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THE USE OF BIOLOGICAL TREATMENT IN RHEUMATOID ARTHRITIS – A REVIEW OF THE CURRENT LITERATURE

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ABSTRACT

Introduction and purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease of autoimmune origin, with an estimated global prevalence of approximately 1% of the population. It can lead to progressive cartilage and bone destruction, ultimately resulting in disability and contributing to premature mortality.
Brief description of the state of knowledge: The disease most commonly develops in individuals between the ages of 30 and 50. In the majority of patients, it follows a relapsing-remitting course, characterized by alternating periods of exacerbation and remission, with gradual joint destruction over time. The most characteristic symptoms include morning stiffness lasting longer than one hour, joint pain and swelling. Rheumatoid arthritis typically affects the small joints of the hands and feet. Diagnostic evaluation often reveals symmetric polyarthritis, particularly involving the wrists, hands and feet, consistent with inflammatory joint disease. Delays in establishing a correct diagnosis are common and may result from patients underestimating their symptoms. The introduction of biologic agents in RA therapy represents a major advancement and offers significant potential for effective disease control and improved patient outcomes.
Conclusions: Rheumatoid arthritis, an increasingly common condition in medical practice, must be diagnosed as soon as possible to halt the progressive effects of inflammation and prevent irreversible complications. Knowledge of risk factors, symptoms and new drug therapies is key to making an accurate diagnosis. The prospects for the use of biologics are extremely promising, as patients achieve a faster and more complete response to treatment while generating lower costs than with standard, long-term conventional treatment.

KEYWORDS

Rheumatoid Arthritis, Biological Treatment, bDMARDs, tsDMARDs, EULAR Recommendations, Disease Activity, Immunotherapy

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that may lead to cartilage and bone destruction, as well as functional disability in the long run. The most common clinical manifestations are morning stiffness, joint pain and swelling. The disease primarily affects small joints of hands and feet, but other joint compartments can also be affected. RA significantly impacts the patient, their family, social functioning and results in a high burden on the healthcare system [10]. Pro-inflammatory cytokines such as interleukin (IL)-1, IL-6 and IL-17 are key mediators of RA pathogenesis, with tumor necrosis factor-alpha (TNF-α) also playing a central role and activated macrophages [11]. Significantly, it also stimulates osteoclasts leading to bone loss and erosive changes [12]. Early treatment is important for the achievement of optimal treatment gain, particularly in patients with well-defined risk factors for a poor prognosis, e.g., increased disease activity, autoantibody positivity (e.g., RF, ACPA) and early structural joint damage [13].

The therapeutic plan includes assessment of disease activity using validated tools such as the Disease Activity Score in 28 joints (DAS28), Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI), development of a treatment strategy and the use of conventional, biological, or targeted synthetic disease-modifying antirheumatic drugs (csDMARDs, bDMARDs, tsDMARDs). Upon achieving the treatment goal — defined as sustained remission or at least low disease activity — gradual tapering of therapy should be considered in suitable patients [14].

This autoimmune inflammatory joint disease affects approximately 1% of the global population [15]. For many years, the conventional therapeutic approach to RA involved the use of glucocorticosteroids in combination with csDMARDs, with methotrexate being the cornerstone of pharmacologic intervention [16]. There is no doubt that biological therapies have transformed the disease course over recent decades. Some of the biologics that are utilized to manage RA are: IL-1 inhibitors (anakinra), CD20 inhibitors (rituximab), TNF-α inhibitors (infliximab, etanercept, adalimumab, golimumab, certolizumab), IL-6 inhibitors (tocilizumab) and inhibitors of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), abatacept [17]. A comprehensive review of the literature confirms the efficacy of biologic therapies, both as monotherapy and also in combination with other DMARDs, in reducing disease activity and halting structural progression [18].

Description of the state of knowledge

Risk factors

Among well-established scientific risk factors for the development of rheumatoid arthritis (RA), female sex is particularly significant—women are affected approximately three times more often than men [10]. Environmental factors include smoking, obesity, inadequate dietary intake of omega-3 fatty acids, air pollution, physical inactivity and infectious etiologic agents like viruses and mycoplasmas. Interestingly, a good correlation has been noted between RA and periodontal disease, especially infection by Porphyromonas gingivalis [11,12]. Genetic susceptibility is also important, especially with the presence of some alleles of the human leukocyte antigen (HLA)-DRB1 locus, one of the major histocompatibility complex (MHC) class II and a positive family history for the condition [13].

Etiology and pathophysiology

The precise etiology of RA remains unknown. However, MHC class II molecules play an important role in the presentation of citrullinated peptides that induce the autoimmune response. Anti-citrullinated protein antibodies (ACPA) bind to citrullinated residues of different proteins, including fibrinogen, type II collagen and histones [14]. ACPA-secreting B lymphocytes are present in peripheral blood as well as synovial tissue and induce macrophage activation and induction of inflammatory responses. Pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-17 and tumor necrosis factor-alpha (TNF-α), in conjunction with macrophages, contribute to the development and progression of erosive bone lesions, which originate at the cartilage–bone interface, leading to cartilage degradation [15]. As a result, joint pain, swelling, periarticular soft tissue inflammation and increased local temperature are already present in the early stages of the disease.

Diagnostics

For the diagnosis of RA, the classification criteria of the European Alliance of Associations for Rheumatology (EULAR, formerly European League Against Rheumatism) and the American College of Rheumatology (ACR) are used. These criteria include: joint involvement (up to 5 points), serology (rheumatoid factor and ACPA tested more than once; 0–3 points), acute-phase reactants (CRP and ESR; 0–1 point) and symptom duration (<6 or >6 weeks; 0–1 point). A score below 6 points does not allow RA classification at that time, but patients may meet the criteria during follow-up assessments [16]. Additionally, patients with typical RA erosions or a well-documented long-standing disease (even if inactive or untreated) that previously fulfilled the classification criteria should still be considered as having RA. Differential diagnosis is crucial, as multisystem connective tissue diseases such as systemic sclerosis, dermatomyositis and polymyositis, mixed connective tissue disease and polymyalgia rheumatica can present with symmetric polyarthritis, including involvement of the metacarpophalangeal and proximal interphalangeal joints [17].

Medical history

Taking history has a crucial impact, not only on the stablishing of suspicions of RA, but also as the first step needed to meet the diagnostic criteria [1, 16]. The most characteristic symptom of this condition is symmetrical pain and swelling in the joints of the hands and feet, followed later by atrophy of the interosseous and lumbar muscles, as well as palmar erythema around the ball of the thumb and the thenar nerve. Similar deformities appear in the joints of the feet. RA diagnosis and treatment are significant since persistent disease without treatment will lead to permanent joint deformity and disability. The other alarm symptom that would lead us to consider this condition is morning stiffness, a feeling of stiffness and limited joint mobility upon awakening – it usually resolves slowly with physical activity. In RA, it lasts more than 60 minutes, which distinguishes it from degenerative changes, where this symptom lasts for a shorter duration – up to 30 minutes [2,3,16]. Comprehensive history and identification of the characteristic clinical symptoms listed above are significant parts of early rheumatoid arthritis diagnostics. At this point, we should consider individual differences in the disease process and severity of symptoms in each patient. An individualized approach is necessary for the accurate diagnosis and optimal treatment planning [5,8].

Physical examination

Physical examination of rheumatoid arthritis (RA) is not only a part of the diagnostic procedure but also of disease activity monitoring and response to treatment. According to the latest recommendations by the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR), it should be performed in a systematic and standardized manner to ensure reliable assessment of the patient's condition and allow for longitudinal comparisons [5,7].

The palpation joint count of tender and swollen joints is one of the basic steps in clinical evaluation of RA. The most common form is the 28-joint count (DAS28), such as the shoulders, elbows, wrists, metacarpophalangeal (MCP), proximal interphalangeal (PIP) and knees [18]. The examination is performed by the detection of tenderness to pressure, swelling, heat, reduced range of motion and effusion. In research settings or in patients with atypical disease presentations, extended joint counts may be employed, assessing 66 joints for swelling and 68 for tenderness [19].

Clinical examination should also include evaluation of joint mobility and the presence of deformities characteristic of established RA, such as swan-neck fingers, boutonnière deformities, subluxations and ulnar deviation of the fingers [20]. Axis deviation, joint instability and impairment should be observed.

An essential component of the examination is the identification of systemic and extra-articular manifestations of the disease, including rheumatoid nodules and involvement of internal organs such as the lungs, blood vessels, eyes or nervous system [21]. Additionally, clinicians should screen for compression syndromes, particularly carpal tunnel syndrome, which frequently coexists with chronic synovial inflammation.

In summary, physical examination of RA constitutes the foundation of accurate clinical assessment and effective monitoring of therapeutic progress.

Clinical scales

To objectively and quantitatively assess the activity of rheumatoid arthritis, standardized clinical scales are recommended [1,16,19]. The most commonly used scale is the DAS28 (Disease Activity Score 28), which integrates tender and swollen joint counts, level of CRP or ESR and the patient's subjective assessment of disease activity (VAS – Visual Analogue Scale). In addition, SDAI (Simplified Disease Activity Index) and CDAI (Clinical Disease Activity Index) are used, which also include physician and patient assessment.The CDAI does not require laboratory measurements of CRP. The HAQ (Health Assessment Questionnaire) is commonly used in clinical practice, providing a tool for assessing the patient's functional status and the degree of physical impairment resulting from the course of the disease.

Auxiliary tests

The diagnosis of RA is based on comprehensive evaluation of clinical findings and outcomes of laboratory and imaging investigations. Laboratory tests normally include elevated erythrocyte sedimentation rate (ESR), elevated levels of CRP and fibrinogen and normocytic anemia. Thrombocytosis during the course of disease activity is a distinguishing feature, whereas thrombocytopenia may be a result of complications of immunosuppressive therapy.

Rheumatoid factor (RF) IgM is present in approximately 70–80% of patients and is linked with the more severe course of the illness and extra-articular features. Anti-CCP antibodies (ACPA) are of particular interest in diagnosis and prognosis, with high specificity (>95%) and moderate sensitivity (>50%) for RA [2,3,21]. They correlate with a more aggressive course and accelerated joint damage. Synovial fluid examination in RA reveals the presence of inflammation: increased number of leukocytes (predominantly neutrophils) and ragocytes—immune complex-phagocytosing cells. RF may be localized in synovial fluid prior to its detection in serum.

Imaging techniques predominantly utilize X-ray, ultrasound, magnetic resonance imaging (MRI) and computed tomography (CT) [22].

X-ray

Plain radiography (X-ray) remains the gold standard imaging method in the assessment of chronic osteoarticular injury [3,16]. It allows for the identification of typical changes in RA, such as joint space narrowing, bone erosions and periarticular demineralization. In spite of the low sensitivity in detecting early inflammatory changes, X-ray remains an important tool in the assessment of radiographic disease progression [18, 22].

Joint ultrasound

Joint ultrasound allows for dynamic assessment of soft tissue, synovial membrane and presence of joint effusion. Power Doppler imaging allows one to visualize active vascular inflammation and is therefore extremely helpful in monitoring disease activity. Furthermore, this examination is more sensitive than X-ray for the detection of erosions in early RA [1,3,22].

Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) enables the assessment of both osseous and soft tissue structures, making it possible to reveal synovitis, erosions and bone marrow edema at an early stage. The sensitivity of the method is high and it is of utmost value for the diagnosis of RA at the preclinical stage of joint involvement. MRI also performs well in identifying lesions that are inaccessible to other methods, predominantly in the wrist and sacroiliac joint areas [1,16].

Computed tomography (CT)

Computed tomography (CT) delivers extremely good spatial resolution and allows diligent assessment of destructive bone changes, including geodes and faint cortical erosions. Although it does not image inflammation that is active, CT may be more sensitive than X-ray for identifying early erosive changes. It is particularly useful in assessing structures that are difficult to analyse with other methods, such as the joints of the cervical spine [1,3,22].

Treatment

The treatment strategy is based on the earliest possible initiation of disease-modifying antirheumatic drug (DMARD) therapy according to the treat-to-target model, the aim of which is to achieve remission or low disease activity in the shortest possible time [5, 8].

Conventional treatment

The first-line treatment of RA, according to clinical recommendations, is methotrexate (MTX), as monotherapy and in combination with short-acting glucocorticosteroids (GCs), which allows earlier therapeutic effect [5,7]. In the presence of contraindications to MTX, leflunomide or sulfasalazine are prescribed [23]. MTX, by inhibiting dihydrofolate reductase, has immunosuppressive and anti-inflammatory effects [24]. Yet it carries with it the potential for side effects such as hepatotoxicity and myelosuppression, which are avoidable by supplementation with folic acid [24].

Biological and synthetic targeted therapy

Biological disease-modifying antirheumatic drugs (bDMARDs)

If the therapeutic target is not achieved within 3–6 months of treatment with conventional disease-modifying antirheumatic drugs (csDMARDs), the 2022 EULAR guidelines recommend the implementation of biologic (bDMARDs) or targeted synthetic (tsDMARDs), usually in combination with methotrexate (MTX) [1,8]. The most commonly used bDMARDs are the tumor necrosis factor α (TNF-α) inhibitors, etanercept, adalimumab, infliximab and golimumab, which have high rates of efficacy in reducing disease activity and inhibiting radiographic progression [25]. In recent years, there has been a significant increase in interest regarding the use of monoclonal antibodies against interleukin-6 (IL-6), i.e., tocilizumab, sarilumab and the newly approved olokizumab [26, 27]. These medications are particularly indicated in patients who have not responded or have been contraindicated for TNF-α inhibitor therapy [26]. Early treatment with anti-IL-6 monotherapy or combined with other drugs greatly enhances the probability of inducing remission and stopping joint damage, as was shown by multicenter clinical trials outcomes [27, 28]. Additionally, tocilizumab can be administered as monotherapy, thereby being particularly useful in cases of MTX intolerance [28].

Synthetic targeted drugs (tsDMARDs)

Janus kinase inhibitors (JAKi), such as tofacitinib, baricitinib and upadacitinib, are a class of synthetic targeted therapies (tsDMARDs) whose mechanism of action involves blocking intracellular signalling pathways dependent on proinflammatory cytokines [29]. Their efficacy, both as monotherapy and in combination with methotrexate, has been confirmed in numerous randomized clinical trials, including the SELECT-COMPARE trial, in which upadacitinib demonstrated superior efficacy over adalimumab in achieving remission and inhibiting radiographic progression [30,31]. These drugs achieve a quick response with an uncomplicated oral formulation that improves compliance to therapy [32]. Despite their efficacy, JAKi use is associated with an increased risk of adverse events, such as infections (including herpes zoster), venous thromboembolism and cardiovascular events, particularly in patients with risk factors [29,33]. Accordingly, according to ACR and EULAR guidelines, periodic safety assessment yearly before and during the course of JAKi therapy must be kept in mind regarding cardiovascular, oncologic and infection risk factors [5,7,33]. Even the FDA has placed boxed warnings regarding the use of JAKi emphasizing individualized decision-making on the basis of a balancing act between benefits and risks [34].

Changes in guidelines in recent years

The latest EULAR recommendations from 2025 propose a more flexible therapeutic approach in cases of standard treatment failure, particularly in the absence of response to methotrexate (MTX) and glucocorticosteroids (GCs) [5]. These recommendations allow for the early use of biologic (bDMARDs) or targeted synthetic (tsDMARDs) drugs, without the initial need for csDMARD combination therapy [5]. They

also emphasize that tapering doses of the drugs gradually after stable clinical remission is achieved can be kept to a minimum as a risk of adverse events [35]. One of the most significant aspects of the new guidelines is individual risk assessment for infection, neoplastic conditions and interstitial lung disease (ILD) before and during target therapy [5,33]. While being more costly upfront, biologic therapy can reduce overall health care costs significantly through reduction of hospitalization, surgery and absenteeism [35,36,37]. Early remission translates into improved patient productivity and reduced indirect cost resulting from work disability and long-term disability [36].

Treat-to-target strategy and integration of biological therapies

The treat-to-target strategy remains the cornerstone of RA therapy, relying on regular monitoring of disease activity (DAS28, SDAI, CDAI) and treatment adjustments to achieve remission or low disease activity [1,8,38]. Initiating a bDMARD or tsDMARD in the absence of response is a key step in second-line therapy [5,7]. Once stable remission has been achieved, dose reduction can be considered with continued close monitoring [35].

Complications

Pharmacotherapy of rheumatoid arthritis (RA), though effective in control of disease activity and prevention of its progression, is not without the risk of a broad spectrum of adverse events potentially able to significantly impair the patient's quality of life and safety of long-term treatment. These complications vary by drug class employed – from conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) to glucocorticosteroids (GCs), to biologics (bDMARDs) and targeted synthetic drugs (tsDMARDs) [5,38].

Methotrexate (MTX), a first-line drug in RA treatment, can lead to hepatotoxicity, bone marrow suppression, interstitial lung lesions (methotrexate-induced ILD) and gastrointestinal symptoms [24]. Regular supervision of liver parameters, blood counts and lung radiography is also significant to its safety monitoring [23]. Sulfasalazine and leflunomide, two other csDMARDs, can also lead to side effects such as skin reactions, cytopenias and liver dysfunction [39].

Glucocorticosteroid treatment, although effective in the acute reduction of inflammatory symptoms, is associated with a risk of osteoporosis, hyperglycemia, hypertension and increased susceptibility to infection [40]. Both the EULAR and ACR guidelines suggest that their use should be for as short a duration as possible and at the lowest effective dose [5,7].

The introduction of biologic and targeted synthetic therapies has significantly changed RA treatment, but not without risk. TNF-α inhibitors (etanercept, infliximab, adalimumab) increase susceptibility to infections, including reactivation of tuberculosis and opportunistic infections and may also cause the induction of autoimmunity or exacerbation of heart failure [41]. Anti-IL-6 antibodies (tocilizumab, sarilumab), besides immunosuppression, may lead to hyperlipidemia, neutropenia and elevation of liver enzymes [42].

Specific interest is now being accorded to the safety of Janus kinase inhibitors (JAKi), such as tofacitinib, baricitinib and upadacitinib. In addition to the risk of infection—especially herpes zoster—an increased incidence of cardiovascular complications (including heart attacks and strokes), venous thromboembolism and cancer, particularly lung cancer and lymphoma, has been documented, especially in patients with additional risk factors [43]. As a result, the FDA and EMA have issued warnings regarding the use of JAKi and the ACR guidelines recommend a detailed risk assessment before their implementation [5,7].

The complications of RA therapy therefore require individualized management, taking into account not only clinical efficacy but also the safety profile, patient's age, comorbidities and previous adverse events. Strict laboratory monitoring, imaging studies and clinical assessment are required to minimize risk and timely detection of complications. A modern "treat-to-target" treatment strategy must therefore encompass not only achieving disease remission but also optimizing treatment safety [38].

Conclusions

Rheumatoid arthritis continues to be a major diagnostic and therapeutic problem in rheumatology, necessitating urgent therapeutic intervention in order to avoid permanent disability. Early diagnosis and the immediate application of therapy according to a "treat-to-target" approach considerably enhance the likelihood of obtaining disease remission. Targeted synthetic and biological therapies (tsDMARDs) have revolutionized RA management by providing enhanced efficacy compared with traditional therapies. TNF-α inhibitors and anti-IL-6 antibodies and JAK kinase inhibitors are good therapeutic options for patients with an unsatisfactory csDMARD response. Potential adverse effects of immunosuppression and cardiovascular, neoplastic and infectious disease risks must be considered. Therefore, physicians are responsible for individualizing treatment and regularly assessing the safety of the drugs used. The new EULAR guidelines from 2025 emphasize therapeutic flexibility, allowing early initiation of biological therapy without the need for escalation of csDMARDs. Biological treatment, although initially expensive, can ultimately reduce the direct and indirect costs associated with long-term disease progression. Effective inflammation control translates into improved quality of life for patients and their social and professional functioning. Treatment of RA should be conducted in accordance with current guidelines and based on holistic, interdisciplinary care.

Disclosure

Author's contribution

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