Diagnosis and Treatment of Rheumatoid Arthritis: an Introduction to Physicians

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Abstract. Rheumatoid arthritis (RA) is a chronic autoimmune disease that causes inflammatory responses around joints, resulting in pain or restricted movement. In the last two decades, RA has received increasing attention with a better understanding of its pathogenesis and the development of innovative treatment methods. Currently, the management of RA focuses on early diagnosis and persistent treatment to control disease progression and alleviate symptoms. This review aims to summarize the diagnosis and treatment of RA with respect to published classification criteria and guidelines. The combined diagnosis based on biomarkers and clinical symptoms covers the preclinical phase of RA for higher sensitivity while maintaining high precision. In RA treatment, non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (GCs) are often used to rapidly alleviate symptoms in conjunction with disease-modifying antirheumatic drugs (DMARDs, especially methotrexate) to inhibit the underlying disease mechanism. Future improvements in the diagnosis (new biomarkers) and treatment (better monitoring and drugs) can provide more effective management of RA.

Keywords: Diagnosis, autoantibodies, acute-phase reactants, treatment, DMARD.

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease where inflammatory symptoms are caused by the body's immune system attacking self-structures especially at joints. RA has a relatively high occurrence in general, approximately 0.5–1.0% globally, and is more prevalent among elder people. If not promptly treated, RA may lead to the accumulation of joint and cartilage damage and deterioration of symptoms, ultimately resulting in an elevated chance of disability and mortality [1]. The symptoms of RA are generally long-term, involving, most significantly, swelling and stiffness of multiple joints in a symmetric pattern and more severe systemic symptoms, such as fever and weight loss, on rarer occasions [2].

Early diagnosis and treatment of RA are crucial for restoring patients' quality of life since structural damage to joints is irreversible [3,4]. A combined diagnosis based on observation of physical symptoms and tests involving biomarkers is generally employed to ensure accurate and early confirmation of RA. The ongoing investigation into the underlying mechanism of RA has identified several important biomarkers. Currently, it is believed that RA is mainly initiated by the production of specific autoantibodies, namely rheumatoid factors (RFs) and/or anti-citrullinated protein antibodies (ACPAs) [1,3].

Rapid treatment would follow once RA is diagnosed to alleviate symptoms and prevent structural damage, which generally involves anti-inflammatory drugs due to the inflammatory nature of RA. NSAIDs and GCs have been used to treat inflammatory diseases including RA with reported effects on pain and stiffness alleviation [5]. The more recent concept of DMARDs is more specific toward the mechanism of RA (hence disease-modifying) and represents the current direction of RA treatment development aiming for fewer side effects compared with previous drugs [4,5].

This review aims to provide a focused overview of the diagnosis of RA based on the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Rheumatoid Arthritis Classification Criteria (ACR/EULAR Criteria), explaining different aspects of diagnosis with respect to the currently understood RA mechanism. In addition, the current strategies

of RA treatment are briefly introduced, with respect to the 2021 ACR Guideline for the Treatment of Rheumatoid Arthritis (2021 Guideline).

2. Diagnosis

2.1. Diagnosis Based on Symptomatic Presentations

Diagnosis of RA is typically done clinically, where a patient's symptoms are inspected by a physician and several laboratory blood tests would be done. The presentation of RA has been studied quite well. The typical symptom is polyarticular (i.e., in multiple joints), involving pain, stiffness, and swelling generally in a bilateral, symmetric pattern [2,4]. The development of symptoms usually takes quite a long time, weeks to months, and is often accompanied by more general symptoms such as weakness and fatigue [2]. Patients with RA often mention morning stiffness lasting for at least an hour, which was included as one criterion in the 1987 ARA Rheumatoid Arthritis Classification Criteria (ARA Criteria) but later excluded in the ACR/EULAR Criteria due to the lack of positive predictive value [2,4]. In the latter scoring system, an increasing number of joints showing swelling or tenderness acquires a higher score; a maximum score of 5 points is assigned to >10 joints with at least one small joint, with an additional 1 point for long symptom duration of ≥6 weeks [4].

Imaging of joints using radiography or ultrasonography can be carried out to help with diagnosis. In fact, a separate marking scheme based on color Doppler ultrasonography was published by Szkudlarek et al. in 2003, where the extent of joint effusion, synovial thickening, and bone erosion were visualized and marked [6]. Imaging offers a clear picture of the patient's joint status. However, RA can be developing for years before causing irreversible joint damage and the disease activity fluctuates with time (flares), presenting difficulties in effectively containing the disease progression using symptoms as the sole criteria in RA diagnosis [3,7]. To overcome this limitation, the presence of specific biomarkers involved in the early development of RA is also considered in the diagnosis.

2.2. Diagnosis Based on Biomarkers

2.2.1 Autoantibodies

The pathogenesis of RA, along with its associated specific biomarkers, is still being studied. Currently, RFs and ACPAs are the two most acknowledged biomarkers in RA diagnosis and studies have proposed that they are involved in RA pathogenesis [1,8]. RFs were initially discovered by their ability to cause hemagglutination and later named for their association with RA in 1949 [9]. Studies have found that RFs are widely present in RA patients and able to target the constant domain (Fc) of immunoglobulin G (IgG) [8,9]. Although the mechanism of RF-immunoactivity towards IgG is not fully understood, the RF test has been used for diagnosis since the ARA Criteria [9].

ACPAs were discovered later and characterized by their ability to target citrullinated peptides catalyzed by peptidyl arginine deiminase (PAD); various susceptible proteins include vimentin, collagen type II, fibrin, and more [10]. The close relationship between the presence of ACPAs and RA has been observed; studies have hypothesized that certain causes, such as epigenetic genes and environmental factors, trigger the production of RA-specific antibodies by B lymphocytes several years before any perceivable RA symptoms [3,8].

At least one type of these two autoantibodies has often been found in patients' sera years before any onset of RA symptoms with the positive percentage increasing to approximately half of patients in their first year with RA symptoms [3]. Given the specificity of these antibodies in RA patients, the ACR/EULAR Criteria have included serology test on at least one of RFs and ACPAs to facilitate RA diagnosis at early stages while structural damage to patients' bone could be prevented or minimized; a maximum score of 3 points is assigned to high positive RFs or high positive ACPAs [4].

Diagnosis using RFs together with ACPAs is promising and Nielen et al. pointed out that healthy individuals with positive RF or ACPA results from serum tests have a higher risk of developing RA later [3]. Moreover, patients with positive serology results tend to experience more severe symptoms

and structural damage as evidenced by radiologic findings [3,4]. It should be noted, though, that RF and ACPA tests have some limitations in their sensitivity and specificity. The positive predictive value of ACPAs is less than 60% in patients with clinically diagnosed RA while positive RFs are present in other immune diseases, such as hepatitis C [2,3,11]. Indeed, the study that put forward the possibility of serology diagnosis also pointed out that the production of autoantibodies may not be essential for RA development given the fact that some patients with RA did not have positive serology results [3]. Nevertheless, it may be recommendable to include these tests in regular physical examinations: positive RFs and/or ACPAs can provide early warnings to individuals who have yet to develop any symptoms of RA, which increases the likelihood of patients getting early diagnosis once RA symptoms develop and thus achieving better treatment outcomes.

2.2.2 Acute-phase reactants

During the acute-phase response to inflammation and tissue injury, patients are observed with higher plasma levels of acute-phase reactants (APRs). In RA patients, APRs are also observed at elevated levels compared to normal values in healthy individuals, the most distinct of which is C-reactive protein (CRP); erythrocyte sedimentation rate (ESR), an important indicator of disease activity within the DAS28 scoring system, is also higher [7,12]. CRP, an acute-phase protein, is produced to cause inflammation mainly in response to infection, but also in autoimmune diseases [12]. Among all APRs, CRP and ESR are most correlated with RA ($p < 0.001$) [7]. ESR correlates quite well with RFs [13]. The ability of RFs to cause hemagglutination might explain the higher ESR observed in patients with RA. In the ACR/EULAR Criteria, abnormal CRP or ESR is given 1 point [4]. It should be noted, though, that elevated APRs might be caused by inflammation response to other diseases; CRP and ESR each have a specificity of around 75% [7,12]. In addition, due to their acute nature, APR tests have a relatively lower value in providing early diagnosis compared to autoantibodies which are involved in the early progression of RA.

2.3. The ACR/EULAR Criteria

This system includes both aspects of symptomatic and serologic diagnosis for higher specificity and is only used if patients' symptoms could not be readily explained by other diseases. It should be noted that the process of RA diagnosis is very personalized; the classification criteria sacrifice some sensitivity for best specificity and thus serve as a guide for physicians [1]. As shown in **Table. 1**, the biomarkers (RFs, ACPAs, CRP, ESR) involved in disease progression share a maximum of 4 points while the resulting perceivable symptoms share a maximum of 6 points; definite RA is confirmed with ≥6 points out of 10. If bone damage due to RA is clearly visible via imaging or long-standing symptoms have been present, diagnosis can be done without applying the scoring system [4]. It is currently believed that various risk factors may be involved in RA, including susceptibility genes, smoking, and exposure to air pollution [1,8].

Table. 1 The ACR/EULAR Criteria with respect to the pathology of RA [4]

Susceptibility to RA	Progression of RA (preclinical) (maximum **3+1** points)		Clinical symptoms (maximum **6** points)
• Genetics and environmental factors	• Autoantibodies: RFs & ACPAs (**3**)	• APRs: CRP & ESR (**1**)	• Swelling/tender joints • Bone erosion

2.4. Undifferentiated Arthritis

In cases where a patient's score is not enough to be diagnosed as having definite RA but suggestive symptoms (swollen joints) are present, a careful history and physical examination would be done; if still no specific diagnosis (trauma, acute inflammatory diseases, or RA) can be made, this kind of presentation can be classified as undifferentiated arthritis (UA). In the progression of RA, UA likely represents the transition from early infiltration of immune cells into joints to the full manifestation of inflammatory symptoms [1]. Therefore, periodical re-evaluation is required for patients with UA to

ensure a timely diagnosis of the underlying disease. Prevention programs can be taken to reduce the risks of developing more severe symptoms from UA. For example, smoking cessation and weight loss might be useful to limit continued exposure to risk factors [8]. Several trials have also been completed to investigate the possibility and strategies of delaying/preventing RA using drugs [1].

Overall, with a growing understanding of the mechanism of RA and the discovery of specific biomarkers, the current aim is to secure an accurate diagnosis of RA and initiate appropriate treatment as early as possible. Higher risks of severe joint damage and bone erosion have been shown in patients with delayed or poorly controlled treatment [14].

3. Current Treatment

This section gives a brief overview of several components involved in RA treatment with respect to the 2021 Guideline, given that mechanisms, efficacy, and side effects of various drugs have been detailed in several reviews [1,5,8,14]. The goal of RA treatment is to control the symptomatic activity of the disease and ideally achieve remission to prevent a long-term decline in patients' functionality.

3.1. The 2021 Guideline and Disease Activity

This guideline is a consensus of a voting panel consisting of clinicians and patients on strategic recommendations which are expected to deliver the highest benefit-to-risk ratios; a recommendation is either strong or conditional based on the level of certainty. The current guideline focuses on the use of pharmacological treatment in the general patient population. Importantly, the decision-making process should be done with patient input given the fact that the personal preferences of patients can be substantially different; an initial goal of achieving low disease activity is recommended over aiming for complete remission because it may not be achievable for many patients [15]. Although drug contradiction is not discussed in the 2021 guideline and this review, careful considerations and/or examinations should be done before initiation of treatment to ensure safety and efficacy.

The severity of RA is often considered in choosing the most appropriate treatment; too mild approaches offer limited control over the symptoms while excessive use of drugs can lead to very severe side effects. Therefore, the benefit-to-risk ratio associated must be analyzed with scientific measures of patients' symptoms, which is done using scoring systems. In addition, such measures allow tracking of the effectiveness of a certain treatment through its course and advise physicians whether switching to another strategy is required. Several scoring systems (e.g., SDAI, CDAI, DAS28) have been developed, generally involving the number of tender/swollen joints, global assessment, and acute-phase reactants; symptom states are categorized into remission, low, moderate, and high disease activity from low to high score [1]. ACPAs and RFs are generally not considered due to their fluctuation in early RA, limiting their use in more quantitative measurements [16].

3.2. Pharmacological Treatment

3.2.1 NSAIDs and GCs

These types of drugs are involved in treating inflammatory symptoms of various diseases; In RA, they are involved in symptomatic treatment [8]. NSAIDs inhibit the COX pathway which produces proinflammatory molecules and blood clotting agents; GCs exert their anti-inflammatory effects by binding to its receptor and downregulating the expression of proinflammatory proteins [5]. Although both NSAIDs and GCs have demonstrated their effectiveness, they are often nonselective and involve more severe side effects. According to the 2021 Guideline, GCs should be used primarily to alleviate symptoms before the action of DMARDs takes place and should be disfavored in long-term use even for enhanced symptomatic management due to high toxicity (adjusting within the framework of DMARD therapy should be favored instead) [15].

3.2.2 DMARDs

These types of drugs are known to suppress autoimmune activity and inflammatory symptoms in selective ways, which is their main advantage over NSAIDs or GCs [1]. It is widely recognized that in RA, DMARD treatment should be initiated as early as possible to achieve optimal results, given the general delay in their action onset of up to six months [8]. DMARDs are divided into three categories: conventional synthetic DMARDs (csDMARDs), targeted synthetic DMARDs (tsDMARDs), and biologic DMARDs (bDMARDs). **Table. 2** summarizes the currently FDA-approved drugs (abbreviation) that are often prescribed for the treatment of RA [8,15].

Conventional and targeted sDMARDs refer to nonbiologic DMARDs of lower molecular weights comparable with or slightly higher than small molecule drugs. While the exact mechanisms associated with some csDMARDs, such as MTX, are not fully understood, the currently available tsDMARDs involve a very specific target, namely the JAK pathway [1]. On the other hand, bDMARDs are often much heavier, involving modified or recombinant antibodies which target specific components, such as immune cells and cytokines, in the inflammation pathways [1,14]. TNF inhibitors, among currently available bDMARDs, offer the highest benefit-to-risk ratio due to low risks of serious bacterial infection and are often used if low efficacy or intolerance is observed with MTX therapy.

Nevertheless, MTX remains the first-line treatment against RA due to its high efficacy among csDMARDs (also compared to some bDMARDs and tsDMARDs) and low cost compared to most bDMARDs, along with acceptable side effects [14]. For DMARD-naïve patients with moderate-to-high disease activity, MTX monotherapy over many other strategies is recommended according to the 2021 Guideline; HCQ monotherapy is recommended for patients with low disease activity due to its better risk profile. Combined therapies of MTX with other drugs or triple csDMARD therapy (HCQ, SZZ, and either MTX or LEF) are only recommended if 1) a patient has poor prognostic factors and rapid action onset is desired, 2) a patient is willing to pursue higher therapeutic effects despite additional risks and costs, or 3) earlier treatment has failed to achieve the desired alleviation of disease symptoms (treat-to-target) [15].

Table. 2 The currently available drugs for RA treatment [8,15]

NSAIDs	Naproxen, ibuprofen, coxibs (selective COX-2 inhibitor)
GCs	Prednisone, hydrocortisone, prednisolone, dexamethasone
csDMARDs	Methotrexate (MTX), leflunomide (LEF), hydroxychloroquine (HCQ), sulfasalazine (SSZ)
tsDMARDs	Tofacitinib, baricitinib, upadacitinib
bDMARDs	TNF inhibitors: etanercept, adalimumab, infliximab, golimumab, certolizumab pegol; T cell activation inhibitor: abatacept; IL-6 inhibition: tocilizumab, sarilumab; anti-CD20 antibody: rituximab

3.3. Treat-to-target (TTT) Approach

This approach is described, in the 2021 Guideline, as systematic monitoring of treatment progress and subsequently making appropriate adjustments to achieve the desired goal (minimization of inflammation and prevention of joint damage). In the initial stage of treatment, oral administration of MTX is generally recommended and should reach a weekly dose of ≥15 mg within 4 to 6 weeks. Progress of treatment and any appearance of side effects should be carefully monitored, and decisions should be reevaluated regularly based on efficacy and tolerability to ensure timely adjustments [1,15].

For patients with toleration issues or not at target with administrating oral MTX, strategies such as split oral dose, subcutaneous injection and/or folic/folinic acid administration are suggested over switching to/addition of other DMARD(s); however, patient preferences should be promptly considered in this scenario. For patients not at target despite a high dose of MTX, the addition of a ts/bDMARD or triple therapy should be considered, with the former strategy being slightly favored due to expected higher and more persistent therapeutic effects overweighting higher costs, especially in patients with comorbidities. For patients not at target despite taking a ts/bDMARD, switching to

another ts/bDMARD of a different class from the current one could be considered for potential greater improvement. For patients not at target despite taking ts/bDMARDs, the treat-to-target approach may be replaced by usual care based on consensus between patients and physicians [15].

For patients achieving their target for less than 6 months, continuous use of at least 1 DMARD and monitoring of disease activity are recommended before tapering/discontinuing treatment due to the relatively high risk of flare associated with RA. After 6 months, the recommendation is a continuation of the current dosage over-dose reduction over gradual discontinuation over abrupt discontinuation. Gradual discontinuation of SZZ is preferred in triple therapy; gradual discontinuation of MTX is preferred in combined therapies with ts/bDMARDs. Patient and physician preferences should be considered in making decisions on tapering/discontinuation [15].

3.4. Nonpharmacological Management

Nonpharmacological management aims to maintain patients' quality of life without the use of drugs. In RA, pain and decreased functional status due to disease activity often lead to depression and anxiety; studies have shown that physical exercise promotes joint flexibility and physical therapies may support pain management [8,14]. Recommendations from prevention management (smoking cessation) of UA should also be considered. This strategy is often used in conjunction with pharmacological treatment for the best results. In patients with severe symptoms, joint surgery might be done to restore functionality and relieve pain; various types of procedures have been established along the advances in the surgical field [8].

4. Discussion and Prospect

4.1. Diagnosis

As the name of the 2010 ACR/EULAR Rheumatoid Arthritis Classification Criteria suggests, the system differs from diagnostic criteria in that it was designed to stratify patients with definite RA for clinical studies and trials, meaning patients with RA may not be all captured [1]. As a result, physicians' familiarity with RA may be required to identify patients with high risks of, but not classified as, having RA using this scoring system.

It is believed that two-thirds of the risks associated with developing RA may be due to genetic factors, especially the HLA-DR alleles, also known as the shared epitope or SE, in ACPA-positive RA associated with a higher risk of more severe bone damage; twin studies have found out that the heritability of RA is around 60% [8,10]. Thus, whether a patient has a family history of RA could be considered during diagnosis and treatment to ensure early diagnosis and treatment. In addition, various cytokines (IL-1β, IL-6, TNF-α, IFN-γ) at elevated levels were identified in RA, presumably due to autoimmune activity from ACPAs and/or RFs [1]. Combined analysis of these cytokines can be easily done in blood tests and provides additional information on the inflammatory process.

Efforts have been devoted to the discovery of novel biomarkers involved in RA. Since 2011, a new type of autoantibody called anti-carbamylated protein antibodies (anti-CarP Abs) has been studied due to its presence in RA patients. Carbamylation generally involves the nonenzymatic reaction between the ε-NH_2 moiety on lysine residue and isocyanic acid, resulting in homocitrulline, similar to citrulline being produced from citrullination. Despite the similarity in their targets, a significant proportion of anti-CarP Abs have been shown to interact only with carbamylated proteins, showing relatively high prevalence and specificity in RA patients [9]. Extensive studies are being done to confirm the predictive value of this newly discovered type of autoantibody.

A clinical study with ACPA-positive patients identified two promising acute-phase biomarkers: naïve B cells enriched in "antecedent cluster 2 (AC2)" transcripts and $CD45^{-}CD31^{-}PDPN^{+}$ (preinflammatory mesenchymal or PRIME) cells enriched in "antecedent cluster 3 (AC3)" transcripts which are associated with fibroblast genes. In patients' peripheral blood, the concentration of naïve B cells increased 2 weeks before a flare, following which the concentration of PRIME cells increased 1 week before a flare; concentrations of both cells (via their associated RNA transcripts) could be

readily obtained from blood transcriptional analysis [17]. More informed diagnoses can be done by considering the presence or absence of these biomarkers with respect to those four included in the ACR/EULAR criteria **(Table. 1).**

4.2. Treatment

Given that the mechanism of RA is not fully understood, the current treatment of RA relies on the initial administration of a "universal" drug with relatively high efficacy and low risks, namely MTX. From patient responses to the current treatment, appropriate adjustments (addition of/switching to another drug) would be made until the goal of alleviation/remission is achieved as dictated by the TTT approach. The current strategy as explained before can become more efficient and accurate with improvements in the disease activity scoring system and the expansion of available drugs.

Many of the currently used scoring systems include subjective assessments of disease activity (e.g., patient global assessment and global health) made by patients and/or physicians. A recent study has put forward an objective scoring system that accurately monitors the current disease activity and predicts disease progression. The multi-biomarker disease activity (MBDA) scoring system converts the serum level of 12 biomarkers involved in inflammatory pathways into a scale from 0 to 100 (low: <30; moderate: 30–44; high: >44). Moderate correlations have been generally observed between MBDA and commonly used scoring systems, confirming its ability to report disease activity. In addition, a higher risk of radiographic progression is associated with a high score (>44) compared with a low score (<30), which is generally not observed with other scoring systems, making it a valuable prognostic marker [16]. Due to the complexity of MBDA involving many biomarkers, it is probably more efficient to perform MBDA over a certain time interval instead of using it in daily monitoring; for example, an evaluation with MBDA several months after tapering/discontinuation of treatment may provide physicians with the probability of relapse.

New potential therapeutic options are constantly being researched. An in vitro study using peripheral blood mononuclear cells (PBMCs) extracted from patients with RA showed beneficial roles of IL-18 binding protein (IL-18BP). IL-18BP is a naturally occurring protein in the human body that regulates the level of IL-18 signaling by preventing it from binding to its receptor. In IL-18BP-treated cells, the differentiation of $CD4^+IL\text{-}17A^+$ and $CD4^+RANKL^+$ T cells was decreased; as a result, the levels of IL-17A and RANKL were also lower. These findings indicate the possibility of using IL-18BP to suppress osteoclastogenesis induced by IL-17 and prevent bone damage [18]. Further in vivo study is warranted to confirm the pharmacology and side effects of IL-18BP.

It should be noted that both the ACR/EULAR Criteria and 2021 Guideline were published in America and Europe. Given the heterogeneity of RA (genetic factors are believed to be involved in the pathogenesis), local requirements and guidelines should always be followed first. Future diagnosis and treatment can be also driven by further exploring the mechanism of RA, which involves various biological processes as evidenced by the diversity of patient responses to targeted treatment [1]. A more comprehensive understanding of RA allows the identification of specific biomarkers, facilitating more accurate diagnosis, and associated pathways, allowing personalized treatment which is safer and more effective than the current treat-to-target approach which relies heavily on a trial-and-error process based on MTX treatment.

5. Conclusion

RA is a heterogeneous disease with various symptoms and severity, involving complicated mechanisms which are still not fully understood. Based on the ACR/EULAR Criteria, both clinical symptoms and biomarkers (such as RFs, ACPAs, CRP, and ESR) involved in the progression of RA with appropriate specificity and/or sensitivity are considered. Importantly, physicians need to be able to use various established methods in RA diagnosis to ensure accurate and early diagnosis.

Various types of drugs have been used in the treatment of RA: DMARDs are strongly recommended given their high efficacy and specificity; GCs are also often used in conjunction to

suppress the symptoms rapidly before the action onset of DMARDs. Careful monitoring of the treatment and any side effects will follow which ensures timely adjustments on the treatment to control RA effectively. Tapering/discontinuation of any treatment should be considered carefully to deliver optimal outcomes.

Overall, the diagnosis of RA is explained by connecting with the current understanding of the disease and its pathogenesis; the treatment of RA is introduced through available drugs and guidelines for their use. In addition, several promising biomarkers not included in the ACR/EULAR Criteria and an example of new potential drugs are presented. In conclusion, this review provides physicians with basic information on RA so that more personalized diagnoses and treatments can be carried out.

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