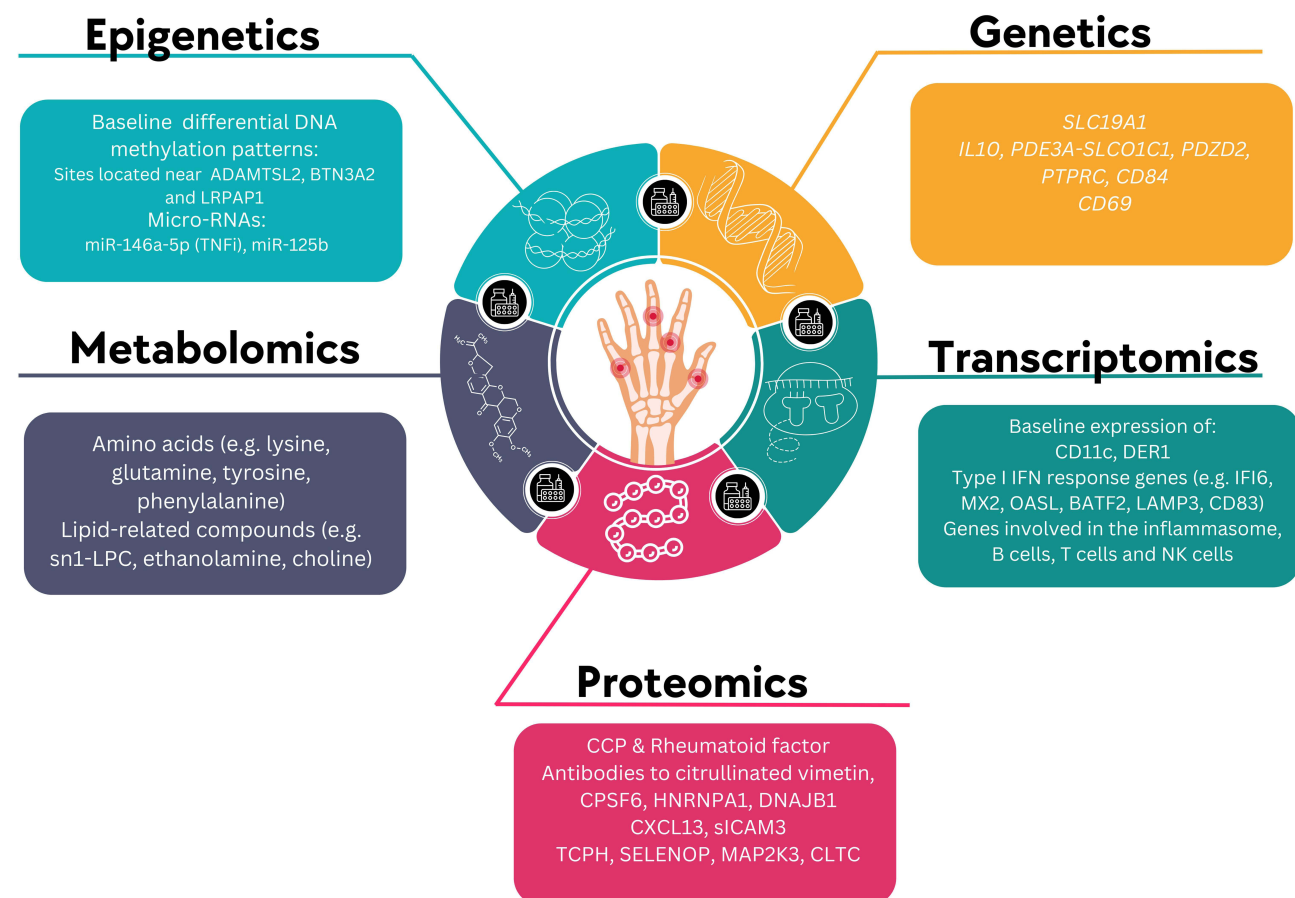
Figure 2 Summary of potential biomarker candidates for treatment response in RA, as identified in the literature. Rather than an exhaustive review of all previously associated predictors of treatment response, this is an overview. References: Genetics: SLC19A1,[37–39] IL10,[40,41] PDE3A-SLCO1C1,[42,43] PDZD2,[44,45] PTPRC,[46–49] CD84,[50,51] CD69.[28,52] References for transcriptomics, proteomics, metabolomics and epigenetics are shown in corresponding tables.

predict radiographic progression.[56] A study by Gilani et al showed that when utilizing the 2C-DAS28 more single nucleotide polymorphisms (SNPs) were replicated with TNFi response compared to the 4C-DAS-28.[57] These observations suggest that development of clinical phenotypes that more closely resemble disease activity may aid discovery of pharmacogenomic biomarkers, leading to stronger associations that could be investigated as part of a stratified clinical trial.

SNP associations with risk of developing severe joint damage or response to B-cell depletion therapy have been discovered in key genes that are targets for therapy such as the IL-6R[58] and IL-6 genes,[59] demonstrating the power of pharmacogenomics to identify potential treatment targets. To date, genome-wide association studies (GWAS) have identified >30 SNPs associated with TNFi response.[40,42,44,46,50,54] One of the strongest effect sizes for being a TNFi non-responder was seen in the rs6028945 SNP of the MAFB gene ($p=6x10^{-3}$; OR: 11.2),[40] a transcription factor regulating macrophage differentiation.[60] However, the target gene for many of the variants discovered through pharmacogenomic studies is still uncertain, as DNA folding can lead to associated variants regulating genes far from the SNP identified. Understanding the target gene and underlying mechanism of treatment response could pave the way to more personalized medicine approaches. Genome editing studies may lead to a greater understanding of how these variants affect gene transcription to alter human physiology and drug response.

Whilst various SNP associations with treatment response have been discovered, it is likely that no one SNP will be able to predict in the clinic which drug an individual will respond to. Through the integration of multiple predictive SNPs, a polygenic risk score providing a weighted single score may, in future, guide clinicians to which drug a patient is more likely to respond to.[61]

Epigenetics

The field of epigenetics explores inheritable changes to the chromatin structure that are not the result of alteration of the nucleotide sequence of DNA. These changes occur through several mechanisms, including DNA methylation, histone modification and RNA-associated silencing. These chemical covalent and noncovalent modifications to DNA molecules and histones are pivotal in influencing gene expression.[62]

Epigenetic modifications are inheritable, but they are reversible and can be altered by environmental exposure.[63] Potentially, epigenetic markers could be monitored over time to assess efficacy of a treatment or to consider individualized dosing adjustment. We summarize studies that investigate epigenetic predictors of response to treatment in Table 1.

Among epigenetic modifications, DNA methylation is the most thoroughly investigated. This process is the addition of a methyl group to cytosine–uanine dinucleotides, referred to as CpGs. Approximately 70–80% of CpGs in the human genome are methylated. There are areas in the genome where CpGs tend to occur together in clusters, known as CpG islands. Methylation is thought to impact on the interaction between transcription factors and DNA. Therefore, in regions

Table 1 Summary of Epigenetic Studies Investigating Predictors of Response to Treatment

Authors	Epigenetic Modification	Sample Size	Sample	Drug	Outcome	Main Findings
Nair et al 2020[64]	DNA methylation	68	Whole blood	MTX	EULAR response at 6 months	2 CpG sites showed methylation changes at 4 weeks associated with treatment response
Gosselt et al 2019[65]	DNA methylation	336	PBMCs	MTX	EULAR response at 3 months	Higher baseline global DNA methylation is associated with non-response
Gosselt et al 2021[66]	DNA methylation	69	PBMCs	MTX	EULAR response at 3 months	No genome-wide significant differences found
Glossop et al 2017[67]	DNA methylation	46	B and T lymphocytes	MTX	EULAR response at 6 months	Baseline methylation levels at 2 sites associated with treatment response
Plant et al 2016[68]	DNA methylation	72	Whole blood	ETN	EULAR response at 3 months	Top 2 DMPs associated with treatment response mapped to exon 7 of LRPAP1 gene

(Continued)

Table I (Continued).

Authors	Epigenetic Modification	Sample Size	Sample	Drug	Outcome	Main Findings
Sode et al 2018[69]	miRNAs	89	Plasma	ADA + MTX	ACR/EULAR remission at 3 months and 12 months	A higher baseline level of miR-27a-3p was associated with remission at 12 months
Krintel et al 2016[70]	miRNAs	180	Whole blood	ADA	EULAR response at 12 months	Combination of low expression of miR-22 and high expression of miR-886-3p associated with treatment response
Cheng et al 2020[71]	miRNAs	96	Plasma	IFX	EULAR response at 24 weeks	Higher baseline miR-125a and miR-125b expression were associated with treatment response
Duroux-Richard et al 2014[72]	miRNAs	32	Blood + serum samples	RTX	EULAR response at 3 months	Higher baseline expression of miR-125b associated with treatment response
Liu et al 2019[73]	miRNAs	Discovery – 19, replication - 92	PBMCs	ETN	EULAR response at 24 weeks	High baseline expression of miR-146a-5p associated with treatment response and high baseline expression let-7a-5p associated with lower odds of treatment response
Castro Villegas et al 2015[74]	miRNAs	Discovery – 10, Replication - 85	Serum	ADA ETN IFX	EULAR response at 6 months	Increased baseline expression of has-miR-23a-3p and has-miR-223-3p associated with lack of treatment response

Abbreviations: ADA, adalimumab; ETN, etanercept; EULAR, European Alliance of Associations for Rheumatology; IFX, Infliximab; MTX, methotrexate; miRNA, microRNA; PBMCs, peripheral blood mononuclear cells; RTX, rituximab

where there are active genes, CpGs tend to be hypomethylated. However, in those regions where CpGs are hypermethylated, there tends to be a decrease in gene expression.[75] DNA methylation has been proposed in several studies to be a predictor of treatment response in RA, both prior to treatment and within 1–3 months of treatment, the purpose of which would be to allow earlier therapeutic changes.

From research arising from the MAximising Therapeutic Utility in Rheumatoid Arthritis (MATURA) consortium, Nair et al 2020 hypothesized that differential methylation patterns could help identify patients recently started on methotrexate therapy who would be unlikely to respond to therapy. Two CpG sites (cg21040096 [RPH2AL] and cg09894276 [WDR27]) showed methylation changes at 4 weeks and were associated with EULAR response at 6 months ($p=2.79×10^{-7}$ and $3.62×10^{-7}$, respectively.[64] However, there were no significant associations at baseline. In contrast, Glossop et al found a correlation between baseline methylation patterns at cg03018489 and cg14345882 in T-lymphocytes and EULAR response at 6 months. These sites were located near the ADAMTSL2 and BTN3A2 genes. Most patients (93.5%) were commencing methotrexate, however 65.2% were commencing at least one other DMARD in addition (sulfasalazine/hydroxychloroquine).[67] The associations failed to replicate, however, in another study of patients commencing DMARD therapy.[66]

In a study of 72 patients, Plant et al identified two differentially methylated regions (DMPs) at baseline associated with response to etanercept. These mapped to the LRPAP1 gene, and methylation levels correlated with the rs3468 genotype. This SNP was also associated with EULAR response in 1204 patients treated with TNFi.[68]

Another category of epigenetic changes are histone modifications. Histone proteins bind to DNA influencing the accessibility of gene promotors for transcription factor binding. Modifications include acetylation, methylation, phosphorylation and citrullination. These processes intricately regulate gene expression and some are associated with chromatin structure.[76] Acetylation and methylation are associated with an aggressive phenotype of synovial fibroblasts in RA, through increased expression of matrix metalloproteinases (MMP-1, MMP-3, MMP9, MMP-13), which cause degradation of proteoglycans and damage to collagen.[77–79] However, to date no studies have investigated whether histone modifications may predict future treatment response. Indeed, they are not ideal biomarkers in view of current technical challenges, thus translational potential is likely limited.[77]

MicroRNAs (miRNAs) are small non-coding RNA molecules that bind to messenger RNAs (mRNAs) and therefore can suppress gene expression at the post-transcriptional stage. These epigenetic modifications are thought to be integral players in the regulation of diverse cellular responses. Immune dysregulation due to expression of specific miRNAs in RA has been observed, and some studies have explored whether changes in miRNA profiles can be used to predict treatment response.[69–74]

Most studies evaluating the predictive utility of miRNAs have focused on TNFi. Associations found include miR-27a-3p,[69] miR-22,[70] miR-886-3p,[70] miR-125a,[71] miR-125b,[71] miR-146a-5p,[73] let-7a-5p,[73] miR-23a-3p,[74] and miR-223-3p.[74] Although further validation is required, there does appear to be some agreement across certain studies, which is promising. For example, high levels of miR-146a-5p were associated with EULAR response at 24 weeks to etanercept using PBMCs from 92 patients at baseline (OR: 1.508 [1.127, 2.018]; p=0.006).[73] Higher levels of miR-146a-5p were also found in the serum of patients after 3 months of TNFi.[74,80] Interestingly, miR-125b has also been associated with response to rituximab.[72] Both miRNA-146-5p and miR-125b are thought to be involved in the NK-κB signaling pathway, which, through downstream effects, induces cytokines and chemokines such as TNF-α and IL-6 that are key drivers of RA inflammation.[81,82]

In summary, the potential of epigenetic markers as biomarkers of future treatment response may be limited due to their relative instability in the face of environmental factors in comparison to other omics fields. However, studies have highlighted important potential mechanisms of pathogenesis.

Transcriptomics

Transcriptomics refers to the examination of global gene expression profiles to uncover associations with a diverse array of traits. Gene expression is highly dynamic and can provide valuable insights into disease pathways as well as response to drug treatments. The total sum of all RNA molecules expressed at any one time in a biological specimen is termed the transcriptome. Various techniques are used to investigate differential gene expression and include RNA sequencing (RNA-Seq), reverse transcription polymerase chain reaction (RT-PCR) and microarray analysis.

Studies exploring whether transcriptomic biomarkers may predict response to treatment, either at baseline or very early in treatment, are outlined in Table 2.

Much of the literature has so far focused on TNFi therapy.[83–93]

Oswald et al did not find any significant differences in gene expression between responders and non-responders to TNFi-treatment at baseline in a cohort of 240 patients.[92] However, after 14 weeks of therapy, responders to treatment did show changes in multiple gene expression modules whereas, despite exposure to TNFi treatments, the non-responder group showed minimal changes across modules. Gene expression modules were mainly related to immunological components, for example B cells, T cells, MHC and inflammation, as well as platelets and downregulation of myeloid lineage. These findings were consistent across three independent RA cohorts.

Oliver et al used whole blood to assess differential gene expression in good responders (n=50) versus non-responders (n=20) to adalimumab therapy.[94] They did not identify any significant differential expression between these groups at either timepoint. They did however find that, within the good responder group, there were 813 differentially expressed transcripts pre-treatment compared to at 3 months; 17 transcripts were validated in a cohort of good responders (n=11). The authors suggest that it is possible that transcriptomic signatures may change earlier than at 3 months, which potentially could help identify non-responders earlier than in current clinical practice. One of these 17 transcripts was CD39 (ENTPD1) expression. The authors observed a higher expression of CD39 pre-treatment compared to post-treatment in good responders.[94] However, a large study of 2936 patients conducted by Spiliopoulou et al 2019 found that a higher genetic score for expression of CD39 on CD4+ T cells was associated with poor response to TNFi, using SJC as the outcome measure. This study also found that increased CD40 transcription was associated with good response.[93]

Baseline expression of CD11c was associated with response to adalimumab in a small study using monocytes.[86] The CD11c protein, also known as integrin, is an established marker for dendritic cells but is also expressed in monocytes and macrophages. It is thought to have a role in cell adhesion.[86] This association was however not replicated in a subsequent

Table 2 Summary of Transcriptomic Studies Investigating Predictors of Response to Treatment

Author	Sample Size	Sample	Drug	Outcome	Main Findings
TNFi					
Lequerré et al 2006[83]	33	PBMCs	IFX	EULAR response at 3 months response	MTCBP-1, AKAP9, RASGRP3, PTPN12, RSP28, HLA-DPB1, EPS15 downregulated and MRPL22 upregulated in responders at baseline
Tanino et al 2009[84]	42 (training), 26 (validation)	Whole blood	IFX	CRP at 14 weeks + EULAR response at 14 weeks	Expression of PSPH, CLGN, C21orf58, TBC1D8, LOC643981, ATP5I, ANKRD55, TMEM141, A_32_P1144 were the top ten biomarkers at baseline associated with treatmen response.
Julià et al 2009[85]	44	Whole blood	IFX	EULAR response at 14 weeks	Expression of HLA-DRB3, SH2D1B, GNLY, CAMP, SLC2A3 and IL2RB, MXD4, TLR5 at baseline associated with treatmen response.
Stuhlmüller et al 2010[86]	7	Monocytes	ADA	ACR20 response	Three gene sets (82, 11, 3) at baseline were predictive of response; CD11c expression was reported to have 100% sensitivity and a specificity of 91.7%.
Van Baarsen et al 2010[87]	33	Whole blood	IFX	DAS-28, TJC, HAQ at week 16	Patients with an increase in type 1 IFN response gene expression levels after 4 weeks of treatment (OAS1 and LGALS3BP) had poorer response to treatment
Toonen et al 2012[88]	42	Whole blood	IFX (27) ADA (15)	EULAR response at week 14	Out of 8 previously published gene sets, this study found that the Lequerré et al[83] 2006 gene set showed the best ability to classify responders and non-responders at baseline
Dennis et al 2014[89]	62	Synovial tissue	IFX	EULAR response at week 16	Higher baseline expression of myeloid gene set
Wright et al 2015[90]	20	Neutrophils	ADA (13) or ETN (5) or GOL (2)	DAS28 at 12 weeks	High type 1 IFN-related gene expression at baseline associated with good response
Smith et al 2015[91]	75	Whole blood	ADA (25) or ETN (50)	EULAR response at 3 months	CD11c expression at baseline not found to be associated with treatment response
Oswald et al 2015[92]	240	Whole blood	IFX (43) ETN (52) or ADA (50) or GOL (80) or CZP (14)	EULAR response at 15 weeks	No significant differences between gene expression between responders and non-responders to TNFi at baseline
Spiliopoulou et al 2019[93]	2938 (mixed cohorts)	Whole blood	IFX (792) or ADA (1255) or ETN (721) or GOL (17) or CZP (34)	SJC at 3–6 months	Increased expression of CD39 on CD4 T cells at baseline associated with poor response; increased expression of CD40 at baseline associated with good response
Oliver et al 2021[94]	70	Whole blood	ADA	EULAR response at 3 months	No significant difference at baseline between responders and non-responders
Cai et al 2022[95]	199 (test), 181 (validation)	Whole blood	IFX	ESR and CRP	Expression of DERL1 (hub gene) at baseline was increased in non-responders

TOC					
Sanayama et al 2014[96]	40 (training), 20 (validation)	PBMCs	TOC	CDAI at 6 months / Physicians' global assessment	Higher expression of IFI6, MX2, OASL (type I IFN response genes) and MTG1 at baseline associated with response
Teitsma et al 2017[97]	60	Whole blood	MTX (17) or TOC (24) MTX+TOC (14)	Sustained drug free remission for 24 or more weeks	Pathways related to differential gene expression at baseline associated with sustained drug-free remission varied according to each arm. MTX: bacterial/biotic stimuli, ph52 and JAK-STAT signaling; TOC: White cell migration MTX + TOC (transcription and translation machinery)
ABA					
Yokoyama-Kokuryo et al 2020[98]	45	Whole blood	ABA	EULAR response at 6 months	Relative expression levels of genes related to type I IFN response (IFIT3, MX1, OAS3) and genes related to activation of dendritic cells (BATF2/LAMP3/CD83) were significantly higher in responders compared to non-responders at baseline
RTX					
Thurlings et al 2010[99]	51	PBMCs	RTX	EULAR response at 24 weeks	Upregulation of 3 IFN response genes at baseline inversely associated with treatment response (Mx-1, double-stranded RNA-activated protein kinase, and IFN-induced protein with tetratricopeptide repeats 1)
Raterman et al 2012[100]	14 (discovery), 26 (validation)	Whole blood	RTX	EULAR response at week 24	Low expression of IFN type I response genes at baseline associated with good clinical response
Sellam et al 2014[101]	68	PBMCs	RTX	EULAR response at week 24	198 differentially regulated genes between responders and non-responders at baseline; upregulated genes including proinflammatory genes that may act on NF-kB complex were associated with response; upregulated genes linked to type I IFN pathway were associated with future non-response
Mixed cohort studies					
Nakamura et al 2016[102]	209	Whole blood	IFX (140) or TCZ (38) or ABA (31)	Remission (CDAI <2.8) at 6 months	*Expression measured at baseline:* IFX: Upregulation of Inflammasome genes were associated non-remission TCZ: Upregulation of B cell expressed genes were associated with remission ABT: Upregulation of genes associated with RNA elongation, regulation of apoptosis and NK specifically expressed genes were associated with non-remission.
Trialle et al 2021[103]	50	Synovial tissue	MTX/ADA/ABA /RTX/ TCZ	EULAR response at 14 weeks	At baseline, patients with a higher expression of genes involved in T cell activation pathways and myeloid activation pathways had a greater degree of downregulation at 16 weeks and were more likely to respond to treatment

Abbreviations: ABA, abatacept; ACR, American College of Rheumatology; ADA, adalimumab; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28, 28 joint disease activity score; ETN, etanercept; EULAR, European Alliance of Associations for Rheumatology; GOL, Golimumab; IFX, infliximab; MTX, methotrexate; PBMCs, peripheral blood mononuclear cells; RTX, rituximab; TOC, tocilizumab

study of patients commencing adalimumab (n=25) or etanercept (n=50).[91] It is possible that this is due to different tissue types or use of different outcome measures.

DERL1 is a gene involved in regulation of autophagy. Higher expression of this gene at baseline was associated with non-response to infliximab in RA.[95] Wright et al suggest that high expression of type I interferon (IFN) response genes at baseline is associated with subsequent response to TNF blockade.[87,90] Van Baarsen et al evaluated whole blood samples for differential gene expression after 4 weeks of exposure to infliximab (IFX) and found that patients with an increase in type I IFN response gene expression levels after 4 weeks' treatment (OAS1 and LGALS3BP) had poorer response to treatment.[87] These studies suggest that a high baseline expression of IFN I response genes may indicate future response to therapy, and that failure to suppress type I IFN response at 4 weeks could provide some support for a change in therapy.[87,90]

Type I IFN response gene expression may also have a role in prediction of response to tocilizumab. Sanayama et al found higher expression of IFI6, MX2 and OASL (type I IFN response genes) at baseline was associated with 6-month CDAI improvement.[96] There may also be a role of these genes in predicting abatacept response. In a study of 45 bDMARD-naïve patients, the type I IFN score was significantly higher in patients at baseline who went on to achieve a response compared to those who went on to fail to respond. Furthermore, IFN scores decreased by 15% (p <0.0005) in responders after exposure to abatacept at 6 months, but not in those who did not respond.[98] Interestingly, in this study, expression levels of genes related to activation of dendritic cells (BATF2/LAMP3/CD83) showed significant differences between responders and non-responders at baseline. Conversely, to TNFi, tocilizumab and abatacept, upregulation of 3 IFN response genes was associated with poor treatment response to rituximab across multiple studies.[99–101]

Teitsma et al analyzed data from 60 patients treated with tocilizumab from the U-Act-early study to identify clusters of differentially expressed genes associated with sustained drug-free remission. Pathways correlating with achieving sustained drug-free remission varied according to arm: in the tocilizumab arm, important pathways were related to white cell migration; in the combined methotrexate/tocilizumab arm, modules identified were related to transcription and translation machinery.[97]

Triaille et al sought to compare transcriptomic effects of abatacept to other commonly used disease modifying agents, namely, tocilizumab, rituximab, methotrexate and adalimumab. Using synovial tissue of 50 RA patients taken at baseline, they identified that patients who had a higher expression of genes involved in T cell and myeloid activation pathways were more likely to respond to treatment. This suggests that common downstream pathways are affected by drugs despite different modes of action.[103] Another study investigated the transcriptomic profile of patients who had failed to respond to methotrexate therapy and were started on tocilizumab, abatacept or infliximab instead. This study did show that different signatures across different treatments were associated with remission. Using gene set enrichment analysis, they found upregulation of genes involved in inflammasome in poor responders to infliximab. Conversely, B cell expressed genes were associated with response to tocilizumab. Finally, NK cell expressed genes were associated with non-response to abatacept.[102]

In the largest biopsy-driven trials to date, the R4RA and STRAP trials sought to combine information related to gene expression and histomorphology using synovial biopsies of participants with RA.[104,105] The R4RA trial, in a cohort of inadequate responders to TNFi, demonstrated the superiority of tocilizumab compared to rituximab in participants classified as having low or absent B cell lineage expression signatures.[105] The objective of the recent STRAP (Stratification of Biological Therapies by Pathobiology in Biologic-Naive Patients With Rheumatoid Arthritis) trial was to determine whether etanercept or tocilizumab (grouped together) were superior to rituximab in biologic-naïve patients with a B cell-poor synovial pathotype at 16 weeks. However, this trial failed to meet its primary endpoint, suggesting that a dichotomic classification of patients into B cell poor or B cell rich may be insufficient for stratification in biologic-naïve patients. However, the trial did demonstrate lower response rates to rituximab in those with a pauci-immune phenotype and increased radiographic progression in participants who were classified as B cell rich.[104]

In summary, many transcriptomic biomarkers of treatment response have been suggested in RA. The IFN pathway in particular shows promise in differentiating patients who may respond better to TNFi/CTLA-4/IL-6 inhibition compared to B cell inhibition; however, it remains to be seen whether this will add predictive value in practice. Evaluating patterns of gene expression in synovial tissue also shows promise, as suggested by clinical trials. The advent of spatial transcriptomics to gain a further in-depth understanding of gene expression at the level of single cells may increase the predictive value of these approaches in future.

Proteomics

The proteome is the tapestry of proteins in a cell or tissue for which the human genome provides the blueprint. The proteome has inherent added layers of complexity due to variable abundance, post-translational modifications and interactions between individual proteins and molecules. Proteins may be dysregulated in diseases such as RA and often the efficacy of a drug is related to binding with these proteins. As proteins are not predictable based on genetic sequences alone, the advent of proteomic technology provides an exciting opportunity for personalized medicine. This may be through discovery of dynamic biomarkers of disease activity and of treatment response, both general and drug specific. Proteomic methodology can be broadly placed in one of two methodologies: mass spectrometry or immunoassays. Immunoassays involve the use of antibodies to bind specific target proteins. Conversely, mass spectrometry, conversely through electron ionization, exploits the difference in mass/charge of different proteins to separate and analyze samples to identify proteins.[106]

We summarize studies investigating whether measurement of proteins at baseline can predict response to treatment in Tables 3 and 4. In discussions of proteomic biomarkers to personalize treatment of RA, one must discuss the role of autoantibodies. Rheumatoid factor (RF) and cyclic citrullinated peptide antibodies (anti-CCP) are used by clinicians in routine practice to aid diagnosis.[107] Several studies have found an association between anti-CCP/RF and treatment response, including TNFi, abatacept, IL-6 inhibitors and JAK inhibitors.[108–111] The largest study was a registry study of 2583 patients in 2021, which used drug retention as a surrogate measure of treatment response. This found that seropositivity was positively associated with treatment response to rituximab and abatacept, but no association was seen with TNFi.[109] This was in contrast to Julia et al, who found that the presence of both RF and CCP was associated with treatment response to TNFi at three months.[108] Treatment response to tofacitinib and sarilumab has also been associated with seropositivity.[110,111] Overall, it does appear that seropositive patients have improved EULAR responses after rituximab therapy compared to seronegative patients. This factor may be taken into consideration when making treatment decisions.[112]

Table 3 Summary of Proteomic (Autoantibody) Studies Investigating Predictors of Response to Treatment

Authors	Sample Size	Drug	Outcome	Main Findings
Halvorsen et al 2008[113]	40	ADA/ETN/IFX	Radiographic progression and ΔDAS-28 at 12 months	Expression oa anti-PAD4 was associated with greater radiographic progression and non-response to treatment
Ferraccioli et al 2012[114]	138	RTX	EULAR response at 6 months	IgG-RF positivity at baseline was associated with response; low BAFF (<1011 pg/mL) was associated with response
De Moel et al 2018[115]	399	MTX + prednisolone	ΔDAS-28 at 4 months	Breadth of autoantibody profile at baseline (anti-CCP(IgG/IgM/IgA)/ RF (IgM/IgA)/ citrullinated AMPAs/ acetylated AMPAs) was associated with greater reduction in DAS-28
Darrah et al 2019[116]	282	MTX + SSZ + HCQ or MTX + ETN	ΔDAS-28 over 48 weeks	Baseline anti-PAD4 was level associated with greater reduction in disease activity
Lourido et al 2020[117]	185	IFX	EULAR response at 6 months	Anti-CENPF was associated with response
Courvoisier et al 2021[109]	27,583	TNFi/RTX/TOC/ABA	Drug retention	Seropositivity (Rf and or anti-CCP positivity at baseline) was associated with higher likelihood of drug retention for TOC, ABA and RTX but not TNFi
Julia et al 2021[108]	80	ADA/CEZ/ETN/GOL	ΔDAS-28 at 3 months	Baseline RF/anti-CCP interaction was associated with better response; baseline anti-CarP/anti-PAD 4 interaction was associated with worse response
Kumar et al 2021[118]	60	ABA	ΔDAS-28 at 6 months	Anti-CarP was associated with response

Abbreviations: ABA, abatacept; ADA, adalimumab; CRP, C-reactive protein; CEZ, certolizumab; ΔDAS28, change in 28 joint disease activity score; ETN, etanercept; EULAR, European Alliance of Associations for Rheumatology; GOL, golimumab; HCQ, hydroxychloroquine; IFX, infliximab; MTX, methotrexate; PBMCs, peripheral blood mononuclear cells; RTX, rituximab; SSZ, sulfasalazine; TNFi, TNF inhibitors; TOC, tocilizumab; BAFF, B cell-activated factor; Anti-CarP, antibodies to carbamylated protein; Anti-CCP, antibodies to cyclic citrullinated peptide; anti-CENPF, antibodies to Centromere protein F; Anti-PAD4, antibodies to peptidyl arginine deiminase 4; RF, rheumatoid factor.

Table 4 Summary of Proteomic (Non-Autoantibody) Studies Investigating Predictors of Response to Treatment

Authors	Sample Size	Study Type	Drug	Outcome	Main Findings
Fabre et al 2008[119]	33	PBA	ETN	Classed as responders if 3 out of 4 criteria achieved (a change of DAS28 ≥1·2, an improvement of 20% of patient assessment disease activity, of CRP or ESR) at 3 months	Higher baseline levels of EGF and MCP-1 in future responders
Trocmé et al 2009[120]	60	SELDI-TOF-MS	IFX	Non-response: ACR 20 negative at week 30 Response: ACR 70 positive at week 30	High baseline levels of PF4/CXCL4 associated with non-response; high baseline levels of apolipoprotein A-I associated with response
Hueber et al 2009[121]	93 (3 independent cohorts)	Antigen Microarray/ cytokine multiplex	ETN	Non-response:<ACR20 at 3 months Response: >ACR50 at 3 months	24-biomarker signature at baseline associated with response (GM-CSF, IL-6, fibromodulin, clusterin, ApoE, H2B/e, clusterin, HSP58, IL-1α, COMP, acetyl-calpastatin, biglycan, osteoglycin, serine protease-11, IL-1β, eotaxin, IP-10, FGF-2, MCP-1, IL-12p70, fibrinogen, FibA, IL-12p40, IL-15)
Fabre et al 2009[122]	46	PBA	RTX	Classed as responders if 3 out of 4 criteria achieved (a change of DAS28 ≥1·2, an improvement of 20% of patient assessment disease activity, of CRP of ESR) at 3 months	No association of baseline profile with response
Dennis et al 2014[89]	198 (ADA), 198 (TOC)	ELISA	ADA or TOC	ACR50 response at 24 weeks	High levels of sICAM3 and low levels of CXCL13 at baseline are associated with response to ADA; conversely, low levels of sICAM3 and high levels of CXCL13 at baseline are associated with response to TOC
Hirata et al 2015[123]	ADA (49), TOC (50), TOF (27)	ELISA	ADA (49), TOC (50), TOF (27)	DAS28-ESR remission at 1 year	Baseline 14-3-3n level was associated with remission in the TOC group, but not associated in the ADA, MTX or TOF groups
Uno et al 2015[124]	43 48 40	MBBA	ETN (biologic naïve) n=43 TOC (biologic naïve) N=48 TOC (non-biologic naïve) N=40	Remission (DAS28 <2.3) at week 16	Baseline levels of IL-9, TNFα and VEGF (in combination) were associated with response to ETN (direction not shown) Baseline levels of IL-6, IP-10 and TNFRII was associated with response to TOC (biologic -naïve group; direction not shown) Baseline levels of IL-6 and IL-8, IP-10 waere associated with response to TOC (biologic-naïve group; direction not shown) High baseline level of sgp130 was associated with response to TOC (both biologic naïve and non-naïve groups).

Obry et al 2015[125]	22	Nano LC-MS/ELISA	ETN	EULAR response at 6 months	High baseline levels of ceruloplasmin, CO7, inter-alpha-trypsin inhibitor heavy chain 1, plasminogen, PROS, protein S100A9 and zinc-alpha2-glycoprotein were associated with future response
Han BK et al 2016[126]	29	ELISA	ADA/ETN	EULAR response at 14 weeks	Baseline CXCL10 and CXCL13 levels were positively associated with response
Folkerson et al 2016[127]	185	ELISA	TNFi (IFX/ADA/ETN/GOL/CEZ)	ΔDAS28 ≥1.2 at 3 months	High levels of sICAM3 and low levels of CXCL13 at baseline were associated with response to TNFi
Rinaudo-Gaujous et al 2019[128]	79	ELISA	IFX	EULAR response at 6 months	Higher baseline MMP3 levels were associated with future response
Chen et al 2019[129]	8	iTRAQ	IFX + MTX + LEF	EULAR response at 14 weeks	Higher levels of B7Z7M2, A0A087WZR4 Q53FL1, P08254, G3V2V8 at baseline were associated with response* Q6MZX9, B3KP77, P0DJI9, P0DJI8, P02787 were downregulated in the responder group* *Top 5 only
Ling et al 2020[130]	MTX (136) ADA (150)	MBBA	Response to MTX at 6 months/ADA at 3 months	EULAR response at 6 months (MTX or 3 months (ADA))	Expression of HNRNPA1 and DNAJB1 was associated with response; in anti-CCP negative subgroup, citrullinated vimentin and CPSF6 was associated with non-response
Zhao et al 2020[131]	60	ELISA	TNFi	EULAR response at 12 weeks	Baseline levels of CXCL13 and sICAM1 were positively associated with response
Ling et al 2023[132]	180	SWATH-MS	ETN	Remission (DAS28 < 2.6) at 3 months	Lower baseline levels of TCPH (Q99832) were associated with future remission
				ΔDAS-28 at 3 months	Higher baseline levels of EHD1 (Q9H4M9) and TCPH (Q99832) were associated with DAS-28 score
				hsCRP measured using ELISA at 6 months.	Lower baseline levels of SELENOP (P49908) and higher baseline levels of MAP2K3 (P46734) and CLTC (Q00610) were associated with hsCRP level

Abbreviations: ABA, abatacept; ADA, adalimumab; CRP, C-reactive protein; CEZ, certolizumab; ΔDAS28, change in 28 joint disease activity score; ELISA, enzyme-linked immunosorbent assay; ESR, erythrocyte sedimentation rate; ETN, etanercept; EULAR, European Alliance of Associations for Rheumatology; LEF, leflunomide; GOL, golimumab; IFX, infliximab; MTX, methotrexate; iTRAQ, isobaric tagging for relative and absolute quantification; LC-MS, liquid nano-chromatography-mass spectrometry; MBBA, multiplex bead-based assay; PBA, protein biochip array; PBMCs, peripheral blood mononuclear cells; RTX, rituximab; SELDI-TOF-MS, Surface-Enhanced Laser Desorption/Ionization Time-Of-Flight Mass Spectrometry; SWATH-MS, Sequential Window Acquisition of all Theoretical Mass Spectra; TNFi, TNF inhibitors; TOC, tocilizumab; TOF, tofacitinib; ApoE, apolipoprotein E; CO7, complement C7; COMP, cartilage oligomeric matrix protein; CXCL13, C-X-C motif chemokine ligand 13; DNAJB1, DnaJ homolog subfamily B member 1; EGF, epidermal growth factor; FGF-2, fibroblast growth factor 23; FibA, alpha subunit of fibrinogen; GMCSF, granulocyte macrophage colony stimulating factor; H2B/e, histone H2B type-E; HNRNPA1, heterogenous nuclear ribonucleoprotein A1; HSP38, heat shock protein 38; IP-10, interferon gamma-induced protein 1, also known as CXCL10 (C-X-C motif chemokine ligand 10); MCP-1, monocyte chemoattractant protein-1; MMP3, matrix metallopeptidase 3; PF4, platelet factor 4, also known as CXCL4, C-X-C motif chemokine ligand 4; PROS, vitamin K-dependent protein S; sICAM3, soluble intercellular adhesion molecule-3; TNFRII, tumor necrosis factor receptor II; VEGF, vascular endothelial growth factor.

Using a multiplex bead-based assay approach, Ling et al found other citrullinated autoantibodies to be associated with treatment response to methotrexate/adalimumab in ACPA-negative patients.[130] In this study, antibodies to citrullinated vimentin and CPSF6 were both found to be negatively associated with response to treatment, whilst antibodies to HNRNPA1 and DNAJB1 were positively associated. However, this added nothing over and beyond commercial CCP2 testing.[130]

Dennis et al found differentiating proteomic markers of treatment response to tocilizumab and adalimumab. High levels of sICAM3 and low levels of CXCL13 at baseline were associated with response to ADA. Conversely, low levels of sICAM3 and high levels of CXCL13 at baseline were associated with response to TOC.[89] Folkerson et al replicated findings for adalimumab in a cohort of 185 patients on various TNFis.[127]

Obry et al found an association of 7 proteins with treatment response to etanercept/methotrexate therapy, whereby two of these proteins, PROS (vitamin K–dependent protein S) and CHIP (E3 ubiquitin-protein ligase carboxyl terminus of heat shock cognate 70-interacting protein), in combination demonstrated high sensitivity (88.9%) and high specificity (100%).[125] A more recent, much larger study used sequential window acquisition of all theoretical fragment ion spectra mass spectrometry (SWATH-MS) in a study of 180 patients on etanercept therapy and identified proteins associated with treatment response.[132] Lower baseline levels of TCPH (Q99832) were associated with future remission and higher baseline levels of EHD1 (Q9H4M9) and TCPH (Q99832) were associated with DAS-28 score. In addition, lower baseline levels of SELENOP (P49908) and higher baseline levels of MAP2K3 (P46734) and CLTC (Q00610) were associated with hsCRP level at 6 months. Notably, however, this study failed to replicate proteomic biomarkers found to be associated with response to etanercept in other cohorts.

Although proteomic studies have clearly found a wealth of potential biomarkers that may help to tailor treatment in RA, lack of validation in large cohorts is a frequent occurrence.

Metabolomics

Metabolomics refers to the quantitative measurement of all small molecular weight metabolites present in a biological specimen. Metabolites can be thought of as the end products formed as a consequence of the interplay between DNA, transcription factors and proteins.[133] The two most common methods used to conduct metabolomic research are mass spectrometry (MS) and nuclear magnetic resonance (NMR).[133] A variety of different biological specimens can be used, such as blood products, urine and synovial fluid.[133] Numerous studies have investigated the metabolic profiles of RA patients to identify metabolites associated with pathogenesis, disease severity, efficacy and a small number have looked specifically at extra-articular manifestations. We focus here on attempts to use metabolomic profiles to predict response to treatment, as summarized in Table 5.

The majority of these studies focus on TNFi.[136–139] The largest of these studies, by Cuppen et al, enrolled 231 patients with RA commencing a TNFi and used LC-MS to evaluate metabolomic profiles of serum samples. Higher baseline levels of lysine and sn1-LPC (15:0), and lower levels of sn1-LPC (18:3-ω3/ω6) and ethanolamine, contributed to a model to predict treatment response with a high degree of accuracy (AUC-ROC=0.841) and outperformed a model using clinical predictors alone (p=0.01). The model showed particular utility in identification of patients unlikely to respond (NRI=0.23).[139] Kapoor et al had also previously found low levels of ethanolamine to be associated with response to TNFi (infliximab/etanercept)[136] but Priori et al found the opposite result for lysine.[138] In addition to these amino acids, Kapoor et al and Priori et al both found that higher baseline levels of glutamine are associated with response to TNFi.[136,138] Low levels of taurine have been associated with treatment response to methotrexate[134] and TNFi.[137]

Some studies have explored prediction of response to non-TNFi therapies.[134,135,137,140,141,143] Sweeney et al found that metabolite profiles related to pathways involving glycerophospholipid, amino acid and energy metabolism can distinguish responders and non-responders to rituximab.[143] In this study, low levels of tyrosine and phenylalanine were associated with treatment response whereas high levels of these amino acids have been associated with response to tocilizumab.[140] Low levels of choline were also associated with response to rituximab and TNFi.[138,143]

Some studies have suggested differences in baseline predictors of treatment response between different modes of action. Takashi et al found that three amino acid metabolites (citric acid, quinic acid and 3-aminobutyric acid) were associated with response to abatacept. These were different metabolites compared to the TNFi arm of the study.[137] Findings by Teitsma et al found that metabolic profiles of early RA patients were associated with sustained drug-free

Table 5 Summary of Metabolomic Studies Investigating Predictors of Response to Treatment

Paper	Sample Size	Sample Type	Technique	Drug	Outcome	Main Findings
Gosselt et al 2020[134]	82	Plasma	LC-MS	MTX	EULAR response at 3 months	Higher concentrations of 1,3-/2,3-diphosphoglyceric acid, glycerol-3-phosphate and phosphoenolpyruvate at baseline were associated with treatment response; lower concentrations of homocysteine, taurine, adenosine triphosphate, guanosine diphosphate and uric acid at baseline were associated with treatment response
Medcalf et al 2022[135]	20	Plasma	LC-MS	MTX	EULAR response at 16 weeks	Lower concentrations of N-methylisoleucine, nornicotine and 2.3-dihydroxybutanoic acid at baseline were associated with treatment response
Kapoor et al 2013[136]	16	Urine	¹H-NMR	TNFi (IFX/ ETN)	EULAR response at 12 months	Higher concentrations of histamine, glutamine, thymine, creatinine, xanthurenic acid, phenylacetic acid and xanthine were associated with treatment response; lower concentrations of ethanolamine, phosphocreatine and p-hydroxyphenylpyruvic acid were associated with treatment response
Takahashi et al 2019[137]	26	Serum	CE-MS	TNFi (ADA/ CEZ/GOL/IFX/ ETN)	EULAR-CRP response at 12 weeks	Higher concentration of betonicine at baseline was associated with response to TNFi Lower concentrations of Glycerol 3-phosphate, N-acetyl-L-alanine, hexanoic acid and taurine at baseline were associated with response to TNFi.
	17			ABA		Higher concentrations of citric acid and quinic acid at baseline were associated with response to ABA; lower concentration of 3-aminobutyric acid at baseline was associated with response to ABA
Priori et al 2015[138]	27	Serum	¹H-NMR	ETN	EULAR response at 6 months	Higher concentrations of N-acetylglycoprotein, glutamine, methionine, pyroglutamine and glucose at baseline were associated with treatment response; lower concentrations of lactate, arginine, lysine, acetate, sarcosine, aspartate, choline at baseline and formate were associated with treatment response
Cuppen et al 2016[139]	231	Serum	LC-MS	TNFi (ADA/ IFX/ETN/GOL/ CEZ)	EULAR response at 3 months	**Higher concentrations of lysine and sn1-LPC (15:0) at baseline were associated with treatment response; Llower concentrations of sn1-LPC (18:3-ω3/ω6) and ethanolamine at baseline were associated with treatment response**
Murillo-Saich et al 2021[140]	40	Plasma	¹H-NMR	TOC	EULAR response at 6 and 12 months	Higher concentrations of isobutyrate, 3-hydroxybutyrate, lysine, phenylalanine, 3G3PC, tryptophan and tyrosine at baseline were associated with treatment response

(*Continued*)

Table 5 (Continued).

Paper	Sample Size	Sample Type	Technique	Drug	Outcome	Main Findings
Teitsma et al 2018[141]	19			TOC + MTX	Sustained drug-free remission	Higher concentrations of 9,12,13-TriHOM, 9,10,13-TriHOM, L-methionine-sulfoxide at baseline were associated with sustained drug-free remission; lower concentrations of histamine, Spha c18:0, LPA c20:3, PA c18:1 and 8.9-DiHETrE at baseline were associated with sustained drug-free remission
	24			TOC		Higher concentrations of prostaglandin E2, L-pipecolic acid, 8.9-DiHETrE, 5.6-DiHETrE, 8-iso-prostaglandin-E2 and 20-carboxy-leukotriene-B4 at baseline were associated with sustained drug-free remission
	17			MTX		Higher concentrations of L-lysine and L-proline at baseline were associated with sustained drug-free remission
Dudka et al 2021[142]	25	Plasma	^{1}H NMR LC-MS	TNFI (ETN/ADA/CEZ) or TOC	EULAR response at 3 months	Using the ^{1}H NMR platform, concentrations of glucose, mannose, GlycA (N-acetylneuraminic acid), glycA (N-acetylglucosamine/galactosamine) and glycerophosphocholine at baseline were associated with treatment response; using the LC-MS platform, higher concentration of theobromine at baseline was associated with treatment response; lower concentrations of decanoylcarnitine, 5-hydroxyhexanoate, γ-glutamyl-leucine, pyroglutamylvaline and prolylhydroxyproline at baseline were associated with treatment response
Sweeney et al 2016[143]	23	Serum	^{1}H NMR	RTX	ACR20 at 6 months	Lower concentrations of phenylalanine, 2-hydroxyvalerate, succinate, choline, glycine, acetoacetate, and tyrosine at baseline were associated with treatment response

Note: Only those metabolites that were associated across both analytic approaches used in these studies are shown here.
Abbreviations: LC-MS, liquid chromatography-mass spectrometry; GC-MS, gas chromatography-mass spectrometry; NMR, nuclear magnetic resonance spectroscopy; ABA, abatacept; ADA, adalimumab; CRP, C-reactive protein; CEZ, certolizumab; ΔDAS28, change in 28 joint disease activity score; ETN, etanercept; EULAR, European Alliance of Associations for Rheumatology; GOL, golimumab; IFX, infliximab; MTX, methotrexate; RTX, rituximab; TNFi, TNF inhibitors; TOC, tocilizumab.

remission. Profiles predictive of response were different in the tocilizumab group, the methotrexate group and the tocilizumab and methotrexate combination group.[141]

Distinct metabolite patterns that may be predictive of treatment response are starting to emerge. Amino acids (eg, lysine, glutamine, tyrosine, phenylalanine) and lipid-related compounds (eg, sn1-LPC, ethanolamine, choline) stand out as potential predictors; however, further validation is required.

Therapeutic Drug Monitoring

A wide variability in serum concentrations of biopharmaceutical drugs exists. Therapeutic drug monitoring is the measurement of drug concentration with the aim of personalizing dosing and therefore optimizing drug efficacy and/or to reducing the risk of adverse effects by maintaining drug concentrations within the therapeutic window.[144] Several studies suggest that the higher drug levels in advanced therapies are associated with clinical efficacy in the case of adalimumab,[31,145] infliximab,[146–148] etanercept[149] and tocilizumab.[150,151]

Anti-drug antibodies (ADAs) have garnered much attention in recent years. Patients sometimes develop these ADAs in response to biologic medications which may contribute to diminished drug concentration through drug neutralization or enhanced drug elimination.[152] It is noted that ADAs are largely not detected for etanercept.[153] The prevalence estimates have been suggested to be up to 67% for infliximab and adalimumab.[154] The association between ADAs and low drug levels for particular drugs is well established for TNFi: adalimumab[153,155] and infliximab.[153,154,156,157] It has also been found for IL-6 receptor inhibitors: tocilizumab and sarilumab[158,159] and, most recently, rituximab.[160]

The presence of ADAs has been associated with reduced clinical efficacy for adalimumab[31,145,154,155,157,161–163] and infliximab.[147,154,157,163] However, this association has appeared to be less clear for tocilizumab,[164,165] sarilumab,[158,164,166] abatacept[154] and rituximab.[154,167] The prospective ABIRISK study aimed to determine whether ADAs were associated with therapeutic response in RA for TNFi, tocilizumab and rituximab. It confirmed a high prevalence of ADAs for those on TNFi therapy (26/68, 38.2%), tocilizumab (10/50, 20%) and rituximab (15/30, 50%). The study found a significant association between presence of ADAs and clinical response for all drugs combined, but it lacked power to detect a difference for each drug class. The biggest difference in response rates was noted in the TNFi group, but results for all drug classes do appear to show the same pattern of results.[168]

Another potential use of measurement of ADAs stems from the hypothesis that, if non-response is caused by immunogenicity, this will inform whether a second TNFi agent will be effective. This theory was tested in a cohort of 292 patients treated with etanercept, 70% of whom had been previously TNFi naïve and the remainder were TNFi inadequate responders (adalimumab or infliximab). Patients who switched from previous TNFi therapy with ADAs were significantly less likely to respond compared to those without ADAs and those who were naïve to TNFi.[169]

A limited number of prospective studies have assessed the use of therapeutic drug monitoring in RA. A study titled INGEBIO recruited a population with different rheumatic diseases, of which 63/169 (37%) had a diagnosis of RA. All patients had been treated with adalimumab and were clinically stable for at least 6 months. ADAs and drug levels were tested in each patient every 2–3 months but only the test results of the intervention group were revealed to clinicians. The risk of flare was reduced in the intervention group compared to the control group (IRR: 0.7252; 95% CI: 0.4997–1.0578), but this did not reach statistical significance.[170] A similar, more recent, study, NOR-DRUM, evaluated the use of therapeutic drug monitoring of patients commencing infliximab in a mixed population of 411 patients with different autoimmune conditions in Norway. Of these patients, 84 had a diagnosis of RA. Although the therapeutic drug monitoring group had fewer infusion reactions compared to the control group, there was no significant difference in remission rates between groups.[171]

Currently, the NICE recommendations (2019) state that there is insufficient evidence to advocate the routine use of therapeutic drug monitoring of TNFi (drug serum levels and ADAs) in RA.[172] More recently, EULAR published points-to-consider for therapeutic drug monitoring in inflammatory rheumatic diseases.[173] It also did not recommend the routine use of proactive TDM in the management of inflammatory rheumatic diseases and highlighted the lack of an identified optimal range of most drugs. However, it also identified some specific situations in which measurement of drug levels/ADAs may be considered. These are as follows:

1. Measurement of drug levels early during treatment with infliximab/adalimumab to guide predictions of future efficacy.
2. Measurement of drug levels and ADAs may help to understand the mechanisms underlying non-response and therefore help guide future treatment.
3. In cases of non-severe hypersensitivity reaction to infusions, measurement of ADAs may help guide decisions to continue treatment.
4. Measurement of drug levels in cases where tapering is being considered.

It appears clear that there does seem to be a role for at least reactive therapeutic drug monitoring. The caveat to all of these points is that further clinical trials and knowledge of the optimum biopharmaceutical therapeutic range and cost-effectiveness are needed to fully appreciate how therapeutic drug monitoring may be used to personalize care in RA in a cost-effective manner.[173]

Machine Learning

Artificial intelligence (AI) is the capability of a machine to perform functions and tasks one would associate with human cognition.[174] In the current technological climate, AI is being increasingly explored and adopted in many fields, including in precision medicine. Machine learning (ML) is thought of as a branch of AI, in which machines can identify patterns and draw inferences of relationships between variables, but without explicit instructions. This process contrasts from traditional hypothesis-driven data analysis approaches.[175]

The use of various machine-learning approaches, both supervised and unsupervised, has been explored in RA. The exponential rise of data, particularly highly dimensional omics data, has led to the problem of predictors outnumbering observations, a phenomenon referred to as "the curse of dimensionality".[176] How we best integrate all this information to inform prediction of treatment response is a considerable challenge.

A large Swedish study of 5475 patients sought to use a combination of four different machine-learning approaches using clinical data only to create a model predicting persistence of methotrexate therapy at one year. However, despite its large sample size and the wealth of clinical data available, only moderate predictive performance (AUC: 0.67, LASSO model) was reached, with only a marginal gain above traditional hypothesis-based models.[177] Miyoshi et al used artificial neural networks to develop a model using clinical covariates alone to predict response to infliximab and reported 92% accuracy. It contained nine variables: ESR/TJC, albumin, monocyte count, red blood cell number, methotrexate dosage, HbA1c, history of bDMARD use and prednisolone dosage.[178] Koo et al analyzed clinical data of 1204 patients treated with various biologics (adalimumab, golimumab, infliximab, abatacept and tocilizumab) and used several machine-learning methods to develop models predicting future remission for each drug type. Interestingly, there were differences in relative importance of clinical features for each drug type. Model accuracy ranged from 52.8% to 72.9% and AUROC ranged from 0.512 to 0.694.[179] These studies emphasize that clinical data alone is not sufficient to personalize treatment.

There have been some attempts to integrate omics data with clinical data, to try to improve model performance. Gosselt et al, using data from the Dutch REACH cohort, developed models to predict response to methotrexate at 3 months using 3 ML methods (LASSO, random forest and XGboost). The selected features included known clinical predictors of treatment response (RF and ACPA status, baseline DAS-28 components) combined with genetic predictors: SNPs in ATP-binding cassette (ABC) transporter genes and erythrocyte folate. Of the four developed models, LASSO performed best (AUC: 0.76) in predicting lack of response to methotrexate.[180] Lim et al aimed to tackle the issue of the high dimensionality of genetics data through identification of likely functional coding haplotypes, to develop a model to predict response to methotrexate. They used supervised machine-learning approaches (neural networks, SVM, logistic regression, elastic nets, random forest and boosted trees). The final model consisted of 100 features, 95 of which were genetic (AUC: 0.828, sensitivity=0.6875, specificity=0.8684). Non-genetic selected features were platelet count, hemoglobin levels, duration of morning stiffness and anti-CCP positivity.[181]

Plant et al also demonstrated the superiority of a model containing both biological and clinical data over that of a model containing clinical covariates alone. They used whole blood samples of patients initiating methotrexate at baseline and at 4 weeks and found that genes involved in the type I interferon signaling pathway were differentially expressed in patients with

insufficient response to treatment at baseline and at 4 weeks post-treatment. The model which included gene expression data achieved an AUC of 0.78±0.11 compared to the model with clinical data alone (AUC: 0.63±0.06).[182]

There have also been attempts to combine clinical and biological features to predict response to bDMARDs, namely, TNFi. Guan et al used a Gaussian process regression model trained on a large sample size of 1892 patients and demonstrated improved accuracy of prediction of response to TNFi (adalimumab/etanercept/infliximab) when genetic predictors were added to demographic and clinical data. This model could correctly classify 78% of responder patients. The contribution of SNP biomarkers, however, was relatively small in comparison to clinical predictors used, particularly baseline DAS28, which showed the greatest association with future treatment response.[183] Similarly, Luque-Tévar et al demonstrated the superiority of prediction to TNFi using both clinical data and molecular data, namely, serum inflammatory profile, oxidative stress markers and NETosis-derived biomolecules. Distinct clinical and molecular profiles were identified through LASSO regression/ridge regression, and integration in a mixed model showed an AUC of 0.91.[184]

The integration of various levels of omics data poses an even greater challenge due to the complexity of underlying pathways, co-correlation of covariates and highly dimensional data. Youssef et al conducted a study involving 39 female RA patients who had previously had an inadequate response to methotrexate. The authors analyzed transcriptomics, proteomics and cell phenotypes data generated from PBMCs collected before treatment with TNFi and at 3 months. Various supervised machine-learning models were developed to attempt prediction of non-response. Of all models developed, the linear model based on transcriptomic data at baseline displayed the best ability to predict response to treatment, and this was with a higher degree of accuracy compared to models based on clinical data alone.[185] Tao et al used a combination of transcriptomic signatures from monocytes, CD4+ T cells and PBMCs and DNA methylation profiling from PBMCs to develop models predictive of treatment response to TNFi (adalimumab and etanercept). Similar to Youssef et al, highest overall accuracy (84.7%) was found for the model based on DEGs of PBMCs.[186]

Tasaki et al sought to use a multi-omics approach to molecular signatures associated with long-term remission. They incorporated transcriptomics, proteomics and immunophenotype data, as well as clinical information to explore the effect of drug treatments (methotrexate, infliximab and tocilizumab) at the molecular level. Interestingly, all three drugs had a similar effect at the immune cell-type level; however, they found that treatment with biologic therapies significantly normalized the molecular signature at all three levels towards that of healthy controls. However, a residual signature remained.[187]

Jung et al used a naïve Bayes classifier to investigate predictors of treatment response based on synovial tissue pathotypes. This unsupervised machine-learning approach yielded three RA subtypes based on gene expression data from the synovial tissues of 180 patients. The first two groups (C1 and C2) showed enrichment of fibroblasts and tissue proliferative signaling pathways whereas C3 showed greater activation of immune cells and proinflammatory signaling pathways. These groups showed differences in clinical characteristics and treatment responses to triple DMARDs and infliximab; those in C3, however, were most likely to respond to both treatments.[188]

Despite much progress in the application of machine-learning approaches to predict RA treatment response, there remain hurdles to overcome before they can be implemented in clinical practice. As has been a theme for many omics fields, there is a lack of external validation. There are differences in cohort study designs, including different platforms for omics data, differences in method and timing of measurement of treatment outcomes and clinical data available. Indeed, one can see that many of the studies report moderate to excellent predictive abilities of models used; however, this may be partly a consequence of "overfitting". This is a phenomenon observed when machine-learning algorithms are constructed, and statistical models developed fit exactly to training data, but is rendered inaccurate for new data. This is more likely to occur in models of greater complexity.[189] Furthermore, consideration of ethical issues that could potentially be associated with the advent of artificial intelligence/machine-learning approaches are important to consider. For example, in some machine-learning algorithms the inner workings of the models may be unclear. This is commonly referred to as the "black box" concept.[189] This poses a problem for applications in treatment decision making, as it is paramount that we understand the basis of how such impactful conclusions are reached.

Despite these barriers, with collaboration between large consortia, as well as between data scientists, biologists and rheumatologists, machine-learning methods have shown great promise, and it is hoped further progress will be made in years to come in terms of implementing them in clinical practice.

Future of Personalized Medicine in Rheumatoid Arthritis

Over recent years, advancement of methodologies and substantial investment has led to an explosion of promising potential biomarkers for treatment response in RA. Furthermore, underlying mechanisms of disease and potential disease endotypes are beginning to emerge. However, most potential markers lack validation in independent cohorts and their utility over and beyond clinical predictors and/or seropositivity is unclear. This lack of replication is driven by a combination of factors. A key problem is the preferred outcome measure. Although TJC and VAS capture important information about the impact of the disease on the patient, they likely do not have the same biomarkers as SJC and inflammation. Another confounding factor is non-adherence. Non-adherence correlates with non-response to treatment and therefore non-adherence can result in patient misclassification as non-responders and severely reduce study power.[35] Furthermore, use of different points and other unmeasured confounders may contribute to lack of replication. Lastly, few studies directly compare different drugs, which makes it difficult to ascertain whether a biomarker is prognostic or truly theragnostic. Most studies, to date, have focused on TNFi therapy, perhaps due to TNFi being the first advanced therapy available. Therefore, despite considerable progress, although the customization of therapy for individuals with RA is on the horizon it remains an elusive goal. To overcome these obstacles, development of outcome measures that more closely resemble the underlying biological process of synovitis is required. It is likely that no one biomarker will predict response and future studies should aim to integrate the available data and explore if the developed models are more predictive than clinical predictors alone. Machine learning has demonstrated its ability to integrate large amounts of data; however, further development of machine-learning techniques is required to prevent over-fitting.

Conclusion

In conclusion, research to date has revealed several promising predictive biomarkers that may pave the way to personalized medicine approaches in rheumatoid arthritis. Further work is required to validate and integrate these biomarkers to create a predictive biomarker panel. To personalize therapy, future biomarker studies should look to compare responders to different targeted therapies to identify unique treatment-associated biomarkers.

Disclosure

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