Review article

Using the Immunophenotype to Predict Response to Biologic Drugs in Rheumatoid Arthritis

Ben Mulhearn 1,2,3,*, Anne Barton 2,3, Sebastian Viatte 2

1Manchester Collaborative Centre for Inflammation Research (MCCIR), Division of Infection, Immunity and Respiratory Medicine, School of Biological Sciences, Faculty of Medicine Biology and Health, Manchester Academic Health Science Centre, University of Manchester.

2Centre for Musculoskeletal Research, Division of Musculoskeletal and Dermatological Sciences, School of Medicine, Faculty of Medicine Biology and Health, Manchester Academic Health Science Centre, University of Manchester.

3Kellgren Centre for Rheumatology, NIHR Manchester BRC, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre.

The corresponding author for this manuscript is Dr Ben Mulhearn MRCP PhD, Manchester Collaborative Centre for Inflammation Research (MCCIR), Division of Infection, Immunity and Respiratory Medicine, School of Biological Sciences, Faculty of Medicine Biology and Health, Manchester Academic Health Science Centre, University of Manchester, Great Britain. Email: ben.mulhearn@manchester.ac.uk. Tel: 07803166292

Abstract: Tumor necrosis factor-α is a key mediator of inflammation in rheumatoid arthritis its discovery led to the development of highly successful anti-TNF therapy. Subsequently, other biologic drugs targeting immune pathways, namely interleukin-6 blockade, B cell depletion, and T cell co-stimulation blockade, have been developed. Not all patients respond to a biologic drug leading to a knowledge gap between biologic therapies available and the confident prediction of response. So far, genetic studies have failed to uncover clinically informative biomarkers to predict response. Given that the targets of biologics are immune pathways, immunological study has become all the more pertinent. Furthermore, advances in single cell technology have enabled the characterization of many leucocyte subsets. Studying the blood immunophenotype may therefore define biomarker profiles relevant to each individual patient’s disease and treatment outcome. This review summarizes our current understanding of how immune biomarkers might be able to predict treatment response to biologic drugs.

Keywords: immunology, rheumatoid arthritis, T cells, cytokines, biologic drugs, precision medicine, biomarkers

1. Introduction

Rheumatoid arthritis (RA) is a highly heterogeneous autoimmune disease characterised by inflammation of synovial joints with a prevalence of 0.5 – 1 % and an incidence of 20 – 50 per 100,000 annually [1]. Inflammation in the joints causes stiffness, pain and swelling and may eventually lead to joint destruction due to cartilage and bone destruction. The heterogeneity of RA is becoming clearer as more evidence supports that the diagnosis encompasses a number of genetically related diseases which share joint inflammation as the presenting feature [2].

As a complex disease, subtle differences will also exist in the underlying immunological aetiopathologies. Current treatment strategies are designed to standardize treatment across patient groups which superficially appear similar but might have very different disease processes. Control of inflammation is critically important in the treatment of RA because there is a window of opportunity between the onset of inflammation and the onset of structural joint damage [3]. Structural joint damage leads to permanent disability which is detrimental to both the individual and societally [4]. Personalized medicine aims to break the ‘one size fits all’ approach by tailoring therapy...
to subgroups of individuals with the aim of achieving a higher degree of treatment success from the outset.

The personalized approach will likely involve clinical, genetic, immunological, and hitherto unknown factors to inform treatment choice. Given that all treatments for RA without exception, target the immune system, whether that be by modulating serum cytokine signaling or by altering the cellular landscape, logic dictates that an understanding of the immune landscape before treatment begins should inform the prediction of treatment success or failure. This review aims to summarize our current understanding of how immunology might inform treatment choice in RA.

2. Current biologic therapies available

There are four main classes of biologic drugs available in the United Kingdom, namely TNF inhibition, IL-6 inhibition, co-stimulation blockade and B cell depletion. Newer targeted therapies such as JAK/STAT pathway inhibitors (eg tofacitinib, baricitinib) are not strictly biologic drugs but act through tyrosine kinase inhibition. In practice, as long as there are no contra-indications, the first-choice biologic/targeted therapy is usually the cheapest agent negotiated by the local Clinical Commissioning Group. In the UK, that is still currently anti-TNF biologics, but the situation may change according to cost. Rituximab first line is reserved for those who have lupus cross-over syndrome, Felty’s syndrome, or where anti-TNF is contra-indicated, but it currently remains a second-line agent for use after anti-TNF failure. Although it is recommended that all biologics are prescribed alongside methotrexate or another conventional DMARD, adalimumab, etanercept, certolizumab pegol, and tocilizumab are licensed for use as monotherapy [5]. Figure 1 shows the sites of action of the main biologics used in RA.
Figure 1. Sites of action of the main biologic drugs used in RA. The cartoon represents the synovial membrane compartment with an associated ectopic lymphoid structure. Cytokine pathways are shown by dashed arrow lines. Abatacept works by blocking co-stimulation between DCs and T cells. Rituximab depletes B cells which may present antigen to T cells and produce autoantibodies. Tocilizumab blocks the actions of IL-6 which has many pro-inflammatory effects within the synovium. Anti-TNF blocks the actions of TNF which is able to activate fibroblasts and osteoclasts resulting in joint damage. [B: B cell, CD8: cytotoxic T cell, DC: dendritic cell, ELS: ectopic lymphoid structure, Fb: fibroblast, MΦ: macrophage, Mo: monocyte, T: T cell, Th0: naïve T helper cell, Th1: T helper 1 cell, Th17: T helper 17 cell].
2.1. Anti-TNFs

At present, anti-TNF therapies available include etanercept, adalimumab, infliximab, golimumab, and certolizumab pegol. Broadly, all are equally efficacious as each other, although for reasons not yet fully understood some work better than others on an individual basis. All, except etanercept, are monoclonal antibodies whilst etanercept consists of the TNF receptor fused to an Fc domain of IgG1 which binds free TNF [6]. The formation of anti-drug antibodies (ADAs) are one of the reasons for secondary failure of anti-TNF monoclonal antibody drugs [7,8].

2.2. Tocilizumab

IL-6 was first found to be an important cytokine in RA as it drives the acute phase response causing systemic inflammation including fever, high CRP and fatigue. Tocilizumab, a monoclonal antibody against the IL-6 receptor, blocks the actions of IL-6 and is effective in RA [9]. Tocilizumab monotherapy also reduces radiographic progression of erosions in those with highly active disease [10]. It also improves the anemia of chronic disease found in active RA compared to other biologics, DMARDs, and tofacitinib [11].

2.3. Abatacept

Cytotoxic T-lymphocyte-associated protein 4 (CTLA4) is a potent molecule found on activated T cells and Tregs and binds the co-stimulatory molecules CD80 and CD86 found on antigen-presenting cells (APCs) with greater affinity than their ligand CD28, which is required for T cell receptor (TCR) activation on T cells (reviewed in [12]). The net effect is that naïve T cell activation is abrogated and CD80/CD86 expression on APCs is downregulated. Abatacept, a CTLA4-Fc fusion protein, was found to be efficacious for RA after inadequate response to an anti-TNF in the ATTAIN trial [13]. It is more expensive, although can be used first line where anti-TNF agents might be contraindicated. It appears to cause fewer serious adverse effects including infections than the other biologics as found in a Cochrane review [14].

2.4. Rituximab

Rituximab is an anti-CD20 antibody which depletes B cells and is effective in RA, further supporting a key role for B cells in RA pathogenesis [15]. The REFLEX trial found long lasting response after one course of rituximab in those with inadequate response to one or more anti-TNFs [16]. Rituximab is effective in 70% of seropositive and 48% of seronegative patients [17]. Its main safety consideration is the development of hypogammaglobulinaemia after multiple cycles which can predispose to serious infections [18].

3. Predicting response to biologic drugs

Predicting response to therapy is not currently possible using any meaningful demographic or biological parameters available in clinic. It is however an active area of research and highlighted below are some of the methods research groups have tried to address this problem. There are some promising results, although to date none of these have been translated into clinical practice. This is likely due to a lack of validation across different RA cohorts, low positive predictive values, and the unavailability in clinical practice of some of the biomarkers used such as gene expression profiling or immunological assays.

3.1. Clinical and demographic predictors of response

Baseline characteristics can predict better or poorer treatment outcomes. Response to biologics is associated with male gender and concomitant methotrexate, whereas non-response is associated with smoking and having a high baseline health assessment questionnaire (HAQ) score [19]. A Regression model using clinical predictors of golimumab found that male gender, younger age, lower health assessment questionnaire (HAQ), erythrocyte sedimentation rate (ESR)/C-reactive peptide
(CRP), tender joint count (TJC)/swollen joint count (SJC), and the absence of co-morbidities, could estimate remission rate using 3000 real-world patients [20]. This approach found that those with no comorbidities and lowest inflammation were more likely to respond, therefore not being particularly informative in terms of choosing a particular biologic drug. Machine learning approaches have also been employed to generate treatment response algorithms. Miyoshi et al., (2016) reported that infliximab response could be predicted by using the 9 variables ESR, TJC, albumin, monocyte count, red blood cell number, prednisolone dose, methotrexate dose, HbA1c, and previous biologic exposure with 92 % accuracy [21]. However, these results were not confirmed in other anti-TNF cohorts and infliximab is rarely used in the UK because it has to be given intravenously compared to the subcutaneous route of other anti-TNFs.

3.2. Immunological predictors of response

Interest has grown in identifying immunological biomarkers of treatment response. Methods include proteomic analysis of serum and flow cytometry to analyze panels of cell surface and intracellular markers of peripheral blood mononuclear cells (PBMCs). Synovial tissue and fluid are other sources of identifying biomarkers which may not be found in peripheral blood in the same quantities, given that the joint is the main site of pathology in RA. However, peripheral blood from patients is readily accessible in the clinic and PBMCs can be used in immunological studies and stimulation assays, whereas serum can be used for proteomics. The following section reviews immune biomarkers at baseline which have been reported to predict the response to biologics. Table 1 shows a summary of the main studies investigating immune biomarkers as predictors of treatment response.

| Biomarker                | Drug                  | Ethnicity | Concurrent DMARDs | Response criteria | Predictor of response | N cases | Reference |
|--------------------------|-----------------------|-----------|-------------------|-------------------|-----------------------|---------|-----------|
| Seropositive status      | Anti-TNFs             | Caucasian | 100 %             | DAS ≥ 1.2         | Low ACPA titre predictive of response (PPV 0.95) | 30      | [22]      |
|                          | Infliximab            | Caucasian | 73 %              | EULAR             | Low RF/ACPA titre     | 1195    | [23]      |
|                          |                       | Asian     | 100 %             | ΔCRP              | Low RF titre          | 62      | [24]      |
|                          | Infliximab            | Caucasian | 100 %             | EULAR             | ACPA not associated with response | 42      | [25]      |
|                          |                       | Caucasian | 100 %             | DAS28             | ACPA not associated with response | 31      | [26]      |
|                          |                       | Mixed     | n/a               | DAS28 ACR20 EULAR | Meta-analysis found no association between seropositive status and anti-TNF response | 5561    | [27]      |
| Adalimumab               | Caucasian             | 100 %     | EULAR DAS28 ACR20 | ACPA+             | 245      | [28]      |
|                          | Infliximab            | Asian     | 100 %             | DAS28             | High RF/ACPA titre    | 307     | [29]      |
|                          |                       | Caucasian | n/a               | CDAI              | No association        | 1715    | [30]      |
|                          | Abatacept             | Caucasian | 64.8 %            | EULAR             | ACPA+ (OR 1.9; 1.2-2.9) | 558     | [31]      |
|                          |                       | Caucasian | 100 %             | EULAR DAS28 ACR20 | High ACPA titre       | 252     | [28]      |
| Drug          | Ethnicity | Response Rate | Measure     | Results                                                                 |
|--------------|-----------|---------------|-------------|-------------------------------------------------------------------------|
| Abatacept    | Caucasian | n/a           | Higher continuation of abatacept in seropositive cohorts | 1357 [32]                                                             |
| Abatacept    | Caucasian | n/a           | CDAI        | ACPA+                                                                  | 566 [30]                                                             |
| Abatacept    | Caucasian | 75 %          | Retention rate | Double RF/ACPA+                                                         | 2350 [33]                                                            |
| Rituximab    | Mixed     | n/a           | ACR20       | EULAR                                                                  | Meta-analysis found RF+ associated with treatment response 2103 [34] |
| Rituximab    | Caucasian | n/a           | DAS28       | EULAR                                                                  | Meta-analysis showing seropositive patients respond better to rituximab than seronegative patients 2177 [35] |
| Caucasian    | 74.6 %    | EULAR         | DAS28       | High ACPA titre                                                        | 114 [36]                                                             |
| Tocilizumab  | Mixed     | n/a           | ACR20       | EULAR                                                                  | Meta-analysis found RF+ associated with treatment response [34]     |
| IL-6         | Etanercept| Asian         | n/a         | n/a                                                                    | Increased IL-6 (with low survivin) associated with response (OR 19.7, CI 4.1 – 94.8) 73 [37] |
| Tocilizumab  | Caucasian | 48.6 %        | EULAR       | Increased IL-6 (with low IL-6R) associated with response               | 63 [38]                                                              |
| IL-33        | Rituximab | Caucasian     | 100 %       | EULAR                                                                  | High IL-33 (and ACPA+) associated with response (OR 29.61, CI 1.3 – 674.8) 74 [39] |
| CXCL13       | Anti-TNFs | Caucasian     | 100 %       | EULAR                                                                  | High CXCL13 (and high CXCL10) associated with response (AUC 0.83) 29 [40] |
| Tocilizumab  | Caucasian | 0 %           | ACR         | EULAR                                                                  | High CXCL13 (with low sICAM1) (AUC 0.65) 198 [41]                     |
| CCL19        | Rituximab | Caucasian     | 100 %       | EULAR                                                                  | High CCL19 associated with response (OR 1.43, CI 1.08 – 1.90) 208 [42] |
| B cells      | Anti-TNFs | Caucasian     | 69 %        | EULAR                                                                  | High CD27+ B cells associated with response (RR 4.9, CI 1.3 – 18.6) 21 [43] |
| Abatacept    | Caucasian | 51.2 %        | EULAR       | High CD27+ and/or CD38+ B cells                                        | 43 [44]                                                              |
Rituximab | Caucasian | 100% | EULAR | High CD27⁺ B cells are associated with response | 154 | [45]

CD8⁺ T cells | Etanercept | Caucasian | n/a | EULAR | High apoptotic epitope-specific CD8⁺ T cells associated with response (AUC 0.82) | 16 | [46]

Abatacept | Caucasian | n/a | DAS28 | Low CD28⁻ CD8⁺ T cells associated with response | 32 | [47]

NK cells | Tocilizumab | Caucasian | 60% | DAS28 | Low CD56⁺bright CD16⁻ NK cells associated with response | 20 | [48]

Type I interferon signature | Anti-TNF | Hispanic | 71 – 100% | EULAR | High type I IFN activity associated with response (OR 1.36, CI 1.05 – 3.29) | 35 | [49]

Rituximab | Caucasian | 55% | EULAR | High type I IFN signature negatively associated with response | 20 | [50]

Caucasian | DAS28 | High type I IFN signature negatively associated with response (AUC 0.87) | 26 | [51]

Table outlines the main studies investigating immune biomarkers predicting treatment response in RA. Immune signatures are listed alongside the biologic drug studied, the ethnicity of the patient group, the percentage of the cohort taking concurrent DMARDs, the outcome measure used, the main findings and the sample size. [ACR: American College of Rheumatology. AUC: area under the curve. DAS: disease activity score. EULAR: European League Against Rheumatism. OR: odds ratio].

3.2.2. Serum biomarkers

Many groups have investigated rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA) positivity to predict response to therapy of all biologics. The reports for anti-TNF therapy are either conflicting [22–24,28,29], or did not find a correlation [25,26]. A meta-analysis of 5561 patients also did not find an association between ACPA/RF status and anti-TNF response [27].

Abatacept response appears to correlate with ACPA positivity with an odds ratio (OR) estimated to be between 1.4 and 1.9 in multiple studies [30–32]. The greatest response rates were seen in those with the highest titer of ACPA [28]. One real-world study found double ACPA/RF positivity resulted in higher abatacept retention rates suggesting efficacy of the drug in this multicenter cohort [33].

High titers of ACPA also predicted the best response to rituximab with an OR of 5.1 for good EULAR response [36]. A meta-analysis of 2177 patients confirmed the association between seropositivity and rituximab response, however the effect was modest [35]. Finally, in another meta-analysis, RF status was associated with rituximab and tocilizumab response but not with abatacept [34].
Serum biomarkers are easy to measure and have been extensively researched because biologic drugs have cytokines as their target. Some promising reports are outlined below, although none have been validated in independent cohorts, to date.

IL-6 at baseline is higher in responders to both etanercept and tocilizumab [37,38]. Furthermore, Shi et al. (2017) noted that high serum IL-6 and low serum survivin at baseline was associated with etanercept response with an OR of nearly 20 [37], and Diaz-Torne et al. (2017) found the patients showing the greatest response to tocilizumab had a combination of high serum IL-6 and low serum soluble IL-6 receptor [38].

IL-33 is a Th2 polarizing cytokine and, when detected and added to ACPA status and serum IgG level, predicted 100% of rituximab responders with an OR of almost 30 in one study [39], although this work is yet to be validated in an independent cohort.

Chemokines direct the migration of leucocytes along a concentration gradient and are important to home cells to the sites of inflammation. ROC analysis found that high pre-treatment titers of the serum chemokines CXCL10 and CXCL13 predicted response to adalimumab and etanercept with an area under the curve (AUC) of 0.83 [40]. CCL19 was modestly associated with response to Rituximab with an OR of 1.48 [42]. In an innovative study integrating histopathology of synovial tissue with transcription profiling and serology, Dennis et al. (2014) found that elevated soluble ICAM1 (sICAM1) in the serum was associated with a synovial myeloid cell pathotype and good response to adalimumab, whereas CXCL13 predicted a synovial lymphoid pathotype and correlated with good tocilizumab response [41].

Proteomic approaches have also been tested for all the biologics, and although serum changes are usually seen in responders after treatment has begun, no baseline signature has yet been detected by most [52–54]. Obry et al., (2015) used quantitative mass spectrometry and identified 12 biomarkers which may have the capacity the predict response to etanercept/methotrexate [55]. This study found that S100A9 protein had the largest influence, although these findings might not be specific to anti-TNF treatment.

3.2.3. Adaptive immune cells

Given that the adaptive immune system is thought to be pivotal in the development and perpetuation of autoimmune diseases, investigating these populations in blood and at sites of inflammation could reveal important treatment response biomarkers. There is, however, a lack of consistency in studies on T and B cells in pre-treatment samples for predicting subsequent response.

Baseline high levels of CD27+ memory B cells associated with treatment response to anti-TNFs in one study with a RR of 4.9 [43]. High baseline memory B cells may also be associated with good response to abatacept [44]. For rituximab, increased pre-treatment CD27- B cells (alongside RF positivity and a normal B cell count) was associated with response in one study [45].

Regarding T cells, CD8+ T cells specific for apoptosis-related antigens seen in chronic inflammation were significantly elevated in responders to anti-TNF therapy [46]. Baseline CD8+CD28- T cells were associated with a 4-fold probability of response to abatacept at 6 months [47].

3.2.4. Innate immune cells

Monocytes can be subdivided into three groups according to their expression of CD14 and CD16 [56]. In RA there is an increase in the number of CD16+ monocytes [57]. Chara et al. (2015) found that high pre-treatment levels of CD14+CD16- and CD14+CD16+ monocytes correlated with reduced response to methotrexate [58]. The same group previously showed that these monocyte subsets remain high in non-responders to adalimumab/methotrexate after 3 months of therapy with 86% positive predictive value (PPV) [59]. Monocyte subsets might therefore prove to be an attractive pre-treatment biomarker and further research should aim to uncover if these cell numbers change in response to other treatment regimens.

Another group studied NK cells and found that low CD56briCD16- NK cells at baseline was associated with response to tocilizumab, but not to anti-TNF therapy [48]. CD56dimCD16+ NK cells
showed no association, thereby leading the authors to conclude that there may be a pathogenetic link between patients who respond to anti-IL-6 therapy and their CD56briCD16- NK cells; interestingly, such NK cells are capable of secreting many cytokines including GM-CSF, IFNγ and TNF [60].

3.2.5. Interferon gene signatures

The interferon gene signature refers to type I interferons and includes genes up and down-regulated by interferons -α and -β. It is often measured indirectly by interferon-response gene quantification where a score is then assigned. 50 % of RA patients with established disease have a high type I interferon signature and some hypothesize that these patients may have different underlying mechanisms of disease [61]. A high baseline interferon signature was significantly associated with anti-TNF response [49]. In contrast, detecting a high type I interferon signature may predict reduced response to rituximab [50]. This was supported by a prospective analysis of 14 RA patients commenced on rituximab with further validation in 26 RA patients, with an AUC of 0.87 [51]. Furthermore, prednisolone treatment drives down type I interferon signatures and prediction of rituximab response was therefore highest in the prednisolone-negative group with an AUC of 0.97 [62]. These data suggest that those patients with a high baseline type I interferon signature respond well to anti-TNF and less well to rituximab, which may indicate differences in pathogenesis in the two groups. However, there is significant methodological variability over different studies in detecting the type I interferon signature which mean its use as a clinical biomarker is limited until a standardized approach is developed [63].

3.3. Multiplexed prediction models

It is likely that a combination of demographic, clinical, laboratory markers, genetics, epigenetics, as well as proteomics, functional immunology, and gene expression profiling will be needed to build up a personalized profile to predict treatment response for each individual patient [64,65]. Dennis et al. used a combination of global gene expression, synovial histology and cellular analyses to identify pre-treatment serum biomarkers which predict response to anti-TNF therapy [41]. Based on synovial gene expression they describe the four synovial pathotypes: lymphoid, myeloid, low inflammatory, and fibroid. They observed differences in the number of B cells in each phenotype with high numbers in the lymphoid and myeloid groups and an absence of B cells in the low inflammatory and fibroid groups. Two serum biomarkers were identified which reflected two different synovial phenotypes: sICAM titers reflected the myeloid phenotype and the chemokine CXCL13 reflected the lymphoid phenotype. Finally, the group found that sICAM1highCXCL13low, i.e. the myeloid pathotype, had higher responses to anti-TNF inhibition with adalimumab, whereas sICAM1lowCXCL13high lymphoid pathotype patients had the largest response rates to tocilizumab.

The COMBINE study used multi-omics data (DNA, RNA, proteomics, flow cytometry) to find predictors of anti-TNF response and found that a combination could explain 51 % of the variation in DAS28 with an AUC of 0.815 [66] although such approaches are not currently feasible on a large scale. The findings require independent validation as the model is likely to be over-fitted, having been derived from a single dataset.

As synovial biopsy becomes more readily performed and accepted by patients, transcriptomics of specific cell types is being performed to build up a transcriptional profile of synovial macrophages [67]. It is likely that such cutting edge technologies will be integrated with clinical and immune biomarkers to further develop prediction models, and this is the subject of several on-going studies including the MATURA program in the UK [68] and the Accelerated Medicines Partnership RA/SLE Network in the US [69].

4. Conclusion

New treatments for rheumatoid arthritis and other autoimmune diseases are now targeted towards specific components of the immune system. Whereas monoclonal antibodies are highly specific for their immune targets, small molecule inhibitors (SMIs) such as JAK-STAT inhibitors target intracellular signaling downstream of cytokine receptors [70]. Immune cells have a central role in
autoimmune pathology and, given that they are also targets of these treatments, investigations of immunophenotyping and treatment response are all the more important. The exploration of serum proteins, for example cytokines, has not so far been fruitful in revealing treatment response biomarkers [71]. Other disciplines have utilized functional immunology to identify diagnostic or theranostic biomarkers. For example, the IFNγ-release assay (IGRA) uses tuberculosis antigens to stimulate CD4+ T cells and measures the level of IFNγ release to determine previous tuberculosis exposure [72]. Currently, immunophenotyping is not yet useful in clinical practice to predict response to therapy in any discipline although intense research is ongoing in the fields of oncology [73], hematology [74], rheumatology [75] and transplant medicine [76]. Developing reproducible methods of immune cell phenotyping is therefore crucial to both understanding mechanisms of disease and to discover cellular immune biomarkers to predict treatment response. The future of treatment prediction will likely include a number of cellular and serum biomarkers which may or may not include a functional assay, combined with the recognized clinical predictors of response.

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