Seminars in Arthritis and Rheumatism 73 (2025) 152740

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Personalised treatment of rheumatoid arthritis based on cytokine profiles and synovial tissue signatures: potentials and challenges

Jérôme Avouac [a,*], Jonathan Kay [b], Ernest Choy [c]

[a] Service de Rhumatologie, Hôpital Cochin, AP-HP Centre Université Paris Cité, 27 rue du Faubourg Saint-Jacques, 75014 Paris, France
[b] Division of Rheumatology, Department of Medicine, UMass Memorial Medical Center and UMass Chan Medical School, 119 Belmont Street, Worcester, MA 01605, United States
[c] Rheumatology Section, Division of Infection and Immunity, Cardiff University School of Medicine, Tenovus Building, Heath Park, Cardiff CF14 4XN, Wales, UK

ARTICLE INFO

Keywords:
Biomarkers
Cytokine profile
DMARDs
Personalised treatment
Precision medicine
Rheumatoid arthritis
Synovial biopsies

ABSTRACT

Background: Rheumatoid arthritis (RA) is an autoimmune, chronic inflammatory disease that mainly affects the joints and periarticular soft tissues. Although there have been significant advances in RA treatment over the past two decades, approximately 40% of patients do not respond to first-line biological disease-modifying antirheumatic drugs (bDMARDs). Physicians often use an empirical, trial-and-error approach to select bDMARDs to treat patients with RA. This is inefficient and can be costly for healthcare systems which have limited resources. Unlike in oncology, where molecular pathology helps guide targeted therapies, reliable, predictive biomarkers for drug response in RA are yet to be identified. This narrative review aims to summarise current knowledge on novel biomarkers of disease activity and drug response in RA, with a particular focus on serum cytokine profiles and macrophage and fibroblast subsets in synovial tissue. We also highlight key areas of further research that could advance the development of targeted therapies for patients with RA.
Methods: We searched PubMed to identify studies pertaining to biomarkers of disease activity and drug response in the treatment of RA.
Results: We present a detailed overview of the key studies that have identified serum cytokine profiles and synovial macrophage and fibroblast subsets as novel biomarkers of disease activity and drug response in RA.
Conclusion: A novel, evidence-based approach to precision medicine in RA, which involves tailoring treatment based on cytokine profiles and synovial tissue signatures, shows promise for improving patient care. However, more research is needed to identify biomarkers that predict drug response.

Background

Rheumatoid arthritis (RA) is an autoimmune, chronic inflammatory disease that mainly affects the joints and periarticular soft tissues [1]. Patients with RA have a substantially reduced quality of life [2], impaired physical functioning [3,4] and work capacity [5] and significantly increased mortality [5–9] compared with the general population. In the early stages of RA, joint inflammation presents with pain, stiffness and swelling of joints. However, if left untreated, chronic joint inflammation results in the formation of hypertrophic, inflamed synovial tissue that erodes adjacent joint cartilage and bone [1].

Prompt initiation of treatment with disease-modifying antirheumatic drugs (DMARDs) early in the disease course reduces structural damage, resulting in improved physical function and better long-term outcomes compared with when initiation of therapy is delayed [10,11]. This has led to the concept of an early 'window of opportunity' after diagnosis, during which treatment with DMARDs is more likely to prevent structural damage and disability than treatment initiated later in the disease course [12]. The American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology both endorse a 'treat-to-target' (T2T) strategy as a fundamental approach to the treatment of RA [13]. A key unresolved challenge in the T2T approach is how to select the optimal therapeutic regimen for each patient using an evidence-based approach [13].

Three main categories of DMARDs are used to manage RA. Conventional synthetic DMARDs (csDMARDs) are low molecular-weight,

* Corresponding author: Jérôme Avouac, Service de Rhumatologie, Hôpital Cochin, AP-HP Centre, Université de Paris, 27 rue du Faubourg Saint Jacques, 75014 Paris, France
E-mail addresses: jerome.avouac@aphp.fr (J. Avouac), jonathan.kay@umassmemorial.org (J. Kay), choyeh@cardiff.ac.uk (E. Choy).

https://doi.org/10.1016/j.semarthrit.2025.152740

Available online 29 April 2025

chemically synthesised medications that may alter the course of disease [14]. Methotrexate remains the cornerstone of first-line csDMARD therapy for most patients [15,16]. Biological DMARDs (bDMARDs) are complex proteins produced in living cells with a range of immunosuppressive mechanisms of action, including tumour necrosis factor (TNF) inhibition, interleukin (IL)-6 receptor antagonism, blockade of T-cell co-stimulation and B-cell depletion [1]. Several bDMARDs are fusion proteins but most are monoclonal antibodies. Lastly, targeted synthetic DMARDs (tsDMARDs) are small chemically synthesised molecules, which target a particular aspect of the immune system involved in the pathogenesis of autoimmune diseases, such as inhibition of signal transduction of cytokine receptors by Janus kinases [17].

For bDMARDs that are no longer protected by patent, biosimilars have been approved as effective and safe alternatives to their reference products and are often less expensive than the originator biopharmaceutical [18]. The use of lower-cost biosimilars could benefit patients with RA by improving equity of access to bDMARDs, thereby facilitating earlier use of bDMARDs with earlier control of disease activity [19]. However, despite the major advances in RA treatment over the last two decades, and strong evidence that earlier, more aggressive pharmacological therapy improves outcomes compared with those achieved using standard care [20,21], approximately 40% of patients do not respond to the initial bDMARD [22,23]. In addition, Hyrich at al. [23] reported that 13% of patients who switched to a second bDMARD discontinued treatment because of inefficacy, and 14% discontinued because of an adverse event. Furthermore, around 5% of patients do not respond to treatment with at least three different classes of bDMARDs because of inefficacy and/or toxicity [22,23]. The current empirical trial-and-error approach employed by physicians after a patient with RA does not respond or is intolerant to first-line methotrexate is inefficient and associated with a huge cost burden in the USA, approaching $US17 billion per year [24].

The mechanisms underlying inadequate response to bDMARDs are yet to be fully elucidated, although several factors have been implicated including female sex, older age (>55 years), obesity, current or past smoking status, poor functional status (Health Assessment Questionnaire >2), high disease activity (Disease Activity Score using a 28-joint count [DAS28] ≥3.2) and elevated erythrocyte sedimentation rate (ESR; >20 mm/h) [25–27]. In addition, it is well known that the formation of anti-drug antibodies can lead to neutralisation of bDMARDs and to subtherapeutic serum drug levels [28–30]. Inter-patient differences in the role of the innate versus adaptive immune system in the pathogenesis of RA have also been suggested to explain variability in bDMARD efficacy [22]. The use of combinations of bDMARDs resulted in significant improvement in Patient Global Impression of Change scores in 50% of treated patients with immune-mediated inflammatory diseases, including RA (but predominantly inflammatory bowel disease and axial spondyloarthritis) [31]. However, unlike in oncology, where molecular pathology is routinely used to guide the administration of targeted therapies [32,33], there are no predictive biomarkers of drug response in RA.

In this narrative review, we provide an overview of studies that aimed to identify novel biomarkers to guide the selection of targeted therapies for patients with RA. We also discuss the novel paradigm of precision medicine in RA involving targeted treatment based on cytokine profiles and synovial tissue signatures.

Biomarkers of disease activity and severity in current clinical practice and their limitations

T2T strategies require physicians to assess RA disease activity in a quantitative manner. Validated measures of disease activity include the Simplified Disease Activity Index (SDAI) and the DAS28 indices, each of which incorporates the acute phase reactants ESR or C-reactive protein (CRP) [34]. To use either of these disease activity measures, a patient must have blood drawn and assayed for the acute phase reactant before their clinic visit. In a study of 223 patients with RA reporting knee arthralgia, Orr et al. [35] reported statistically significant positive correlations between CRP, ESR, and DAS28-CRP and the degree of synovial inflammation. However, an important limitation when using ESR or CRP as an individual biomarker of disease activity is that both have been found to be within the normal range in up to 58% of patients with RA and active joint inflammation [35–37]. The Clinical Disease Activity Index (CDAI) is more often used in clinical practice because it does not include an acute-phase reactant [34,38]. Another important measure of disease activity is power Doppler ultrasonography (PDUS), which can detect subclinical synovitis not identified by routine clinical or laboratory assessments [39]. Kawashiri et al. [40] showed that PDUS scores from 24 synovial sites in 22 patients with RA were correlated positively and significantly with DAS28, SDAI, CDAI and serum angiogenic factors. PDUS scores were also correlated with levels of the angiogenic markers Tie-2 mRNA, soluble vascular cell adhesion molecule-1 and angiostatin in another study conducted in 125 patients with established RA [41]. Imaging studies, such as plain radiographs and magnetic resonance imaging, are biomarkers of RA disease severity. Radiographic assessment, employing the van der Heijde or Genant modifications of the Sharp score, or other radiographic scores, such as the Larsen or Ratingen score, is a well-established method of measuring progression of structural damage [42]. Magnetic resonance imaging is used in clinical trials to predict the effect of drug therapy on the development of erosions but is not widely used for this purpose in clinical practice.

Calprotectin, a member of the S100 protein family, has been implicated in the pathogenesis of RA [43]. A 2015 systematic review of the utility of calprotectin as an indicator of disease activity reported that this protein was a significant and independent predictor of therapeutic response and progression of structural damage, particularly in patients who achieved responses to bDMARD treatment [44]. Several studies have found calprotectin levels to correlate with CRP levels [45,46], ultrasound global scores, PDUS and synovial hypertrophy and therefore have potential applicability as a good biomarker of disease activity in RA [47–50]. Standardisation of laboratory measurement and additional well-designed studies are needed to fully validate calprotectin as an RA biomarker before it can be used in routine clinical practice [44]. Other potential biomarkers of disease activity include angiogenic markers, particularly TIE2, a surrogate of active synovitis [41], and semaphorins, which have been shown to correlate with validated markers of inflammation and angiogenesis [51].

The fundamental importance of proinflammatory cytokines, such as TNFα and IL-6, in the pathogenesis of RA is well established [52–54]. An overview of key cytokines implicated in the pathogenesis of RA is presented in Table 1. The applicability of cytokines as biomarkers of disease activity in RA is a promising avenue of research. Alex et al. [55] assessed the utility of cytokine scores based on array data to identify active joint disease in 1467 patients with RA. 'Discordant' patients (high tender and/or swollen joint counts with normal ESR and CRP levels) were stratified into low, medium and high disease activity groups. Overall, cytokine scores did not differ between the three subgroups, indicating that these scores did not differentiate between levels of disease activity in patients with RA and normal acute-phase reactant levels. Dissanayake et al. [56] quantified cytokine expression (TNF-α, IL-1β, IL-10 and IL-17A) in peripheral blood mononuclear cells (PBMCs) from patients with active RA and from healthy controls using the enzyme-linked immunosorbent spot assay and assessed the association between cytokine levels and RA disease activity indices. The number of PBMCs that secreted IL-17A was significantly higher in DMARD-naïve patients with early RA than in healthy controls, but not in patients with established disease. The number of PBMCs secreting IL-17A also correlated moderately with five clinical measures of disease activity (DAS28, CDAI, joint pain-visual analogue scale, swollen and tender joint counts). In multivariate linear regression models, IL-17A was an important predictor of both DAS-28 and CDAI, suggesting that IL-17A has potential applicability as a biomarker of disease activity in RA.

Table 1
Cytokines implicated in rheumatoid arthritis pathogenesis [52–54,137].

Immunoregulatory cytokines
IL-10
TGFβ
IL-2
Proinflammatory cytokines
GM-CSF
IFN-γ
IL-1α/β
IL-6
IL-8
IL-12
IL-17A/F
IL-18
IL-21
IL-22
IL-23
TNFα
Regulators of angiogenesis
TIE-2
VCAM-1
VEGF

GM-CSF: granulocyte macrophage-colony stimulating factor, IFN: interferon, IL: interleukin, RA: rheumatoid arthritis, TGF: transforming growth factor, TIE-2: TEK receptor tyrosine kinase, TNF: tumour necrosis factor, VCAM: vascular cell adhesion molecule, VEGF: vascular endothelial growth factor.

The multi-biomarker disease activity (MBDA) test measures 12 serum biomarkers relevant to the pathophysiology of RA: CRP, epidermal growth factor, IL-6, leptin, matrix metalloproteinase (MMP)-1, MMP3, resistin, serum amyloid A, TNF receptor type I, vascular cell adhesion molecule 1, vascular endothelial growth factor A and cartilage glycoprotein. Using a validated proprietary algorithm, biomarker concentrations are combined to generate a score ranging between 1 and 100 [57–59]. The MBDA score correlated with DAS28-CRP and other clinical measures of RA disease activity, including CDAI and the Health Assessment Questionnaire Disability Index in patients treated with TNF inhibitors (TNFis) [58,60,61]. However, the MBDA score reflects not only disease activity but also the mechanism of action of the medications used to treat the disease. Thus, despite very similar improvements in DAS28-CRP and other measures of disease activity (CDAI, SDAI and Routine Assessment of Patient Index Data 3) over 2 years among patients enrolled in the Abatacept vs Adalimumab Comparison in Biologic-Naïve RA Subjects with Background Methotrexate (AMPLE) trial, there was marked discordance between the mean change (improvement) in MBDA score from baseline over 2 years when patients treated with the T-cell co-stimulation modulator abatacept were compared with those treated with the TNFi adalimumab [62]. Although the change in MBDA scores reflected improvement in disease activity among patients treated with either abatacept or adalimumab in the AMPLE trial, the influence of the mechanism of action of a specific medication on the MBDA score does not allow use of this score to compare response of disease activity to different medications in a clinical trial. Overall, the MBDA data reflected the different mechanisms of action of the two drugs, which the other disease activity indices were not sensitive enough to detect. However, the MBDA can be used to support assessment of biosimilarity of a biosimilar candidate to its reference product, which both share the same mechanism of action [63].

In another study, correlations of the MBDA with DAS28-CRP and agreement with low/moderate/high disease activity categories decreased over 24 weeks of treatment with tocilizumab, a monoclonal antibody targeted to the IL-6 receptor (IL-6R) [64]. These findings can be explained by the direct inhibition of CRP production by tocilizumab [65–67]. Thus, any disease activity measure that includes CRP (SDAI, DAS28-CRP or MBDA) will not accurately reflect changes in disease activity in patients treated with tocilizumab (or other IL-6R-targeted drugs).

Biomarkers of treatment response

Precision medicine in RA aims to use biomarkers and cellular/molecular pathways to stratify patients according to the likelihood of clinical response to DMARD therapy before treatment, paving the way for targeted treatment of RA and improved outcomes [68–70]. An important consideration in evaluating cytokine profiles as biomarkers of treatment response is the accuracy and reliability of measurements of cytokine levels in the serum, plasma and PBMC preparations [71–73]. A key limitation when quantifying serum cytokine levels is that cytokines often circulate as proteins bound to soluble receptors, inhibitors or carrier proteins, which may mask their detection by enzyme-linked immunosorbent assay (ELISA) or radioimmunoassay methodologies [74–76]. Furthermore, many cytokines are virtually undetectable in serum because they are produced locally and have a very short half-life. For example, the half-life of TNFα is 18.2 min [77]. Other cytokines have highly regulated and temporally orchestrated patterns of secretion [78]. A good example of this is the pleiotropic cytokine IL-6, which is secreted in a biphasic circadian pattern with two nadirs at about 08.00 and 21.00 hours and two zeniths at about 19.00 and 05.00 hours [79]. Further limitations include data variability across different methodologies [80]. An additional unresolved issue is the optimal timing of these analyses. It is well known that the majority of bDMARDs, particularly TNFis, induce rapid improvement at both a clinical and molecular level as early as 48 hours to 4 weeks after treatment initiation [81,82]. Thus, cytokine profiles probably should be evaluated early in the course of treatment during the 'window of opportunity' mentioned in Section 1 [12].

Given the central role of proinflammatory cytokines in the pathogenesis of RA [53,54], a reasonable hypothesis is that variability in expression of disease-associated cytokine pathways could account, at least in part, for the variability in clinical response to bDMARDs. To date, the few studies that have tested this hypothesis have produced only weak supporting evidence. An analysis of biomarker samples and clinical data from five phase III trials of tocilizumab found that baseline serum IL-6 levels were significantly, albeit weakly, associated with subsequent treatment response to tocilizumab. In addition, none of the tested single-nucleotide polymorphisms (SNPs) in IL-6 or IL-6R showed an association with treatment response to tocilizumab [83]. Osiri et al. [84] reported the results of a study in which serum samples from a cohort of 81 patients with long-standing RA treated with combined csDMARDs (methotrexate and at least one other csDMARD) or a bDMARD were measured for 12 cytokines. Overall, weak correlations between cytokine levels and RA disease activity were observed; the

highest correlation coefficients observed were with levels of IL-6, IL-33 and IL-8. Boyapati et al. [85] carried out a post hoc analysis of two phase III studies (MONARCH and MOBILITY) to investigate whether baseline IL-6 levels were predictive of sarilumab treatment responses. In MONARCH, the magnitude of clinical improvement with sarilumab versus adalimumab was greater in patients with high baseline IL-6 levels (defined as ≥3 times the upper limit of normal) than in those with low IL-6 levels. In MOBILITY, compared with patients with low IL-6 levels, patients with high IL-6 levels exhibited greater clinical improvement when treated with sarilumab plus methotrexate than with placebo plus methotrexate. In another post hoc analysis of MONARCH trial data, Strand et al. [86] evaluated the potential of baseline IL-6 levels to differentially predict health-related quality of life improvements with sarilumab versus adalimumab. Patients with high baseline IL-6 levels reported better improvements in health-related quality of life with sarilumab versus adalimumab than did patients with low IL-6 levels. In summary, some evidence indicates that patients with high IL-6 levels are more likely to benefit from sarilumab compared with adalimumab or methotrexate than are patients with low IL-6 levels. However, so far, the search for novel biomarkers of treatment response in peripheral blood or serum has been largely unsuccessful [87].

A recent study compared serum cytokine profiles (TNFα, IL-1β, IL-17, IL-6, interferon [IFN]-γ and IL-10) between methotrexate-treated and methotrexate-naïve patient groups using ELISA. The authors found that the methotrexate-treated group had significantly reduced serum levels of TNFα, IL-17 and IFNγ compared with the methotrexate-naïve group, consistent with the known anti-inflammatory effect of methotrexate in patients with RA [88].

Using Luminex technology and analysis of 17 potential biomarkers, Lesturgie-Talarek et al. [89] found that patients with RA (active [DAS28 >3.2] refractory [resistance to ≥2 lines of targeted therapy], active non-refractory or non-active [DAS28 ≤3.2]) demonstrated a proinflammatory and proangiogenic profile compared with controls. However, the serum profile observed in active refractory RA closely resembled that seen in active non-refractory RA. Patients with active refractory RA exhibited a poor correlation profile, with only three associations between biomarkers and disease activity markers. In contrast, a rich correlation profile was detected in patients with active non-refractory RA, with positive correlations between CRP levels and 10 circulating biomarkers and between the DAS28 and eight circulating biomarkers.

Several multiplex immunoassay approaches have been developed for serum biomarker discovery, including high-performance electrochemiluminescence [90], Luminex's xMAP® Technology [91], the Proximity Extension Assay (Olink) method [92], the SomaLogic SOMAscan assay [93] and the CRISPR/Cas (Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-associated proteins) biosensing technology [94]. It remains to be determined which of these approaches is optimal for cytokine profiling in RA.

Molecular biomarkers

Autoantibodies against citrullinated peptides (ACPA) and rheumatoid factor (RF) appear years before the onset of RA [95–97] and are used as diagnostic and prognostic biomarkers in this disease [98]. The existence of these autoantibodies led researchers to explore B cells as a potential therapeutic target in RA. The efficacy of B-cell depletion therapy (BCDT) in treating RA highlighted the important role of B cells in the disease process [99,100]. Further studies revealed that patients who are seropositive for ACPA or RF tend to respond better to BCDT with rituximab [101–103] compared to those who are seronegative, suggesting that these autoantibodies could be useful prognostic biomarkers for guiding treatment decisions [104,105].

In a study of 138 seropositive patients with RA undergoing rituximab treatment, Ferraccioli et al. [106] found that a higher percentage of patients who achieved a good response according to the European Alliance of Associations for Rheumatology (EULAR) response criteria tested positive for 3 to 5 of the autoantibodies studied (which included immunoglobulin [Ig]M-RF, IgA-RF, IgG-RF, IgG-ACPA, IgA-ACPA, IgM-ACPA, and anti-mutated citrullinated vimentin) compared to non-responders (84.8% vs 46.7%; $p < 0.001$). Logistic regression analysis revealed that factors such as the absence of corticosteroid therapy, a lymphocyte count below 1875/μL, RF-IgG levels above 52.1 IU/mL, and B-cell activating factor (BAFF) levels below 1011 pg/mL were independent predictors of a good EULAR response to rituximab. Adlowitz et al. [107] conducted a longitudinal study on RA patients undergoing rituximab therapy to better understand the factors affecting B-cell depletion and reconstitution and to identify biomarkers predicting treatment response. Their study found that B-cell TNF production decreased after BCDT and B-cell reconstitution. The presence of activated memory B-cells after treatment correlated with a poor clinical response, while a higher ratio of transitional (naïve) to activated memory B-cells was associated with better outcomes. These findings suggest that the success of BCDT depends on the balance between protective and pathogenic B-cell subsets after treatment and B-cell reconstitution. Further research is needed to fully understand the mechanisms and biomarkers involved in response to BCDT for RA patients.

Chemokines play a key role in the pathogenesis of RA and may serve as potential biomarkers for predicting treatment response [108]. One study by Sellam et al. [109] found that C—C Motif Chemokine Ligand 19 (CCL19) levels could predict a RA patient's response to rituximab. However, this relationship was not significant after adjusting for autoantibody status. Other studies have shown that C-X-C motif chemokine ligand (CXCL) 13 (CXCL13) levels are associated with the response to TNFi in RA [110–112]. Additionally, a small study of 25 RA patients found that higher serum CXCL10 levels were associated with a better response to abatacept [113].

Dennis et al. [114] identified four major cell phenotypes in the RA synovium: lymphoid, myeloid, low inflammatory and fibroid. Each of these phenotypes has a unique chemokine gene expression signature. High baseline serum intercellular adhesion molecule 1 (sICAM1) levels were associated with the myeloid phenotype, while high baseline CXCL13 levels were associated with the lymphoid phenotype. The study also found that high sICAM1 with low CXCL13 levels predicted a better response to adalimumab, whereas low sICAM1 and high CXCL13 levels were associated with a better response to tocilizumab. Similarly, Zhao et al. [115] found that RA patients with high baseline sICAM1 levels had a significantly higher rate of response to TNFi therapy compared to those with low sICAM1 levels. They also found that sICAM-1 was an independent predictor of TNFi response in patients who responded inadequately to treatment with csDMARDs. However, these results were not consistent with other studies that found no relationship between baseline serum CXCL13 levels and TNFi response [115]. A systematic review examining CXCL13 as a biomarker for disease activity and treatment response in RA revealed conflicting evidence regarding its role in predicting treatment outcomes with bDMARDs [116]. In conclusion, while there is interest in using chemokines as a biomarkers for treatment response in RA, there is insufficient robust evidence to support their routine clinical use at this time.

PrismRA is a blood-based, molecular signature response classifier (MSRC) test that predicts inadequate response to TNFi therapy in bDMARD-naïve patients. It combines a patient's unique molecular signature derived from 23 biomarkers involved in RA pathobiology (10 SNPs, eight transcripts, two laboratory tests [CRP and ACPA] and three clinical metrics [sex, body mass index and patient disease assessment]) [117]. The MSRC test was validated clinically in blood samples from 391 bDMARD-naïve and 113 TNFi-exposed patients with RA. Patients with an MSRC signal of TNFi inadequate response (based on ACR criteria improvement from baseline of 50%) showed a 4.1-fold lower likelihood of responding adequately to TNFi therapy (95% confidence interval 2.0–8.3; $p = 0.0001$) [118]. Further work by Strand and colleagues showed that the responses to non-TNFi therapies of patients with a

molecular signature indicating TNFi inadequate response were significantly better than their responses to TNFis [119,120]. Overall, these data suggest that the MSRC can stratify patients according to likelihood of inadequate response to TNFi therapy, thereby providing patient-specific data to guide choice of treatment for both bDMARD--naïve and TNFi-exposed patients [118].

Novel synovial molecular signatures and effector cell states as predictors of treatment response

The development of clinical synovitis is widely accepted as one of the hallmarks of early-stage RA [1,121]. In recent years, investigators have turned to ultrasound-guided synovial biopsy techniques combined with transcriptomics to identify novel molecular signatures and effector cell states implicated in disease pathogenesis and treatment response. The key studies that have defined the field are summarised in Table 2.

Immune cell targets in the synovium

Zhang et al. [122] applied single-cell RNA sequencing (scRNA-seq), bulk RNA-seq, mass cytometry and flow cytometry to T cells, B cells, monocytes and fibroblasts from 51 samples of synovial tissue from patients with RA and osteoarthritis (OA). These analyses revealed the existence of expanded immune cell populations in RA synovia that are potentially key mediators of joint inflammation in RA: THY1+ HLA--DRA^{hi} sublining fibroblasts, IL1B+ proinflammatory monocytes, ITGAX+TBX21+ autoimmune-associated B cells and PDCD1+ peripheral T helper (Th) cells and follicular Th cells.

Alivernini et al. [123] used scRNA-seq to profile synovial tissue macrophages (STMs) (which had been previously shown to persist in patients in remission [124] in patients with early RA, patients with treatment-refractory RA and those in sustained remission. These analyses revealed two STM subpopulations (MerTK+TREM2^{high} and MerTK+LYVE1+) predominant in the synovium of patients who experienced disease remission. These STMs contained unique remission transcriptomic signatures enriched for negative regulators of inflammation. In addition, they induced the repair response of synovial fibroblasts in vitro. These findings suggest that therapeutic enhancement of MerTK+ STM-mediated synovial homeostasis could be a potential approach towards achieving sustained remission of disease activity.

Wang et al. [125] showed that, compared with nonresponders, responders to TNFis are characterised by baseline activation of inflammatory pathways in synovial tissue, including chemokine signalling, Th1/Th2 cell differentiation and Toll-like receptor signalling. In addition, lymphocyte, myeloid and fibroblast cell populations were elevated in the synovial tissue of responders relative to nonresponders. Overall, these data suggest that responders to TNFi therapies are characterised at baseline by activation of immune pathways.

Synovial fibroblast subsets. Zhang et al. [126] profiled the full spectrum of cells in 82 inflamed synovial tissue samples from 79 patients with RA ($n = 70$) or OA ($n = 9$) using multi-modal scRNA-seq and surface protein data. With this information, they developed a comprehensive single-cell atlas of RA synovial tissue. The tissues were stratified into six groups, each characterised by diverse selectively enriched cell states, that were associated with disease-relevant cell states, cytokines, risk genes, and histology and serology metrics, which could be used to predict treatment response.

Mizoguchi et al. [127] identified functional and transcriptional differences between fibroblast subsets from human synovial tissues using scRNA-seq and bulk RNA-seq techniques. One fibroblast subset, characterised by the expression of podoplanin, THY1 membrane glycoprotein and cadherin-11, was three-fold enriched in the synovium of patients with RA relative to patients with OA. These fibroblasts localised to the perivascular zone in inflamed synovium, secreted proinflammatory cytokines, and had an in vitro phenotype characteristic of

Table 2
Summary of synovial biomarker studies (ordered by year of publication).

Authors	Objectives	Sample size, n	Key findings
Mizoguchi et al. 2018 [127]	To determine the functional and transcriptional characteristics of synovial fibroblast subsets in RA	4	A fibroblast subset characterised by the expression of podoplanin, THY1 membrane glycoprotein and cadherin-11 was three-fold expanded in the synovium of patients with RA relative to the synovium of patients with OA
Croft et al. 2019 [128]	To use scRNA-seq to identify distinct subsets of synovial fibroblasts responsible for mediating inflammation or tissue damage in the pathogenesis of RA	20	FAPα+ THY1+ fibroblasts were expanded in the synovium of patients with RA compared with the synovium of patients with OA
Zhang et al. 2019 [122]	To define the cell populations that drive joint inflammation in RA using scRNA-seq and mass cytometry in samples of synovial tissue from patients with RA or OA	51	Expanded cell populations exist in RA synovia that are potentially key mediators of joint inflammation in RA: THY1+ HLA-DRA^{hi} sublining fibroblasts, IL-1B+ proinflammatory monocytes, ITGAX+ TBX21+ autoimmune-associated B cells and PDCD1+ peripheral Th cells and follicular Th cells
Alivernini et al. 2020 [123]	To use scRNA-seq to explore the phenotypic and functional changes in STM subpopulations in patients with early/active RA, treatment-refractory/ active RA and RA in sustained remission	122	Two STM subpopulations (MerTK+ TREM2^{high} and MerTK+ LYVE1+) predominant in the synovium of patients who achieved disease remission. These STMs contained unique remission transcriptomic signatures enriched for negative regulators of inflammation
Wei et al. 2020 [129]	To elucidate the transcriptional gradient that encodes synovial fibroblast identity and RA pathology	12	NOTCH3 and *Notch* target genes are markedly upregulated in synovial fibroblasts in active RA. In a mouse model of inflammatory arthritis, genetic deletion of the *Notch3* gene *or* monoclonal antibody-blockade of NOTCH3 signalling attenuated inflammation and prevented joint damage in inflammatory arthritis
Humby et al. 2021 [132]	To compare the effect of tocilizumab with rituximab in patients with RA who had an inadequate response to TNFi therapy stratified for synovial B-cell status (B-cell poor or rich)	164	In patients with synovial biopsies classified as B-cell poor with RNA sequencing, the tocilizumab group had a significantly higher response rate (CDAI ≥50% improvement) than the rituximab group
Korsunsky et al. 2022 [131]	To profile fibroblasts derived from inflamed and non-inflamed synovium, intestine, lungs and salivary glands from individuals with RA,	74	Two clusters of proinflammatory fibroblast phenotypes were common to RA, IBD, ILD and Sjögren's syndrome: CXCL10+

(*continued on next page*)

Table 2 (*continued*)

Authors	Objectives	Sample size, n	Key findings
	IBD, ILD and Sjögren's syndrome, respectively, using scRNA-seq		CCL19+ immune-interacting and SPARC+ COL3A1+ vascular-interacting fibroblasts
Rivellese et al. 2022 [133]	To investigate the mechanisms of response and inadequate response to rituximab and tocilizumab via histopathological and RNA-seq characterisation of synovial tissue at baseline and longitudinally in post-treatment biopsies at 16 weeks	164	Molecular predictors of treatment response to each individual therapy were identified, together with a refractory stromal/fibroblast signature associated with resistance to both therapies
Wang et al. 2022 [125]	To understand the mechanistic basis of response to TNFi therapy and to determine whether transcriptomic changes in the synovium are reflected in peripheral protein markers	46	Compared with nonresponders to TNFis, responders are characterised by baseline activation of synovial tissue inflammatory pathways, including chemokine signalling, Th1/Th2 cell differentiation and Toll-like receptor signalling. In addition, lymphocyte, myeloid and fibroblast cell populations were elevated in the synovial tissue of responders relative to nonresponders
Rivellese et al. 2023 [134]	A biopsy-driven trial to compare the response to rituximab, etanercept and tocilizumab in biologic-naïve patients with RA stratified for synovial B-cell status	226	The synovial B-cell-poor group did not have a significantly lower response to rituximab vs etanercept and tocilizumab, and therefore the dichotomous classification of synovial B-cell status did not predict treatment response to B-cell depletion with rituximab in bDMARD-naïve patients
Zhang et al. 2023 [126]	To provide a more granular understanding of cell states and synovial phenotypes in inflamed joints by profiling the full spectrum of cells in inflamed synovium from patients with RA using multi-modal scRNA-seq and surface protein data to develop a comprehensive single-cell atlas of RA synovial tissue	82	The tissues were stratified into six groups, each characterised by selectively enriched cell states. The groups demonstrated the diversity of synovial inflammation in RA, with samples showing enrichment for T and B cells and others largely lacking lymphocytes. Each group was associated with disease-relevant cell states, cytokines, risk genes, histology and serology metrics. The groups were dynamic and could be used to predict treatment response
Zou et al. 2024 [130]	To show that the transcription factor Arid5b is involved in the differential programming of pathologic synovial fibroblast phenotypes in RA	NR	Arid5b played a dual role by both inhibiting fibroblast inflammatory activation and enhancing invasiveness

bDMARD: biologic disease-modifying antirheumatic drug, CCL19: chemokine (C—C motif) ligand 19, CDAI: Clinical Disease Activity Index, COL3A1: collagen type III alpha 1 chain, CXCL10: C-X-C motif chemokine ligand 10, FAP: fibroblast activation protein alpha, HLA-DRA: human leukocyte antigen, DR alpha chain, IBD: inflammatory bowel disease, IL: interleukin, ILD: interstitial lung disease, ITGAX: integrin subunit alpha X, LYVE1: lymphatic vessel endothelial hyaluronan receptor 1, MERTK: MER proto-oncogene: tyrosine kinase, NOTCH: neurogenic locus notch homolog protein, NR, not reported; OA: osteoarthritis, PDCD1: programmed cell death 1, RA: rheumatoid arthritis, RNA-seq: RNA sequencing, scRNA-seq: single-cell RNA sequencing, SPARC: secreted protein acidic and rich in cysteine, STM: synovial tissue macrophage, TBX21: T-box transcription factor 21, Th: T helper, TNFi: tumour necrosis factor inhibitor, THY1: Thy-1 cell surface antigen, TREM2: triggering receptor expressed on myeloid cells 2.

proliferative and invasive cells, similar to those of pannus tissue.

Croft et al. [128] used scRNA-seq in synovial biopsies from patients with RA and murine models of arthritis to identify two anatomically and functionally distinct fibroblast subsets within the fibroblast activation protein-α (FAPα)+ population: FAPα+THY1+ immune effector fibroblasts located in the synovial sublining and FAPα+THY1- destructive fibroblasts restricted to the synovial lining layer. FAPα+ THY1+ fibroblasts had an immune effector profile with high expression of chemokines and cytokines, including IL-6, IL-33 and IL-34. In contrast, FAPα+ THY1-expressing fibroblasts expressed high levels of chemokine ligand 9 (CCL9) and TNF superfamily member 11, both potent inducers of osteoclast activity, as well as MMP3, MMP9 and MMP13, MMPs involved in cartilage degradation. Consistent with these findings, the authors identified an expanded population of FAPα+ THY1+ immune effector fibroblasts in the synovium of patients with RA and persistently inflamed joints, compared with the synovium of patients with OA. These findings suggest that the development of therapies that selectively target downregulation of FAPα+ THY1+ immune effector fibroblasts might be a promising approach to treating RA

Using scRNA-seq, Wei et al. [129] found that NOTCH3 and Notch target genes are markedly upregulated in synovial fibroblasts in active RA. In a mouse model of inflammatory arthritis, the authors showed that genetic deletion of *Notch3* or monoclonal antibody blockade of NOTCH3 signalling attenuated inflammation and prevented joint damage in inflammatory arthritis. These results identify NOTCH3 as a critical receptor in synovial fibroblast differentiation and pathologic expansion in RA and suggest NOTCH3 signalling as a potential therapeutic target in the treatment of RA. Using scRNA-seq and bulk RNA-seq, Zou et al. [130] identified that the transcription factor Arid5b was also involved in synovial fibroblast RA pathology; it played a dual role by both inhibiting fibroblast inflammatory activation and enhancing invasiveness.

Korsunsky et al. [131] used scRNA-seq to profile fibroblasts from the inflamed synovium, intestine, lungs and salivary glands of individuals with RA, inflammatory bowel disease, interstitial lung disease and Sjögren's syndrome, respectively. The authors found two clusters of proinflammatory fibroblast phenotypes that were common to all four chronic inflammatory diseases: C-X-C motif chemokine ligand 10 (CXCL10+) CCL19+ immune-interacting and SPARC+ COL3A1+ vascular-interacting fibroblasts. In the context of RA, it will be important to study how these fibroblast populations respond to DMARD-based therapy.

Synovial molecular biomarkers. In the R4RA randomised controlled trial of patients with RA who had responded inadequately to at least one TNFi, a low or absent synovial B-cell molecular signature was associated with a lower response rate to BCDT with rituximab compared with IL-6R inhibition by tocilizumab. However, it is important to note that the trial did not reach its primary endpoint (statistically significant difference of at least a 50% improvement in CDAI at Week 16) [132]. Further, detailed molecular analysis of the same synovial biopsies by Rivellese et al. [133] identified molecular predictors of treatment response to

each individual therapy, together with a refractory stromal/fibroblast signature associated with resistance to both rituximab and tocilizumab. This landmark study supports the idea that diverse molecular pathology pathways may account for the heterogeneity of observed clinical and treatment-response RA phenotypes. The authors highlighted the importance of integrating synovial molecular pathology signatures into existing clinical algorithms to optimise the selection of targeted therapies and to inform the development of new drugs for patients with RA who are refractory to existing therapies.

Rivellese et al. [134] carried out the STRAP (Stratification of Biological Therapies for RA by Pathobiology) and STRAP-EU phase III clinical trials in bDMARD-naïve patients who responded inadequately to csDMARDs. In these open-label, biopsy-driven trials, B-cell-poor and -rich patients, based on the B-cell molecular signature identified in the R4RA trial discussed above, were randomly assigned to receive rituximab, tocilizumab or etanercept (TNFi). These trials aimed to determine whether BCDT with rituximab would be associated with a worse response than that with etanercept and tocilizumab (as assessed by the primary endpoint: ACR criteria improvement from baseline of 20% at Week 16) in patients who were synovial B-cell poor. However, as with the R4RA trial [132], the primary endpoint was not reached, indicating that the synovial B-cell-poor group did not have a significantly lower response to rituximab than to etanercept or tocilizumab. Thus, the dichotomous classification of synovial B-cell status did not predict treatment response to B-cell depletion with rituximab in bDMARD-naïve patients.

Future perspectives

Predictive biomarkers of drug response in RA that can be used in routine clinical practice are yet to be identified. The clinical heterogeneity of disease manifestations and the variability among RA patients in their response to b/tsDMARDs may be related to variability in the expression of immunopathogenic cytokines and of synovial molecular signatures, predominantly of fibroblasts and B cells. A new precision medicine paradigm targeting specific cytokine profiles and subsets of fibroblasts and macrophages that modulate synovial tissue inflammation is needed. Clinical trials comparing the efficacy and safety of personalised treatments based on cytokine profiles and synovial fibroblast and macrophage molecular signatures with standard, empirical therapy based on physician choice are warranted. However, requiring patients to consent to undergo a synovial biopsy in a clinical trial may make it more challenging to enrol subjects into such trials.

Use of potentially lower-cost biosimilars of bDMARDs to treat RA could make it easier to initiate treatment with targeted therapies earlier, especially in healthcare systems with limited resources. There is a need to compare the cytokine profiles and the molecular signatures of synovial fibroblasts and macrophages in treatment naïve patients with those in patients with established disease, particularly those who have responded inadequately to one or more DMARDs with different mechanisms of action. Significant efforts have been made to identify genetic biomarkers that predict responses to methotrexate and TNFis, the most commonly prescribed DMARDs. These investigations have focused primarily on genome-wide association studies and gene variants involved in the molecular pathways of drug action and metabolism [135,136]. Additionally, transcriptomic studies are needed to identify genetic biomarkers associated with response to methotrexate and bDMARDs, particularly those found in the synovium rather than in blood. A proposed research agenda incorporating these concepts is presented in Table 3.

Funding sources

Medical writing assistance for this article was funded by Fresenius Kabi.

Table 3
A proposed research agenda aimed at the identification of novel biomarkers for the prediction of disease progression and drug response in rheumatoid arthritis.

Objective	Proposed research activities	Expected outcomes
To identify and validate reliable biomarkers that can predict disease progression, treatment response and adverse events	Large-scale genome-wide association studies to identify genetic markers associated with RA Proteomic, transcriptomic and metabolomic profiling to discover protein, molecular and metabolite biomarkers Utilisation of existing serum biomarkers in combination with new findings Validation of identified biomarkers through longitudinal cohort studies and clinical trials Implementation of synovial biopsies to identify novel biomarkers directly from the affected tissue	A comprehensive list of validated biomarkers for RA, incorporating genetic biomarkers, as well as serum and synovial biopsy-derived biomarkers
To address the limitations associated with the quantitation of serum cytokine levels and enhance their reliability as biomarkers	Investigation of the impact of cytokine binding to soluble receptors, inhibitors or carrier proteins on cytokine detectability by ELISA or radioimmunoassay Development of methods to account for the short half-life and local production of cytokines Exploration of the temporal secretion patterns of cytokines Standardisation of methodologies to reduce data variability and account for patient-specific factors Determination of the optimal timing for cytokine analysis	Improved detection and interpretation of circulating cytokines, leading to more accurate biomarker-based treatment personalisation
To understand the biological mechanisms by which biomarkers influence RA pathogenesis and treatment responses	Investigation of the role of identified genetic, transcriptomic, proteomic and metabolomic biomarkers in immune response modulation Use of animal models, *ex vivo* and in vitro systems to study biomarker pathways and functions Collaboration between clinicians, researchers and computational biologists to model biomarker interactions and predict outcomes Study of the cellular and molecular pathways identified through synovial biopsies to understand tissue-specific mechanisms	Mechanistic insights that explain how biomarkers affect RA progression and treatment responses
To develop and validate algorithms that integrate biomarker data for personalised treatment plans	Development of algorithms that use biomarker profiles, including serum and synovial biopsy data, to recommend specific treatments Testing these algorithms in biomarker RCTs to compare biomarker-guided treatment versus standard care	Effective treatment algorithms that improve patient outcomes through personalised medicine

(*continued on next page*)

Table 3 (*continued*)

Objective	Proposed research activities	Expected outcomes
	Refine algorithms based on trial outcomes and integrate machine learning approaches	
To facilitate the clinical adoption of biomarker-guided treatment strategies and monitor their long-term effectiveness	Development of guidelines and protocols for the use of biomarkers in clinical practice Training of healthcare professionals on biomarker interpretation and application Development of registries and RWE studies to monitor the long-term effectiveness and safety of biomarker-guided treatments Implementation of monitoring systems that utilise both serum biomarkers and synovial biopsy data for ongoing patient assessment	Standardised clinical protocols and evidence supporting the long-term benefits of personalised treatment in RA
To promote collaboration across disciplines and institutions to advance biomarker research in RA	Establishment of consortia and collaborative networks involving rheumatologists, immunologists, geneticists and data scientists Sharing of data and resources through centralised databases and biobanks Engagement with patient advocacy groups to incorporate patient perspectives and enhance recruitment for studies Foster collaborations between clinical and research institutions to facilitate synovial biopsy studies	Enhanced research productivity and innovation through collaborative efforts

ELISA: enzyme-linked immunosorbent assay, RA: rheumatoid arthritis, RCTs: randomised controlled trials, RWE: real-world evidence.

CRediT authorship contribution statement

Jérôme Avouac: Writing – review & editing, Writing – original draft, Validation, Investigation, Conceptualization. **Jonathan Kay:** Writing – review & editing, Writing – original draft, Investigation. **Ernest Choy:** Writing – review & editing, Investigation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Article publishing charges and writing assistance were provided by Fresenius Kabi AG. Jonathan Kay reports a relationship with Aker BioMarine AS that includes: funding grants. Jonathan Kay reports a relationship with Alfasigma SpA that includes: funding grants. Jonathan Kay reports a relationship with Biogen that includes: funding grants. Jonathan Kay reports a relationship with Alvotech Swiss AG that includes: consulting or advisory. Jonathan Kay reports a relationship with Amgen Inc that includes: consulting or advisory. Jonathan Kay reports a relationship with Biohaven Ltd that includes: consulting or advisory. Jonathan Kay reports a relationship with Boehringer Ingelheim GmbH that includes: consulting or advisory. Jonathan Kay reports a relationship with Bristol Myers Squibb Co that includes: consulting or advisory. Jonathan Kay reports a relationship with Celltrion, Inc. that includes: consulting or advisory. Jonathan Kay reports a relationship with Fresenius Kabi AG that includes: consulting or advisory. Jonathan Kay reports a relationship with Gate Bioscience Inc that includes: consulting or advisory. Jonathan Kay reports a relationship with Immunovant Inc that includes: consulting or advisory. Jonathan Kay reports a relationship with Istesso that includes: consulting or advisory. Jonathan Kay reports a relationship with Novartis that includes: consulting or advisory. Jonathan Kay reports a relationship with Organon LLC that includes: consulting or advisory. Jonathan Kay reports a relationship with Pfizer Inc that includes: consulting or advisory. Jonathan Kay reports a relationship with Redridge Bio AG that includes: consulting or advisory. Jonathan Kay reports a relationship with Samsung Bioepis.Co., Ltd. that includes: consulting or advisory. Jonathan Kay reports a relationship with Sana Biotechnology that includes: consulting or advisory. Jonathan Kay reports a relationship with Sandoz Inc that includes: consulting or advisory. Jonathan Kay reports a relationship with Spyre Therapeutics that includes: consulting or advisory. Jonathan Kay reports a relationship with Teijin Pharma Limited that includes: consulting or advisory. Jonathan Kay reports a relationship with UCB Inc that includes: consulting or advisory. Jonathan Kay reports a relationship with Viatris Inc that includes: consulting or advisory. Jonathan Kay reports a relationship with Yuhan Corporation that includes: consulting or advisory. Ernest Choy reports a relationship with AbbVie Inc that includes: consulting or advisory and funding grants. Ernest Choy reports a relationship with Bio-Cancer that includes: consulting or advisory and funding grants. Ernest Choy reports a relationship with Biocon Limited that includes: consulting or advisory and funding grants. Ernest Choy reports a relationship with Biogen that includes: consulting or advisory and funding grants. Ernest Choy reports a relationship with Chugai Pharmaceutical Co Ltd that includes: consulting or advisory and funding grants. Ernest Choy reports a relationship with Eli Lilly and Company that includes: funding grants. Ernest Choy reports a relationship with Fresenius Kabi AG that includes: consulting or advisory and funding grants. Ernest Choy reports a relationship with Galapagos that includes: consulting or advisory and funding grants. Ernest Choy reports a relationship with Gedeon Richter Plc that includes: consulting or advisory and funding grants. Ernest Choy reports a relationship with Gilead Sciences Inc that includes: consulting or advisory and funding grants. Ernest Choy reports a relationship with Janssen Pharmaceuticals Inc that includes: consulting or advisory and funding grants. Ernest Choy reports a relationship with Pfizer that includes: consulting or advisory and funding grants. Ernest Choy reports a relationship with Sanofi that includes: consulting or advisory and funding grants. Ernest Choy reports a relationship with UCB that includes: consulting or advisory and funding grants. Ernest Choy reports a relationship with Viatris that includes: funding grants. Jerome Avouac reports a relationship with Eli Lilly and Company that includes: speaking and lecture fees. Jerome Avouac reports a relationship with Pfizer that includes: speaking and lecture fees. Jerome Avouac reports a relationship with AbbVie Inc that includes: speaking and lecture fees. Jerome Avouac reports a relationship with Bristol Myers Squibb Co that includes: funding grants and speaking and lecture fees. Jerome Avouac reports a relationship with Sanofi that includes: speaking and lecture fees. Jerome Avouac reports a relationship with Roche-Chugai that includes: speaking and lecture fees. Jerome Avouac reports a relationship with Nordic Pharma that includes: funding grants and speaking and lecture fees. Jerome Avouac reports a relationship with Medac that includes: speaking and lecture fees. Jerome Avouac reports a relationship with Novartis that includes: funding grants and speaking and lecture fees. Jerome Avouac reports a relationship with Biogen Inc that includes: speaking and lecture fees. Jerome Avouac reports a relationship with Fresenius Kabi AG that includes: funding grants and speaking and lecture fees. Jerome Avouac reports a relationship with Janssen Pharmaceuticals Inc that includes: speaking and lecture fees. Jerome Avouac reports a relationship with Celltrion, Inc. that includes: speaking and lecture fees. Jerome Avouac reports a relationship with MSD that includes: speaking and lecture fees. Jerome

Avouac reports a relationship with Galapagos that includes: funding grants and speaking and lecture fees. Jerome Avouac reports a relationship with Alfasigma that includes: funding grants and speaking and lecture fees. Royalties: Wolters Kluwer NV (for UpToDate). JK If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Medical writing assistance was provided by Fernando Gibson, PhD, and Caroline Spencer, BPharm, of Rx Communications (Mold, UK), and was funded by Fresenius Kabi.

References

[1] Di Matteo A, Bathon JM, Emery P. Rheumatoid arthritis. Lancet 2023;402 (10416):2019–33. https://doi.org/10.1016/S0140-6736(23)01525-8. Epub 20231027PubMed PMID: 38240831.

[2] Matcham F, Scott IC, Rayner L, Hotopf M, Kingsley GH, Norton S, et al. The impact of rheumatoid arthritis on quality-of-life assessed using the SF-36: a systematic review and meta-analysis. Semin Arthritis Rheum 2014;44(2):123–30. https://doi.org/10.1016/j.semarthrit.2014.05.001. Epub 20140529PubMed PMID: 24973898.

[3] Lemmey AB, Wilkinson TJ, Clayton RJ, Sheikh F, Whale J, Jones HS, et al. Tight control of disease activity fails to improve body composition or physical function in rheumatoid arthritis patients. Rheumatol (Oxford) 2016;55(10):1736–45. https://doi.org/10.1093/rheumatology/kew243. Epub 20160610PubMed PMID: 27288209.

[4] Santo R, Baker JF, Dos Santos LP, Silva JMS, Filippin LI, Portes JKS, et al. Changes in physical function over time in rheumatoid arthritis patients: a cohort study. PLoS One 2023;18(1):e0280846. https://doi.org/10.1371/journal.pone.0280846. Epub 20230123PubMed PMID: 36689423; PubMed Central PMCID: PMC9870154.

[5] Sokka T, Kautiainen H, Pincus T, Verstappen SM, Aggarwal A, Alten R, et al. Work disability remains a major problem in rheumatoid arthritis in the 2000s: data from 32 countries in the QUEST-RA study. Arthritis Res Ther 2010;12(2): R42. https://doi.org/10.1186/ar2951. Epub 20100312PubMed PMID: 20226018; PubMed Central PMCID: PMC2888189.

[6] Abhishek A, Nakafero G, Kuo CF, Mallen C, Zhang W, Grainge MJ, et al. Rheumatoid arthritis and excess mortality: down but not out. A primary care cohort study using data from Clinical Practice Research Datalink. Rheumatol (Oxford) 2018;57(6):977–81. https://doi.org/10.1093/rheumatology/key013. PubMed PMID: 29796636; PubMed Central PMCID: PMC5965085.

[7] Dadoun S, Zeboulon-Ktorza N, Combescure C, Elhai M, Rozenberg S, Gossec L, et al. Mortality in rheumatoid arthritis over the last fifty years: systematic review and meta-analysis. Joint Bone Spine 2013;80(1):29–33. https://doi.org/10.1016/j.jbspin.2012.02.005. Epub 20120327PubMed PMID: 22459416.

[8] Gonzalez A, Maradit Kremers H, Crowson CS, Nicola PJ, Davis 3rd JM, Therneau TM, et al. The widening mortality gap between rheumatoid arthritis patients and the general population. Arthritis Rheum 2007;56(11):3583–7. https://doi.org/10.1002/art.22979. PubMed PMID: 17968923.

[9] van den Hoek J, Boshuizen HC, Roorda LD, Tijhuis GJ, Nurmohamed MT, van den Bos GA, et al. Mortality in patients with rheumatoid arthritis: a 15-year prospective cohort study. Rheumatol Int 2017;37(4):487–93. https://doi.org/10.1007/s00296-016-3638-5. Epub 20161228PubMed PMID: 28032180; PubMed Central PMCID: PMC5357293.

[10] Lard LR, Visser H, Speyer I, vander Horst-Bruinsma IE, Zwinderman AH, Breedveld FC, et al. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med 2001;111(6):446–51. https://doi.org/10.1016/s0002-9343(01)00872-5. PubMed PMID: 11690569.

[11] van Aken J, Lard LR, le Cessie S, Hazes JM, Breedveld FC, Huizinga TW. Radiological outcome after four years of early versus delayed treatment strategy in patients with recent onset rheumatoid arthritis. Ann Rheum Dis 2004;63(3): 274–9. https://doi.org/10.1136/ard.2003.010298. PubMed PMID: 14962962; PubMed Central PMCID: PMC1754928.

[12] Burgers LE, Raza K, van der Helm-van Mil AH. Window of opportunity in rheumatoid arthritis - definitions and supporting evidence: from old to new perspectives. RMD Open 2019;5(1):e000870. https://doi.org/10.1136/rmdopen-2018-000870. Epub 20190403PubMed PMID: 31168406; PubMed Central PMCID: PMC6525606.

[13] van Vollenhoven R. Treat-to-target in rheumatoid arthritis - are we there yet? Nat Rev Rheumatol 2019;15(3):180–6. https://doi.org/10.1038/s41584-019-0170-5. PubMed PMID: 30700865.

[14] Kesharwani D, Paliwal R, Satapathy T, Das Paul S. Rheumatiod Arthritis: an Updated Overview of Latest Therapy and Drug Delivery. J Pharmacopuncture 2019;22(4):210–24. https://doi.org/10.3831/KPI.2019.22.029. Epub 20191231PubMed PMID: 31970018; PubMed Central PMCID: PMC6970574.

[15] Fraenkel L, Bathon JM, England BR, St Clair EW, Arayssi T, Carandang K, et al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol 2021;73(7):1108–23. https://doi.org/10.1002/art.41752. Epub 20210608PubMed PMID: 34101376.

[16] Smolen JS, Landewe RBM, Bergstra SA, Kerschbaumer A, Sepriano A, Aletaha D, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis 2023;82(1):3–18. https://doi.org/10.1136/ard-2022-223356. Epub 20221110PubMed PMID: 36357155.

[17] Tanaka Y, Luo Y, O'Shea JJ, Nakayamada S. Janus kinase-targeting therapies in rheumatology: a mechanisms-based approach. Nat Rev Rheumatol 2022;18(3): 133–45. https://doi.org/10.1038/s41584-021-00726-8. Epub 20220105PubMed PMID: 34987201; PubMed Central PMCID: PMC8730299.

[18] Conran CA, Moreland LW. A review of biosimilars for rheumatoid arthritis. Curr Opin Pharmacol 2022;64:102234. https://doi.org/10.1016/j.coph.2022.102234. Epub 20220509PubMed PMID: 35552095.

[19] Smolen JS, Caporali R, Doerner T, Fautrel B, Benedetti F, Pieper B, et al. Treatment journey in rheumatoid arthritis with biosimilars: from better access to good disease control through cost savings and prevention of nocebo effects. RMD Open 2021;7(2). https://doi.org/10.1136/rmdopen-2021-001637. PubMed PMID: 34099538; PubMed Central PMCID: PMC8186742.

[20] Schipper LG, Vermeer M, Kuper HH, Hoekstra MO, Haagsma CJ, Den Broeder AA, et al. A tight control treatment strategy aiming for remission in early rheumatoid arthritis is more effective than usual care treatment in daily clinical practice: a study of two cohorts in the Dutch Rheumatoid Arthritis Monitoring registry. Ann Rheum Dis 2012;71(6):845–50. https://doi.org/10.1136/annrheumdis-2011-200274. Epub 20111230PubMed PMID: 22210852.

[21] van Eijk IC, Nielen MM, van der Horst-Bruinsma I, Tijhuis GJ, Boers M, Dijkmans BA, et al. Aggressive therapy in patients with early arthritis results in similar outcome compared with conventional care: the STREAM randomized trial. Rheumatol (Oxford) 2012;51(4):686–94. https://doi.org/10.1093/rheumatology/ker355. Epub 20111213PubMed PMID: 22166255; PubMed Central PMCID: PMC3306166.

[22] Buch MH. Defining refractory rheumatoid arthritis. Ann Rheum Dis 2018;77(7): 966–9. https://doi.org/10.1136/annrheumdis-2017-212862. Epub 20180327PubMed PMID: 29588276.

[23] Hyrich KL, Lunt M, Watson KD, Symmons DP, Silman AJ. British Society for Rheumatology Biologics R. Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. Arthritis Rheum 2007;56(1):13–20. https://doi.org/10.1002/art.22331. PubMed PMID: 17195186.

[24] Meehan RT, Amigues IA, Knight V. Precision Medicine for Rheumatoid Arthritis: the Right Drug for the Right Patient-Companion Diagnostics. Diagnostics (Basel) 2021;11(8). https://doi.org/10.3390/diagnostics11081362. Epub 20210729PubMed PMID: 34441297; PubMed Central PMCID: PMC8391624.

[25] Khader Y, Beran A, Ghazaleh S, Lee-Smith W, Altorok N. Predictors of remission in rheumatoid arthritis patients treated with biologics: a systematic review and meta-analysis. Clin Rheumatol 2022;41(12):3615–27. https://doi.org/10.1007/s10067-022-06307-8. Epub 20220816PubMed PMID: 35974226; PubMed Central PMCID: PMC9652218.

[26] Baker JF, OD JR, England BR, Giles JT, Newcomb JA, George MD, et al. Lower body mass and lower adiposity are associated with differential responses to two treatment strategies for rheumatoid arthritis. Ann Rheum Dis 2024;83(4):429–36. https://doi.org/10.1136/ard-2023-225014. Epub 20240312PubMed PMID: 38171598; PubMed Central PMCID: PMC11019773.

[27] Gremese E, Carletto A, Padovan M, Atzeni F, Raffeiner B, Giardina AR, et al. Obesity and reduction of the response rate to anti-tumor necrosis factor alpha in rheumatoid arthritis: an approach to a personalized medicine. Arthritis Care Res (Hoboken) 2013;65(1):94–100. https://doi.org/10.1002/acr.21768. PubMed PMID: 22730143.

[28] Bastida C, Ruiz V, Pascal M, Yague J, Sanmarti R, Soy D. Is there potential for therapeutic drug monitoring of biologic agents in rheumatoid arthritis? Br J Clin Pharmacol 2017;83(5):962–75. https://doi.org/10.1111/bcp.13192. Epub 20170118PubMed PMID: 27990682; PubMed Central PMCID: PMC5401978.

[29] Prado MS, Bendtzen K, Andrade LEC. Biological anti-TNF drugs: immunogenicity underlying treatment failure and adverse events. Expert Opin Drug Metab Toxicol 2017;13(9):985–95. https://doi.org/10.1080/17425255.2017.1360280. Epub 20170814PubMed PMID: 28772079.

[30] Ternant D, Bejan-Angoulvant T, Passot C, Mulleman D, Paintaud G. Clinical Pharmacokinetics and Pharmacodynamics of Monoclonal Antibodies Approved to Treat Rheumatoid Arthritis. Clin Pharmacokinet 2015;54(11):1107–23. https://doi.org/10.1007/s40262-015-0296-9. PubMed PMID: 26123705.

[31] Guillo L, Flachaire B, Avouac J, Dong C, Nachury M, Bouguen G, et al. Efficacy and safety of combination targeted therapies in immune-mediated inflammatory disease: the COMBIO study. Dig Liver Dis 2023;55(1):61–8. https://doi.org/10.1016/j.dld.2022.07.012. Epub 20220816PubMed PMID: 35985961.

[32] Cao LQ, Sun H, Xie Y, Patel H, Bo L, Lin H, et al. Therapeutic evolution in HR+/HER2- breast cancer: from targeted therapy to endocrine therapy. Front Pharmacol 2024;15:1340764. https://doi.org/10.3389/fphar.2024.1340764. Epub 20240124PubMed PMID: 38327984; PubMed Central PMCID: PMC10847323.

[33] de Jager VD, Timens W, Bayle A, Botling J, Brcic L, Buttner R, et al. Developments in predictive biomarker testing and targeted therapy in advanced stage non-small cell lung cancer and their application across European countries. Lancet Reg Health Eur 2024;38:100838. https://doi.org/10.1016/j.lanepe.2024.100838. Epub 20240301PubMed PMID: 38476742; PubMed Central PMCID: PMC10928289.

[34] Smolen JS, Aletaha D. Scores for all seasons: SDAI and CDAI. Clin Exp Rheumatol 2014;32(5 Suppl 85). S–75–9Epub 20141030. PubMed PMID: 25365093.
[35] Orr CK, Najm A, Young F, McGarry T, Biniecka M, Fearon U, et al. The Utility and Limitations of CRP, ESR and DAS28-CRP in Appraising Disease Activity in Rheumatoid Arthritis. Front Med (Lausanne) 2018;5:185. https://doi.org/10.3389/fmed.2018.00185. Epub 20180803PubMed PMID: 30123796; PubMed Central PMCID: PMC6085449.
[36] Kay J, Morgacheva O, Messing SP, Kremer JM, Greenberg JD, Reed GW, et al. Clinical disease activity and acute phase reactant levels are discordant among patients with active rheumatoid arthritis: acute phase reactant levels contribute separately to predicting outcome at one year. Arthritis Res Ther 2014;16(1):R40. https://doi.org/10.1186/ar4469. Epub 20140203PubMed PMID: 24485007; PubMed Central PMCID: PMC3978994.
[37] Sokka T, Pincus T. Erythrocyte sedimentation rate, C-reactive protein, or rheumatoid factor are normal at presentation in 35%-45% of patients with rheumatoid arthritis seen between 1980 and 2004: analyses from Finland and the United States. J Rheumatol 2009;36(7):1387–90. https://doi.org/10.3899/jrheum.080770. Epub 20090501PubMed PMID: 19411389.
[38] Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol 2005;23(5 Suppl 39):S100–8. PubMed PMID: 16273793.
[39] Bhasin S, Cheung PP. The Role of Power Doppler Ultrasonography as Disease Activity Marker in Rheumatoid Arthritis. Dis Markers 2015;2015:325909. https://doi.org/10.1155/2015/325909. Epub 20150503PubMed PMID: 26063952; PubMed Central PMCID: PMC4433665.
[40] Kawashiri SY, Kawakami A, Iwamoto N, Fujikawa K, Satoh K, Tamai M, et al. The power Doppler ultrasonography score from 24 synovial sites or 6 simplified synovial sites, including the metacarpophalangeal joints, reflects the clinical disease activity and level of serum biomarkers in patients with rheumatoid arthritis. Rheumatol (Oxford) 2011;50(5):962–5. https://doi.org/10.1093/rheumatology/keq415. Epub 20101223PubMed PMID: 21186172.
[41] Leblond A, Pezet S, Trouvin AP, Elhai M, Gonzalez V, Allanore Y, et al. Linking systemic angiogenic markers to synovial vascularization in rheumatoid arthritis. PLoS One 2018;13(9):e0203607. https://doi.org/10.1371/journal.pone.0203607. Epub 20180906PubMed PMID: 30188942; PubMed Central PMCID: PMC6126858.
[42] Edwards CJ, Kiely P, Arthanari S, Kiri S, Mount J, Barry J, et al. Predicting disease progression and poor outcomes in patients with moderately active rheumatoid arthritis: a systematic review. Rheumatol Adv Pract 2019;3(1):rkz002. https://doi.org/10.1093/rap/rkz002. Epub 20190215PubMed PMID: 31431990; PubMed Central PMCID: PMC6649936.
[43] Inciarte-Mundo J, Frade-Sosa B, Sanmarti R. From bench to bedside: calprotectin (S100A8/S100A9) as a biomarker in rheumatoid arthritis. Front Immunol 2022;13:1001025. https://doi.org/10.3389/fimmu.2022.1001025. Epub 20221103PubMed PMID: 36405711; PubMed Central PMCID: PMC9672845.
[44] Abildtrup M, Kingsley GH, Scott DL. Calprotectin as a biomarker for rheumatoid arthritis: a systematic review. J Rheumatol 2015;42(5):760–70. https://doi.org/10.3899/jrheum.140628. Epub 20150301PubMed PMID: 25729036.
[45] Bae SC, Lee YH. Calprotectin levels in rheumatoid arthritis and their correlation with disease activity: a meta-analysis. Postgrad Med 2017;129(5):531–7. https://doi.org/10.1080/00325481.2017.1319729. Epub 20170424PubMed PMID: 28425837.
[46] Zeng J, Liu X, Liu J, Wu P, Yang L. Linkage of calprotectin with inflammation, activity and treatment response of rheumatoid arthritis: a meta-analysis. Biomark Med 2022;16(17):1239–49. https://doi.org/10.2217/bmm-2022-0216. Epub 20230120PubMed PMID: 36661047.
[47] Hurnakova J, Hulejova H, Zavada J, Komarc M, Cerezo LA, Mann H, et al. Serum calprotectin may reflect inflammatory activity in patients with active rheumatoid arthritis despite normal to low C-reactive protein. Clin Rheumatol 2018;37(8):2055–62. https://doi.org/10.1007/s10067-018-4091-5. Epub 20180414PubMed PMID: 29656372.
[48] Inciarte-Mundo J, Ramirez J, Hernandez MV, Ruiz-Esquide V, Cuervo A, Cabrera-Villalba SR, et al. Calprotectin and TNF trough serum levels identify power Doppler ultrasound synovitis in rheumatoid arthritis and psoriatic arthritis patients in remission or with low disease activity. Arthritis Res Ther 2016;18(1):160. https://doi.org/10.1186/s13075-016-1032-z. Epub 20160708PubMed PMID: 27391315; PubMed Central PMCID: PMC4938924.
[49] Jarlborg M, Courvoisier DS, Lamacchia C, Martinez Prat L, Mahler M, Bentow C, et al. Serum calprotectin: a promising biomarker in rheumatoid arthritis and axial spondyloarthritis. Arthritis Res Ther 2020;22(1):105. https://doi.org/10.1186/s13075-020-02190-3. Epub 20200506PubMed PMID: 32375861; PubMed Central PMCID: PMC7201559.
[50] Jonsson MK, Sundlisaeter NP, Nordal HH, Hammer HB, Aga AB, Olsen IC, et al. Calprotectin as a marker of inflammation in patients with early rheumatoid arthritis. Ann Rheum Dis 2017;76(12):2031–7. https://doi.org/10.1136/annrheumdis-2017-211695. Epub 20170816PubMed PMID: 28814431.
[51] Avouac J, Pezet S, Vandebeuque E, Orvain C, Gonzalez V, Marin G, et al. Semaphorins: from Angiogenesis to Inflammation in Rheumatoid Arthritis. Arthritis Rheumatol 2021;73(9):1579–88. https://doi.org/10.1002/art.41701. Epub 20210806PubMed PMID: 33605067.
[52] Alunno A, Carubbi F, Giacomelli R, Gerli R. Cytokines in the pathogenesis of rheumatoid arthritis: new players and therapeutic targets. BMC Rheumatol 2017;1:3. https://doi.org/10.1186/s41927-017-0001-8. Epub 20171128PubMed PMID: 30886947; PubMed Central PMCID: PMC6383595.
[53] Kondo N, Kuroda T, Kobayashi D. Cytokine Networks in the Pathogenesis of Rheumatoid Arthritis. Int J Mol Sci 2021;22(20). https://doi.org/10.3390/ijms222010922. Epub 20211010PubMed PMID: 34681582; PubMed Central PMCID: PMC8539723.
[54] Ridgley LA, Anderson AE, Pratt AG. What are the dominant cytokines in early rheumatoid arthritis? Curr Opin Rheumatol 2018;30(2):207–14. https://doi.org/10.1097/BOR.0000000000000470. PubMed PMID: 29206659; PubMed Central PMCID: PMC5805125.
[55] Alex AM, Sayles H, Mikuls TR, Kerr GS. Evaluation of cytokine profiles in rheumatoid arthritis patients with clinically active disease and normal inflammatory indices. Clin Rheumatol 2019;38(4):1075–81. https://doi.org/10.1007/s10067-018-4379-5. Epub 20181201PubMed PMID: 30506404.
[56] Dissanayake K, Jayasinghe C, Wanigasekara P, Sominanda A. Potential applicability of cytokines as biomarkers of disease activity in rheumatoid arthritis: enzyme-linked immunosorbent spot assay-based evaluation of TNF-alpha, IL-1beta, IL-10 and IL-17A. PLoS One 2021;16(1):e0246111. https://doi.org/10.1371/journal.pone.0246111. Epub 20210126PubMed PMID: 33497394; PubMed Central PMCID: PMC7837465.
[57] Centola M, Cavet G, Shen Y, Ramanujan S, Knowlton N, Swan KA, et al. Development of a multi-biomarker disease activity test for rheumatoid arthritis. PLoS One 2013;8(4):e60635. https://doi.org/10.1371/journal.pone.0060635. Epub 20130409PubMed PMID: 23585841; PubMed Central PMCID: PMC3621826.
[58] Curtis JR, van der Helm-van Mil AH, Knevel R, Huizinga TW, Haney DJ, Shen Y, et al. Validation of a novel multibiomarker test to assess rheumatoid arthritis disease activity. Arthritis Care Res (Hoboken) 2012;64(12):1794–803. https://doi.org/10.1002/acr.21767. PubMed PMID: 22736476; PubMed Central PMCID: PMC3508159.
[59] Ma MHY, Defranoux N, Li W, Sasso EH, Ibrahim F, Scott DL, et al. A multi-biomarker disease activity score can predict sustained remission in rheumatoid arthritis. Arthritis Res Ther 2020;22(1):158. https://doi.org/10.1186/s13075-020-02240-w. Epub 20200624PubMed PMID: 32580789; PubMed Central PMCID: PMC7313155.
[60] Hirata S, Dirven L, Shen Y, Centola M, Cavet G, Lems WF, et al. A multi-biomarker score measures rheumatoid arthritis disease activity in the BeSt study. Rheumatol (Oxford) 2013;52(7):1202–7. https://doi.org/10.1093/rheumatology/kes362. Epub 20130207PubMed PMID: 23392591; PubMed Central PMCID: PMC3685330.
[61] Hirata S, Li W, Defranoux N, Cavet G, Bolce R, Yamaoka K, et al. A multi-biomarker disease activity score tracks clinical response consistently in patients with rheumatoid arthritis treated with different anti-tumor necrosis factor therapies: a retrospective observational study. Mod Rheumatol 2015;25(3):344–9. https://doi.org/10.3109/14397595.2014.958893. Epub 20141008PubMed PMID: 25295918.
[62] Fleischmann R, Connolly SE, Maldonado MA, Schiff M. Brief Report: estimating Disease Activity Using Multi-Biomarker Disease Activity Scores in Rheumatoid Arthritis Patients Treated With Abatacept or Adalimumab. Arthritis Rheumatol 2016;68(9):2083–9. https://doi.org/10.1002/art.39714. PubMed PMID: 27111089; PubMed Central PMCID: PMC6099512.
[63] Kay J, Bock AE, Rehman M, Zhang W, Zhang M, Iikuni N, et al. Use of multibiomarker disease activity scores in biosimilarity studies for the treatment of patients with rheumatoid arthritis. RMD Open 2022;8(2). https://doi.org/10.1136/rmdopen-2022-002423. PubMed PMID: 36180101; PubMed Central PMCID: PMC9528718.
[64] Reiss WG, Devenport JN, Low JM, Wu G, Sasso EH. Interpreting the multi-biomarker disease activity score in the context of tocilizumab treatment for patients with rheumatoid arthritis. Rheumatol Int 2016;36(2):295–300. https://doi.org/10.1007/s00296-015-3285-2. Epub 20150531PubMed PMID: 26026604; PubMed Central PMCID: PMC4723630.
[65] Bari SF, Khan A, Lawson T. C reactive protein may not be reliable as a marker of severe bacterial infection in patients receiving tocilizumab. BMJ Case Rep 2013;2013. https://doi.org/10.1136/bcr-2013-010423. Epub 20131031PubMed PMID: 24177456; PubMed Central PMCID: PMC3822052.
[66] Fujiwara H, Nishimoto N, Hamano Y, Asanuma N, Miki S, Kasayama S, et al. Masked early symptoms of pneumonia in patients with rheumatoid arthritis during tocilizumab treatment: a report of two cases. Mod Rheumatol 2009;19(1):64–8. https://doi.org/10.1007/s10165-008-0111-7. Epub 20080830PubMed PMID: 18758893.
[67] Yanagawa Y, Hirano Y, Kato H, Iba T. The absence of typical pneumonia symptoms in a patient with rheumatoid arthritis during tocilizumab and steroid treatment. BMJ Case Rep 2012;2012. https://doi.org/10.1136/bcr.02.2012.5835. Epub 20120523PubMed PMID: 22669023; PubMed Central PMCID: PMC3369370.
[68] Humby F, Lewis M, Ramamoorthi N, Hackney JA, Barnes MR, Bombardieri M, et al. Synovial cellular and molecular signatures stratify clinical response to csDMARD therapy and predict radiographic progression in early rheumatoid arthritis patients. Ann Rheum Dis 2019;78(6):761–72. https://doi.org/10.1136/annrheumdis-2018-214539. Epub 20190316PubMed PMID: 30878974; PubMed Central PMCID: PMC6579551.
[69] Johnson KJ, Sanchez HN, Schoenbrunner N. Defining response to TNF-inhibitors in rheumatoid arthritis: the negative impact of anti-TNF cycling and the need for a personalized medicine approach to identify primary non-responders. Clin Rheumatol 2019;38(11):2967–76. https://doi.org/10.1007/s10067-019-04684-1. Epub 20190913PubMed PMID: 31520227.

[70] Wijbrandts CA, Tak PP. Prediction of Response to Targeted Treatment in Rheumatoid Arthritis. Mayo Clin Proc 2017;92(7):1129–43. https://doi.org/10.1016/j.mayocp.2017.05.009. PubMed PMID: 28688467.

[71] Bienvenu JA, Monneret G, Gutowski MC, Fabien N. Cytokine assays in human sera and tissues. Toxicology 1998;129(1):55–61. https://doi.org/10.1016/s0300-483x(98)00063-8. PubMed PMID: 9769110.

[72] Heney D, Whicher JT. Factors affecting the measurement of cytokines in biological fluids: implications for their clinical measurement. Ann Clin Biochem 1995;32(Pt 4):358–68. https://doi.org/10.1177/000456329503200402. PubMed PMID: 7486794.

[73] O'Mahony L, Holland J, Jackson J, Feighery C, Hennessy TP, Mealy K. Quantitative intracellular cytokine measurement: age-related changes in proinflammatory cytokine production. Clin Exp Immunol 1998;113(2):213–9. https://doi.org/10.1046/j.1365-2249.1998.00641.x. PubMed PMID: 9717970; PubMed Central PMCID: PMC1905038.

[74] Dugue B, Leppanen E, Grasbeck R. Preanalytical factors and the measurement of cytokines in human subjects. Int J Clin Lab Res 1996;26(2):99–105. https://doi.org/10.1007/BF02592351. PubMed PMID: 8856362.

[75] Levine SJ. Mechanisms of soluble cytokine receptor generation. J Immunol 2004;173(9):5343–8. https://doi.org/10.4049/jimmunol.173.9.5343. PubMed PMID: 15494479.

[76] Wadhwa M, Thorpe R. Cytokine immunoassays: recommendations for standardisation, calibration and validation. J Immunol Methods 1998;219(1–2):1–5. https://doi.org/10.1016/s0022-1759(98)00093-3. PubMed PMID: 9831384.

[77] Oliver JC, Bland LA, Oettinger CW, Arduino MJ, McAllister SK, Aguero SM, et al. Cytokine kinetics in an in vitro whole blood model following an endotoxin challenge. Lymphokine Cytokine Res 1993;12(2):115–20. PubMed PMID: 8324076.

[78] Lacy P, Stow JL. Cytokine release from innate immune cells: association with diverse membrane trafficking pathways. Blood 2011;118(1):9–18. https://doi.org/10.1182/blood-2010-08-265892. Epub 20110511PubMed PMID: 21562044.

[79] Vgontzas AN, Bixler EO, Lin HM, Prolo P, Trakada G, Chrousos GP. IL-6 and its circadian secretion in humans. Neuroimmunomodulation 2005;12(3):131–40. https://doi.org/10.1159/000084844. PubMed PMID: 15905620.

[80] Knight V, Long T, Meng QH, Linden MA. Rhoads DD. Variability in the Laboratory Measurement of Cytokines. Arch Pathol Lab Med 2020;144(10):1230–3. https://doi.org/10.5858/arpa.2019-0519-CP. PubMed PMID: 32401053.

[81] Smeets TJ, Kraan MC, van Loon ME, Tak PP. Tumor necrosis factor alpha blockade reduces the synovial cell infiltrate early after initiation of treatment, but apparently not by induction of apoptosis in synovial tissue. Arthritis Rheum 2003;48(8):2155–62. https://doi.org/10.1002/art.11098. PubMed PMID: 12905468.

[82] Tak PP, Taylor PC, Breedveld FC, Smeets TJ, Daha MR, Kluin PM, et al. Decrease in cellularity and expression of adhesion molecules by anti-tumor necrosis factor alpha monoclonal antibody treatment in patients with rheumatoid arthritis. Arthritis Rheum 1996;39(7):1077–81. https://doi.org/10.1002/art.1780390702. PubMed PMID: 8670314.

[83] Wang J, Platt A, Upmanyu R, Germer S, Lei G, Rabe C, et al. IL-6 pathway-driven investigation of response to IL-6 receptor inhibition in rheumatoid arthritis. BMJ Open 2013;3(8):e003199. https://doi.org/10.1136/bmjopen-2013-003199. Epub 20130819PubMed PMID: 23959753; PubMed Central PMCID: PMC3753518.

[84] Osiri M, Wongpiyabovorn J, Sattayasomboon Y, Thammacharoenrach N. Inflammatory cytokine levels, disease activity, and function of patients with rheumatoid arthritis treated with combined conventional disease-modifying antirheumatic drugs or biologics. Clin Rheumatol 2016;35(7):1673–81. https://doi.org/10.1007/s10067-016-3306-x. Epub 20160517PubMed PMID: 27188857.

[85] Boyapati A, Schwartzman S, Msihid J, Choy E, Genovese MC, Burmester GR, et al. Association of High Serum Interleukin-6 Levels With Severe Progression of Rheumatoid Arthritis and Increased Treatment Response Differentiating Sarilumab From Adalimumab or Methotrexate in a Post Hoc Analysis. Arthritis Rheumatol 2020;72(9):1456–66. https://doi.org/10.1002/art.41299. Epub 20200825PubMed PMID: 32343882; PubMed Central PMCID: PMC7496495.

[86] Strand V, Boklage SH, Kimura T, Joly F, Boyapati A, Msihid J. High levels of interleukin-6 in patients with rheumatoid arthritis are associated with greater improvements in health-related quality of life for sarilumab compared with adalimumab. Arthritis Res Ther 2020;22(1):250. https://doi.org/10.1186/s13075-020-02344-3. Epub 20201020PubMed PMID: 33081825; PubMed Central PMCID: PMC7574446.

[87] Cuppen BV, Welsing PM, Sprengers JJ, Bijlsma JW, Marijnissen AC, van Laar JM, et al. Personalized biological treatment for rheumatoid arthritis: a systematic review with a focus on clinical applicability. Rheumatol (Oxford). 2016;55(5):826–39. https://doi.org/10.1093/rheumatology/kev421. Epub 20151229PubMed PMID: 26715775.

[88] Lama M, Sarkar R, Ghosh B. Serum Cytokine Profiles in Patients with Rheumatoid Arthritis Before and After Treatment with Methotrexate. J Interferon Cytokine Res 2023;43(8):344–50. https://doi.org/10.1089/jir.2023.0078. PubMed PMID: 37566477.

[89] Lesturgie-Talarek M, Gonzalez V, Combier A, Thomas M, Boisson M, Wanono S, et al. Altered serum inflammatory and angiogenic signatures in refractory rheumatoid arthritis [Conference abstract]. In: EULAR Conference, Vienna, Austria, June 12–15 2024; 2024.

[90] Bastarache JA, Koyama T, Wickersham NE, Ware LB. Validation of a multiplex electrochemiluminescent immunoassay platform in human and mouse samples. J Immunol Methods 2014;408:13–23. https://doi.org/10.1016/j.jim.2014.04.006. Epub 20140421PubMed PMID: 24768796; PubMed Central PMCID: PMC4120713.

[91] Laborde CM, Castro-Santos P, Diaz-Pena R. Contribution of Multiplex Immunoassays to Rheumatoid Arthritis Management: from Biomarker Discovery to Personalized Medicine. J Pers Med 2020;10(4). https://doi.org/10.3390/jpm10040202. Epub 20201030PubMed PMID: 33142977; PubMed Central PMCID: PMC7712300.

[92] Masic D, Stengaard-Pedersen K, Bridal Logstrup B, Horslev-Petersen K, Hetland ML, Junker P, et al. Plasma levels of multiple cardiovascular- and inflammation-related proteins analysed for associations with disease activity and anti-cyclic citrullinated peptide status in active early rheumatoid arthritis. Clin Exp Rheumatol 2023;41(9):1801–7. https://doi.org/10.55563/clinexprheumatol/hrjqdm. Epub 20230316PubMed PMID: 36995323.

[93] Yuan J, Wang E, Fox BA. Immune Monitoring Technology Primer: protein microarray ('seromics'). J Immunother Cancer 2016;4:2. https://doi.org/10.1186/s40425-016-0106-4. Epub 20160119PubMed PMID: 26788323; PubMed Central PMCID: PMC4717589.

[94] Chen Q, Tian T, Xiong E, Wang P, Zhou X. CRISPR/Cas13a Signal Amplification Linked Immunosorbent Assay for Femtomolar Protein Detection. Anal Chem 2020;92(1):573–7. https://doi.org/10.1021/acs.analchem.9b04403. Epub 20191219PubMed PMID: 31849223.

[95] Machold KP, Stamm TA, Nell VP, Pflugbeil S, Aletaha D, Steiner G, et al. Very recent onset rheumatoid arthritis: clinical and serological patient characteristics associated with radiographic progression over the first years of disease. Rheumatol (Oxford) 2007;46(2):342–9. https://doi.org/10.1093/rheumatology/kel237. Epub 20060809PubMed PMID: 16899498.

[96] Nielen MM, van Schaardenburg D, Reesink HW, van de Stadt RJ, van der Horst-Bruinsma IE, de Koning MH, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. Arthritis Rheum 2004;50(2):380–6. https://doi.org/10.1002/art.20018. PubMed PMID: 14872479.

[97] Rantapaa-Dahlqvist S, de Jong BA, Berglin E, Hallmans G, Wadell G, Stenlund H, et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. Arthritis Rheum 2003;48(10):2741–9. https://doi.org/10.1002/art.11223. PubMed PMID: 14558078.

[98] Trouw LA, Rispens T, Toes REM. Beyond citrullination: other post-translational protein modifications in rheumatoid arthritis. Nat Rev Rheumatol 2017;13(6):331–9. https://doi.org/10.1038/nrrheum.2017.15. Epub 20170309PubMed PMID: 28275265.

[99] Edwards JC, Cambridge G. Sustained improvement in rheumatoid arthritis following a protocol designed to deplete B lymphocytes. Rheumatol (Oxford) 2001;40(2):205–11. https://doi.org/10.1093/rheumatology/40.2.205. PubMed PMID: 11257159.

[100] Edwards JC, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med 2004;350(25):2572–81. https://doi.org/10.1056/NEJMoa032534. PubMed PMID: 15201414.

[101] Isaacs JD, Cohen SB, Emery P, Tak PP, Wang J, Lei G, et al. Effect of baseline rheumatoid factor and anticitrullinated peptide antibody serotype on rituximab clinical response: a meta-analysis. Ann Rheum Dis 2013;72(3):329–36. https://doi.org/10.1136/annrheumdis-2011-201117. Epub 20120611PubMed PMID: 22689315.

[102] Maneiro RJ, Salgado E, Carmona L, Gomez-Reino JJ. Rheumatoid factor as predictor of response to abatacept, rituximab and tocilizumab in rheumatoid arthritis: systematic review and meta-analysis. Semin Arthritis Rheum 2013;43(1):9–17. https://doi.org/10.1016/j.semarthrit.2012.11.007. Epub 20130102PubMed PMID: 23290690.

[103] Sellam J, Hendel-Chavez H, Rouanet S, Abbed K, Combe B, Le Loet X, et al. B cell activation biomarkers as predictive factors for the response to rituximab in rheumatoid arthritis: a six-month, national, multicenter, open-label study. Arthritis Rheum 2011;63(4):933–8. https://doi.org/10.1002/art.30233. PubMed PMID: 21225699.

[104] Conti V., Corbi G., Costantino M., De Bellis E., Manzo V., Sellitto C., et al. Biomarkers to Personalize Treatment Rheumatoid Arthritis 2020;10(12). Epub 20201214. doi: 10.3390/biom10121672. PubMed PMID: 33327600; PubMed Central PMCID: PMC7765045.

[105] Kiely PD. Biologic efficacy optimization–a step towards personalized medicine. Rheumatol (Oxford) 2016;55(5):780–8. https://doi.org/10.1093/rheumatology/kev356. Epub 20150930PubMed PMID: 26424837.

[106] Ferraccioli G, Tolusso B, Bobbio-Pallavicini F, Gremese E, Ravagnani V, Benucci M, et al. Biomarkers of good EULAR response to the B cell depletion therapy in all seropositive rheumatoid arthritis patients: clues for the pathogenesis. PLoS One 2012;7(7):e40362. https://doi.org/10.1371/journal.pone.0040362. Epub 20120730PubMed PMID: 22859946; PubMed Central PMCID: PMC3408482.

[107] Adlowitz DG, Barnard J, Biear JN, Cistrone C, Owen T, Wang W, et al. Expansion of Activated Peripheral Blood Memory B Cells in Rheumatoid Arthritis, Impact of B Cell Depletion Therapy, and Biomarkers of Response. PLoS One 2015;10(6):e0128269. https://doi.org/10.1371/journal.pone.0128269. Epub 20150605PubMed PMID: 26047509; PubMed Central PMCID: PMC4457888.

[108] Murayama MA, Shimizu J, Miyabe C, Yudo K, Miyabe Y. Chemokines and chemokine receptors as promising targets in rheumatoid arthritis. Front Immunol 2023;14:1100869. https://doi.org/10.3389/fimmu.2023.1100869. Epub 20230213PubMed PMID: 36860872; PubMed Central PMCID: PMC9968812.

[109] Sellam J, Rouanet S, Hendel-Chavez H, Miceli-Richard C, Combe B, Sibilia J, et al. CCL19, a B cell chemokine, is related to the decrease of blood memory B cells and predicts the clinical response to rituximab in patients with rheumatoid arthritis.

Arthritis Rheum 2013;65(9):2253–61. https://doi.org/10.1002/art.38023. PubMed PMID: 23740460.
[110] Greisen SR, Schelde KK, Rasmussen TK, Kragstrup TW, Stengaard-Pedersen K, Hetland ML, et al. CXCL13 predicts disease activity in early rheumatoid arthritis and could be an indicator of the therapeutic 'window of opportunity. Arthritis Res Ther 2014;16(5):434. https://doi.org/10.1186/s13075-014-0434-z. Epub 20140924PubMed PMID: 25249397; PubMed Central PMCID: PMC4201737.
[111] Han BK, Kuzin I, Gaughan JP, Olsen NJ, Bottaro A. Baseline CXCL10 and CXCL13 levels are predictive biomarkers for tumor necrosis factor inhibitor therapy in patients with moderate to severe rheumatoid arthritis: a pilot, prospective study. Arthritis Res Ther 2016;18:93. https://doi.org/10.1186/s13075-016-0995-0. Epub 20160422PubMed PMID: 27102921; PubMed Central PMCID: PMC4840903.
[112] Odai T, Matsunawa M, Takahashi R, Wakabayashi K, Isozaki T, Yajima N, et al. Correlation of CX3CL1 and CX3CR1 levels with response to infliximab therapy in patients with rheumatoid arthritis. J Rheumatol 2009;36(6):1158–65. https://doi.org/10.3899/jrheum.081074. Epub 20090415PubMed PMID: 19369458.
[113] Yukawa K, Mokuda S, Kohno H, Oi K, Kuranobu T, Tokunaga T, et al. Serum CXCL10 levels are associated with better responses to abatacept treatment of rheumatoid arthritis. Clin Exp Rheumatol 2020;38(5):956–63. Epub 20200120. PubMed PMID: 31969227.
[114] Dennis Jr G, Holweg CT, Kummerfeld SK, Choy DF, Setiadi AF, Hackney JA, et al. Synovial phenotypes in rheumatoid arthritis correlate with response to biologic therapeutics. Arthritis Res Ther 2014;16(2):R90. https://doi.org/10.1186/ar4555. Epub 20140430PubMed PMID: 25167216; PubMed Central PMCID: PMC4060385.
[115] Zhao J, Ye X, Zhang Z. The predictive value of serum soluble ICAM-1 and CXCL13 in the therapeutic response to TNF inhibitor in rheumatoid arthritis patients who are refractory to csDMARDs. Clin Rheumatol 2020;39(9):2573–81. https://doi.org/10.1007/s10067-020-05043-1. Epub 20200323PubMed PMID: 32206975.
[116] Bechman K, Dalrymple A, Southey-Bassols C, Cope AP, Galloway JB. A systematic review of CXCL13 as a biomarker of disease and treatment response in rheumatoid arthritis. BMC Rheumatol 2020;4(1):70. https://doi.org/10.1186/s41927-020-00154-3. Epub 20201102PubMed PMID: 33292827; PubMed Central PMCID: PMC7604968.
[117] Mellors T, Withers JB, Ameli A, Jones A, Wang M, Zhang L, et al. Clinical validation of a blood-based predictive test for stratification of response to tumor necrosis factor inhibitor therapies in rheumatoid arthritis patients. Network Syst Med 2020;3:1.
[118] Cohen S, Wells AF, Curtis JR, Dhar R, Mellors T, Zhang L, et al. A Molecular Signature Response Classifier to Predict Inadequate Response to Tumor Necrosis Factor-alpha Inhibitors: the NETWORK-004 Prospective Observational Study. Rheumatol Ther 2021;8(3):1159–76. https://doi.org/10.1007/s40744-021-00330-y. Epub 20210619PubMed PMID: 34148193; PubMed Central PMCID: PMC8214458.
[119] Strand V, Cohen SB, Curtis JR, Zhang L, Kivitz AJ, Levin RW, et al. Clinical utility of therapy selection informed by predicted nonresponse to tumor necrosis factor-a inhibitors: an analysis from the Study to Accelerate Information of Molecular Signatures (AIMS) in rheumatoid arthritis. Expert Rev Mol Diagn 2022;22(1):101–9. https://doi.org/10.1080/14737159.2022.2020648. Epub 20211230PubMed PMID: 34937469.
[120] Strand V, Zhang L, Arnaud A, Connolly-Strong E, Asgarian S, Withers JB. Improvement in clinical disease activity index when treatment selection is informed by the tumor necrosis factor-a inhibitor molecular signature response classifier: analysis from the study to accelerate information of molecular signatures in rheumatoid arthritis. Expert Opin Biol Ther 2022;22(6):801–7. https://doi.org/10.1080/14712598.2022.2066972. Epub 20220423PubMed PMID: 35442122.
[121] Gravallese EM, Firestein GS. Rheumatoid Arthritis - Common Origins, Divergent Mechanisms. N Engl J Med 2023;388(6):529–42. https://doi.org/10.1056/NEJMra2103726. PubMed PMID: 36780677.
[122] Zhang F, Wei K, Slowikowski K, Fonseka CY, Rao DA, Kelly S, et al. Defining inflammatory cell states in rheumatoid arthritis joint synovial tissues by integrating single-cell transcriptomics and mass cytometry. Nat Immunol 2019;20(7):928–42. https://doi.org/10.1038/s41590-019-0378-1. Epub 20190506PubMed PMID: 31061532; PubMed Central PMCID: PMC6602051.
[123] Alivernini S, MacDonald L, Elmesmari A, Finlay S, Tolusso B, Gigante MR, et al. Distinct synovial tissue macrophage subsets regulate inflammation and remission in rheumatoid arthritis. Nat Med 2020;26(8):1295–306. https://doi.org/10.1038/s41591-020-0939-8. Epub 20200629PubMed PMID: 32601335.
[124] Alivernini S, Tolusso B, Petricca L, Bui L, Di Sante G, Peluso G, et al. Synovial features of patients with rheumatoid arthritis and psoriatic arthritis in clinical and ultrasound remission differ under anti-TNF therapy: a clue to interpret different chances of relapse after clinical remission? Ann Rheum Dis 2017;76(7):1228–36. https://doi.org/10.1136/annrheumdis-2016-210424. Epub 20170124PubMed PMID: 28119289; PubMed Central PMCID: PMC5530352.
[125] Wang J, Conlon D, Rivellese F, Nerviani A, Lewis MJ, Housley W, et al. Synovial Inflammatory Pathways Characterize Anti-TNF-Responsive Rheumatoid Arthritis Patients. Arthritis Rheumatol 2022;74(12):1916–27. https://doi.org/10.1002/art.42295. Epub 20221021PubMed PMID: 35854416.
[126] Zhang S, Li P, Wu P, Yang L, Liu X, Liu J, et al. Predictors of response of rituximab in rheumatoid arthritis by weighted gene co-expression network analysis. Clin Rheumatol 2023;42(2):529–38. https://doi.org/10.1007/s10067-022-06438-y. Epub 20221114PubMed PMID: 36374432.
[127] Mizoguchi F, Slowikowski K, Wei K, Marshall JL, Rao DA, Chang SK, et al. Functionally distinct disease-associated fibroblast subsets in rheumatoid arthritis. Nat Commun 2018;9(1):789. https://doi.org/10.1038/s41467-018-02892-y. Epub 20180223PubMed PMID: 29476097; PubMed Central PMCID: PMC5824882.
[128] Croft AP, Campos J, Jansen K, Turner JD, Marshall J, Attar M, et al. Distinct fibroblast subsets drive inflammation and damage in arthritis. Nature 2019;570(7760):246–51. https://doi.org/10.1038/s41586-019-1263-7. Epub 20190529PubMed PMID: 31142839; PubMed Central PMCID: PMC6690841.
[129] Wei K, Korsunsky I, Marshall JL, Gao A, Watts GFM, Major T, et al. Notch signalling drives synovial fibroblast identity and arthritis pathology. Nature 2020;582(7811):259–64. https://doi.org/10.1038/s41586-020-2222-z. Epub 20200422PubMed PMID: 32499639; PubMed Central PMCID: PMC7841716.
[130] Zou A., Kongthong S., Murphy C., Watts G., Mueller A., Brenner M. Arid5b controls pathologic inflammatory versus invasive fibroblast behavior [Conference abstract]. Arthritis rheumatol [Internet].Accessed 6 December 2024. https://acrabstracts.org/abstract/arid5b-controls-pathologic-inflammatory-versus-invasive-fibroblast-behavior/.
[131] Korsunsky I, Wei K, Pohin M, Kim EY, Barone F, Major T, et al. Cross-tissue, single-cell stromal atlas identifies shared pathological fibroblast phenotypes in four chronic inflammatory diseases. Med 2022;3(7):481–518.e14. https://doi.org/10.1016/j.medj.2022.05.002. Epub 20220531PubMed PMID: 35649411; PubMed Central PMCID: PMC9271637.
[132] Humby F, Durez P, Buch MH, Lewis MJ, Rizvi H, Rivellese F, et al. Rituximab versus tocilizumab in anti-TNF inadequate responder patients with rheumatoid arthritis (R4RA): 16-week outcomes of a stratified, biopsy-driven, multicentre, open-label, phase 4 randomised controlled trial. Lancet 2021;397(10271):305–17. https://doi.org/10.1016/S0140-6736(20)32341-2. PubMed PMID: 33485455; PubMed Central PMCID: PMC7829614.
[133] Rivellese F, Surace AEA, Goldmann K, Sciacca E, Cubuk C, Giorli G, et al. Rituximab versus tocilizumab in rheumatoid arthritis: synovial biopsy-based biomarker analysis of the phase 4 R4RA randomized trial. Nat Med 2022;28(6):1256–68. https://doi.org/10.1038/s41591-022-01789-0. Epub 20220519PubMed PMID: 35589854; PubMed Central PMCID: PMC9205785.
[134] Rivellese F, Nerviani A, Giorli G, Warren L, Jaworska E, Bombardieri M, et al. Stratification of biological therapies by pathobiology in biologic-naive patients with rheumatoid arthritis (STRAP and STRAP-EU): two parallel, open-label, biopsy-driven, randomised trials. Lancet Rheumatol 2023;5(11):e648–ee59. https://doi.org/10.1016/S2665-9913(23)00241-2. PubMed PMID: 38251532.
[135] Acosta-Herrera M, Gonzalez-Serna D, Martin J. The Potential Role of Genomic Medicine in the Therapeutic Management of Rheumatoid Arthritis. J Clin Med 2019;8(6). https://doi.org/10.3390/jcm8060826. Epub 20190610PubMed PMID: 31185701; PubMed Central PMCID: PMC6617101.
[136] Pallio G, Mannino F, Irrera N, Eid AH, Squadrito F, Bitto A. Polymorphisms Involved in Response to Biological Agents Used in Rheumatoid Arthritis. Biomolecules 2020;10(9):1023. https://doi.org/10.3390/biom10091203. Epub 20200819PubMed PMID: 32825059; PubMed Central PMCID: PMC7565539.
[137] Elshabrawy HA, Chen Z, Volin MV, Ravella S, Virupannavar S, Shahrara S. The pathogenic role of angiogenesis in rheumatoid arthritis. Angiogenesis 2015;18(4):433–48. https://doi.org/10.1007/s10456-015-9477-2. Epub 20150722PubMed PMID: 26198292; PubMed Central PMCID: PMC4879881.