Chapter

Diagnostic Challenges and Management Update in Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis is a chronic, systemic inflammatory disease, with certain evidence of multiple factors involved, but also with the strong autoimmune component, leading to a high potential for disability, through synovial inflammation and joint destruction. Diagnostic methods and management possibilities have recently improved, thus leading to a better outcome, based on the treat to target recommendation. Although biologic agents represent efficient therapeutic agents, in the last few years, the advances in understanding the mediators involved in rheumatoid arthritis pathogenesis have provided new targeted therapies, represented by small molecule inhibitors against the Janus kinases that contribute in the signaling pathways of various cytokine receptors.

Keywords: rheumatoid arthritis, autoimmune disease, biologic agents, new therapies

1. Introduction

Rheumatoid arthritis (RA) is a chronic, autoimmune, systemic disease that targets primarily the synovial joint lining and causes progressive disability. Untreated, PR leads to the destruction of the joints by the erosion of cartilage and bone material. Loss of physical function is the aftermath, which is why early treatment is vital for controlling disease activity and for preventing joint damage.

Angiogenesis is an important process for the growth and development of all tissues, during which new blood vessels are formed from pre-existing vascularization and play a critical role in the pathogenesis of several inflammatory autoimmune diseases, such as PR. Angiogenesis is triggered by the dominance of pro-angiogenic factors over endogenous angiostatic mediators. Studies conducted over the past two decades have suggested the involvement of numerous pro-angiogenic factors such as metabolites, ions, growth factors, hypoxia-inducible

factors, cytokines, chemokines, extracellular matrix metalloproteinases, and adhesion molecules, in RA pathogenesis.

Also, these pro-angiogenic factors were targets for possible therapies. Thus, the research has led to the emergence of new therapies with a key role in modulating the activity of the cellular immune response and inflammation in the synovial tissue.

According to studies, patients with RA, after treatment with biological agents, showed a significant decrease compared to the initial levels of acute-phase reactants and inflammatory proteins: C-reactive protein (CRP), the red blood cells sedimentation rate (ESR), pro-inflammatory cytokines (tumor necrosis factor-alpha, TNF-α; interleukins, IL-17, IL-8, IL-18), chemokines (CXCL12), growth factors (angiopoietins, Ang-1, Ang-2; growth factor of vascular endothelium, VEGF), adhesion molecules (vascular adhesion molecule 1, VCAM-1) and matrix metalloproteinases (MMP-9 and MMP-13).

Biological therapy has brought many benefits for patients, by improving the prognosis, evolution, stopping or reducing destructive lesions, obtaining remission and thus increasing the quality of life and maintaining social integration.

Biological therapy is no longer reserved only for cases that do not respond to classical therapy, as clinical studies have shown that the number of swollen and painful joints decreases, as well as the rate of osteoarticular destructive lesions.

2. Rheumatoid arthritis: pathogenesis

The pathological mechanisms that drive the synovial inflammation and structural damage in RA are complex.

Research in the field of RA pathogenesis has been an essential tool in the development of disease-modifying drugs, biologic therapy, and the more recent targeted therapy. There are separate domains of research that combine to offer a complete picture of the disease etiopathogenesis. These include the study of trigger agents, autoantigen-autoantibody interaction, genetic susceptibility, articular and extraarticular pathology. Major disease subtypes defined by anti-citrulline peptide antibody (ACPA) positivity provide some differences in genetic associations, immune response, disease severity and treatment effectiveness [1].

The presence of ACPA is highly specific for RA [2] and occurs in response to a set of citrullinated proteins, such as fibrin, fibronectin, vimentin, type II collagen and histones [3]. Citrullination is catalyzed by peptidylarginine-deiminase (PAD), a calcium-dependent enzyme. Another post-translational process that drives the formation of autoantigen in RA is carbamylation. It is defined by the change of the amino acid lysine to homocitrulline. Smoking and chronic inflammation, both characteristic features in the context of RA pathogenesis, are thought to enhance the process of carbamylation [4].

A series of environmental factors, such as cigarette smoking and silica have been associated with RA development. Smoking has provided some strong evidence of the potential to generate citrullinated proteins. In a historical Danish twin cohort study, Svendsen et al. concluded that 20 years of smoking doubles the risk of RA development [5]. Environmental factors can generate an epigenetic regulation and influence specific RA immune reactions to citrullinated proteins [6]. Exposure to smoke, silica or carbon-derived nanomaterials can activate antigen-presenting cells and PADs by triggering mucosal toll-like receptors.

Pathogenic infections associated with the onset of rheumatoid arthritis can lead to a faulty immunological tolerance towards essential self-antigens. This can subsequently cause chronic joint inflammation along with an imbalance between the various T helper subsets [7].

Among the infectious agents regarded as potential triggering factors, *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* are of particular interest. Studies on both microorganisms have linked periodontal infection to RA autoimmunity. *P. gingivalis* is constitutively equipped with the PAD enzyme [8]. The presence of *P. gingivalis* has been linked to both autoantigen release and ACPA production [3]. Periodontal space and lungs are thus considered potential triggering sites for RA. The role of *Epstein–Barr virus* (EBV), *cytomegalovirus* and *parvovirus B19* (B19) are controversial. Sherina et al. conclude in a 2017 study that high antiviral antibody levels for EBV and B19 may, in fact, have a protective role against ACPA-positive RA [9].

When highlighting the etiopathogenesis of RA, certain species of *Collinsella* are involved by establishing an increase in gut permeability, a decrease in the activity of tight junction proteins and by way of regulating the synthesis of IL-17A at the level of the epithelium. More broadly, gut dysbiosis has been implicated in the pathogenesis of RA through the recruitment of essential inflammatory mediators such as TNF-alfa, IL-6, and IL-17A [10]. One metagenome-wide association study recently revealed a link between RA and multiple species belonging to the genus *Prevotella,* such as *Prevotella denticola* [11].

There has not been thus far sufficient evidence to advocate for a clinical correlation between an infection with *Helicobacter pylori* (*H. pylori*) and RA, despite the results of experiments performed in vitro, which have revealed that chronic stimulation of B lymphocytes with the urease made by the *H. pylori* leads to an increased production of autoantibodies, specifically rheumatoid factor (RF), an immunoglobulin M (IgM) antibody directed to the Fc portion of IgG. While RA patients are at risk of developing peptic ulcers, it is unclear whether this is due to an increased prevalence of *H. pylori* infection or because of the ample use of anti-inflammatory, non-steroidal medication [12].

It is known that viruses can modify the clinical picture depending on genetic background, immune responses elicited by the host and the type of virus strain involved. Certain viruses such as *parainfluenza* have been associated with a higher incidence of RA in men, and more broadly with both male and female patients below the age of 40 [13].

There is an overall agreement that pathogenesis in RA is linked with genetic susceptibility. Studies have found more than 100 susceptibility loci in RA patients [14]. Twin studies in which heritability is reported to be ~60% provides strong evidence for this matter. It is also speculated that the interplay between environmental factors and genetics may, in fact, lay the foreground for the specific autoimmune reactions and further transition to the joint disease stage. A major genetic risk factor associated with RA concerns the human leucocyte antigen (HLA) class II region. The conserved amino acid sequence located at the antigen-binding site of the antigen-presenting molecule, encoded by the alleles of HLA-DRB1 is referred to as the shared epitope (SE) [14]. The strongest genetic associations in RA are identified in the HLA-DR1 and HLA-DR4 serotypes. Some studies do not link the HLA II locus to ACPA response directly [15, 16], rather to the progression from ACPA(+) to ACPA(+) RA, through a process of maturation via T cells which activate ACPA-producing B-cells. It is assumed that SEs play an important role in the antigen presentation process. Thus the different alleles at the SE level can influence the interaction between HLA class-II and the specific receptor of T lymphocytes (TCR) or between HLA class-II and antigen. Studies on SE phenotypes and specific HLA-DRB1 subtypes revealed that HLA-DRB1*04 has a significantly higher frequency in RA and is associated with seropositivity independent of the smoking status [17, 18].

ACPA(+) and ACPA(−) RA patients have similar hereditability, reported at 68% and 66%, respectively. The two serotypes display differences in genetic

susceptibility, including a significantly lower SE contribution in the seronegative disease of 2.4%, compared to 18% in ACPA(+) RA [19]. A major genetic risk factor outside the HLA region concerns the protein tyrosine phosphatase non-receptor 22 (PTPN22) gene [14]. Other non-HLA susceptibility genes identified in both disease subgroups include TNFAIP3, GIN1/C5orf30, STAT4, ANKRD55/IL6ST, BLK [14]. The protective role of specific HLA-DRB1 alleles has been reported in one meta-analysis, in which HLA-DRB1*13 accounted for a lower risk of ACPA-positive RA [20]. Studies on the outcome of patients with undifferentiated arthritis determined several susceptibility loci (PTPN22, TRAF1/C5, AFF3, KIF5A, TAGAP) related to disease severity [21]. These genetic loci may provide a tipping point in the disease progression and identify as prognosis markers for the transition to an established RA [14].

Autoantibody secretion generated by the autoantigen release can precede the onset of fulminant joint disease by several years [22]. High-titer RF is of high diagnostic and prognostic value and is linked to erosive RA. ACPA is the most specific marker antibodies for RA and is linked, similarly to RF with erosive disease. Another autoantigen with potential pathogenetic relevance is the heterogeneous nuclear ribonucleoprotein-A2 (RA33) which is targeted by autoreactive T cells [2].

Both the innate and adaptive immune systems contribute to initial antibody production and further development of sustained chronic synovitis. The fibroblast-like synoviocytes interact with cells of the innate immune system which include macrophages, monocytes, mast cells, and dendritic cells. ACPA target citrullinated proteins on the surface of macrophages and monocytes, which in turn enhances the production of pro-inflammatory mediators [3]. Activated mast cells have an essential contribution to the pro-inflammatory milieu through IL-17 A secretion [23]. The involvement of the adaptive immune response is based on the antigen activation of major histocompatibility complex (MHC) class II dependent on T cells (cell-mediated immunity), cytokine release, and stimulation of B-cell antibody production (humoral immunity).

The exact relationship between reported antibodies relating to the disease and the pathogenic features observed remains a mystery due to lack of research. Limited data thus far comparing RA serotypes indicate different underlying processes that can drive parallel pathways towards similar clinical phenotypes. There is evidence of T-cell-mediated immune dysregulation in RA irrespective of autoantibody production [24]. Serotype distinctions include differences in immune cells subtypes, cytokines and chemokines [25].

The synovium in patients with established RA displays an inflammatory infiltrate composed of a heterogeneous set of immune cells. Neutrophils present in the synovial fluid have an extended lifespan and feature an enhanced production of reactive oxygen species and neutrophil extracellular traps (NETosis) [25]. Synovial T cells, especially CD28-CD4+ T cells are autoreactive, produce interferon-gamma (IFN-γ) and are resistant to apoptosis [26]. Differentiated effector T cells, helper types (Th1, Th2, Th17) contribute to cytokine secretion. Antigen-specific T cells or T cells activated by the pro-inflammatory milieu of the synovia are capable of stimulating monokine production by monocytes and macrophage-like synoviocytes, especially interleukins (IL-1, IL-6) and TNF-α [26]. The T-cell dependent IL-17 cytokine has a significant pathogenic role by inducing cartilage degradation and bone erosion through stimulation of receptor activator of NF-κB ligand expression on osteoblasts. The Th17 cells population is increased both in joints and peripheral blood of patients with RA [27]. IL-23 produced by dendritic cells promotes the survival and expansion of Th17 cells. It is thought that an imbalance between IL-12 (Th17 inhibitor) and IL-23 secretion by dendritic cells contributes to RA pathogenesis [26].

Various chemokines, cytokines, growth factors, and cell adhesion molecules promote neovascularization in the setting of chronic inflammation. In RA, there is an abundance of angiogenic factors, of which VEGF is of major importance. Inflammatory cytokines, such as TNF-α, IL-1, IL-6, IL-17, IL-18, granulocyte and granulocyte-macrophage colony-stimulating factors (GM-CSF), may also induce angiogenesis through VEGF-dependent pathway [28, 29]. Affected patients have been shown to have high levels of VEGF and significantly lower levels of IL-35 [30, 31].

The inflammatory cascade and synovial neoangiogenesis drive specific structural changes related to RA pathology. Synovial hypertrophy is related to abnormal proliferation of dysfunctional fibroblast-like synoviocytes (FLS), resistant to apoptosis. FLS sustain joint damage by the secretion of MMPs and tissue inhibitors of metalloproteinases. Cartilage damage is induced by the action of MMPs which cause disassembly of the type II collagen network. Also, chondrocyte apoptosis is enhanced by cytokine, mainly IL-1 and IL-17A. Inflammatory cytokines promote bone erosion through pro-osteoclastogenic effects. Also, osteoclast differentiation may be induced via immune complexes and antigen-binding of ACPA on osteoclast precursors. Bone erosions are usually located at the site where the joint capsule inserts on the periosteum [32, 33].

3. Rheumatoid arthritis: clinical aspects

3.1 Clinical picture of early arthritis

One of the most important things to remember about RA is that it should be diagnosed as early as possible. This is of paramount importance since rheumatoid arthritis is a disease characterized by structural bone lesions that lead to bone deformity and functional disability. However, trying to make an early diagnosis of this disease can prove to be extremely difficult sometimes, and that is because there is no specific or particular symptom or sign of either early or very early RA (eRA).

Moreover, the 2010 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for RA, which tries to capture patients as early as possible, is to be applied ONLY to people having at least one joint with CLINICAL SYNOVITIS [34]. But, even when synovitis is present, it is not always the expression of early RA.

While early signs and symptoms of RA can be mimicked by other diseases, there are some which should be taken into consideration, such as fatigue, minimal joint pain, joint warmth, joint stiffness, limping, reduction of range of motion, fever, anemia, and depression. It is easy to see that all these are not at all specific, not even for full blown rheumatoid arthritis and even less so for early/very eRA [35].

The interest of knowing how to interpret symptoms in eRA derives from multiple reasons, one of the most important being that it would be extremely useful (on a personal, as well as a societal level) to be able to predict, based on the symptoms of people, who will develop RA and who will not. Unfortunately, with the knowledge we have today, this is not yet feasible. There are still too few studies designed especially for assessing symptoms during this initial period of the disease [36].

Nevertheless, if one tries to group the symptoms which may appear during the early stages of RA, one can delineate three categories [37]:

a. Non-specific symptoms: which are in fact, general (systemic) symptoms produced through the intervention of pro-inflammatory cytokines, which may, thus, intervene in any inflammatory disease, articular or not. Among them, we

can outline fatigue, a general feeling of being "un-wellbeing," anxiety, depression, non-specific myalgia or sharp/dull pain near the joints but not in the joints. Sometimes there is low-grade unexplained fever and, rather frequently, sleep disturbances which worsen the general feeling of being "un-wellbeing." To take just one example, fatigue, which is a very common and, frequently, overlooked symptom in RA, correlates with active disease in the sense that it is more pronounced when the disease activity is higher. Its origin is not well understood; it may be the response of the organism to the presence of chronic inflammation, mediated by the action of IL-6. Poor sleep and anemia can contribute to fatigue in RA. This symptom can affect relationships, emotions, mood, productivity, creativity, the general feeling of happiness. Fatigue from RA can associate with poor appetite and weight loss [35].

All these non-specific symptoms may appear in variable proportions in people affected by eRA and their importance resides in the significance pertaining to the risk of a person presenting these symptoms, to develop established RA.

b. Symptoms related to the joints; may vary from mild joint stiffness (sometimes, without having the so-called characteristics of inflammatory joint stiffness) to non-explicable, non-specific joint pain, usually of short duration, with no local signs of inflammation of the joint. As one can see, these are also totally unspecific to the possibility of later developing RA; which is why their presence should prompt a very careful evaluation. On the other hand, when people complain of joint pain, diagnosing them might be easier as pain can motivate people to see a doctor.

c. Symptoms related to functional capacity. These symptoms interfere with one's ability to perform daily living activities. For instance, when one is not capable of performing the opposing movement of the thumb, and hence, not able to make a fist, one will not be able to open a jar's lid. Likewise, if the symptoms are located in the lower limbs, one might not be able to walk or wear shoes. As can be ascertained, these are elements of functional disability that one can encounter in the established RA patient, as well as in other diseases. Therefore, as these are also non-specific to the early phase of RA, they should also be evaluated with care, to reach a correct diagnosis, more so a therapeutic one.

Regardless of the category of symptoms an individual has, the interpretation of their significance is much more difficult and doctors would like to be able to have some hints as to WHAT should he investigate in order not to miss the right diagnosis, in the given window of opportunity. Investigations should be primarily directed to populations or subjects at high risk including female gender, smoking, alcohol, obesity, unhealthy dietary intake, having a family member diagnosed with RA, presence of ACPA, poor dental health, low socioeconomic status. As such, people having symptoms of the above and also one or more of the mentioned risk factors should be given the most attention in assessing their presenting health condition [38].

One other method used to evaluate symptoms of eRA is to, retrospectively, question patients with established RA about their original symptoms [39], followed by making appropriate questionnaires, which are to be used prospectively, to make an early diagnosis. Such an analysis of the literature on this topic was made by Stack et al. and, reviewing 26 papers concentrating on the way patients diagnosed with RA reported their initial symptoms, they found 5 "themes" that describe patient's initial complaints [39].

The first is concerning the swelling of the joint. It was often described as being severe and was most frequently localized at the hands and feet [40–42]. It also has an impact on the ability to perform activities of daily living [43, 44]. Patients reported that it was a progressive feature [45, 46] and that it was sometimes associated with some degree of joint pain [47, 48]. These findings suggest that it might be rational to closely monitor a person complaining of recent onset sensation of joint swelling, even if the swelling itself is not apparent to the doctor.

The second theme used by established RA patients to retrospectively describe their initial symptoms is one of pain and local sensibility, with multiple localizations, again, more frequently, on the hands and feet [49–52] and rarely on the shoulders and hips. Two rather descriptive patterns were identified:

a. gradual occurrence of pain: the most often used descriptors were "episodic pain," "gradual pain," "easy pain," "vague pain." The interpretation given by patients was usually taking into account the activities performed during the day, therefore not much attention was given to the pain until it became persistent and higher in intensity [53–55];

b. acute onset of pain: the most often used descriptors in this circumstance, were "severe pain," "resistant pain," "disability provoking pain," "unbearable pain." Some of the patients describe the occurrence of pain like an "on-off switch" phenomenon. Most often, this pattern was rapidly followed by the occurrence of other symptoms, as well. As such, this kind of joint pain is the one that will get the patient to visit the doctor much faster [45, 46, 55].

The third theme of patients' symptoms is joint stiffness. Quite surprisingly, this was very briefly mentioned and patients never gave a full description, neither was any emphasis put on the significance of the term [46]. In some instances, it was associated with other symptoms, such as fatigue and swelling of the joint [55].

The fourth theme reported retrospectively by patients with established RA, to describe their initial symptoms, is fatigue and muscular weakness [56]. Some patients have reported this as the impossibility to "lift my food tray" [57] or to "lift my toddler" [43]. It appears that fatigue is a really important feature of the beginning of eRA [56]. Some patients even described a "flu-like" sensation of muscular weakness all over their bodies [58].

The fifth and last theme that patients referred to when remembering their initial symptoms of RA is the emotional impact of prolonged suffering [55, 59–61]. It is easily conceivable that a state of sustained discomfort in which the patient does not know for how long it will last and how it may evolve will produce emotional distress. Due to this, patients reported feelings of fear, anger, anxiety, uncertainty, ambivalence. For some patients, this emotional impact was so strong that they had depression and even suicidal ideation [59]. When the emotional disturbance is significant, finding a diagnosis, even that of established RA, comes as a relief [60].

These five themes revealed by Stack et al. are useful for daily clinical practice due to the fact that they can point out of the mass of patients that a physician sees every day, those that the physician should actively follow closely, in order to be able to make the right diagnosis of (preferably) eRA, if this should be the case [39].

Since RA is a systemic disease, potentially affecting any organ system in the body, in the proper context, some of the extraarticular manifestations of the disease, can point out the necessity to further search for a correct diagnosis. Of the numerous such manifestations, one should perhaps remember the following, as a possible manifestation of eRA: peripheral nerve entrapment (e.g. carpal tunnel syndrome), "idiopathic" pulmonary fibrosis or nodules, unexplained amyloidosis,

cardiac nodules of unknown origin, cutaneous nodules (that can and should probably be biopsied when unexplained), "idiopathic" vasculitis [38].

As we know, in 2014, Zhao et al. developed classification criteria for eRA, which take into account both clinical and biological aspects of the disease and perform at a variable but acceptable specificity and sensitivity [62, 63]. Nevertheless, they imply that the presence of clinically evident arthritis; and this is, sometimes, not eRA, since everybody tries to make the diagnosis as early as possible! Therefore, these criteria are useful but will miss some of the early or very early RA cases.

One must not forget that we also have the EULAR recommendations on treatment of eRA [64], which state, as one of the overarching principles that "A definitive diagnosis in a patient with early arthritis should only be made after a careful history taking and clinical examination, which should also guide laboratory testing and additional procedures," while in the recommendations it is mentioned that "Clinical examination is the method of choice for detecting arthritis" and that "if a definite diagnosis cannot be reached and the patient has early undifferentiated arthritis, risk factors for persistent and/or erosive disease, including number of swollen joints, acute phase reactants, rheumatoid factor, ACPA and imaging findings, should be considered in management decisions. Patients at risk of persistent arthritis should be started on DMARDs as early as possible (ideally, within 3 months), even if they do not fulfill classification criteria for an inflammatory rheumatological disease." Thus, EULAR provides us with some guidance as to how to attempt to make a diagnosis as early as possible, as well as following it swiftly with the correct management [64].

Identifying (especially) seronegative future established RA patients in the earliest stage of their disease is a difficult endeavor. Until now, we do not know for certain if the symptoms of a person are, by themselves, enough to efficiently stratify the risk of a person to develop established RA [65]. And this is an important unmet need in the field of RA, which precludes continuous study to lower the pressure on the healthcare system, by preventing the major, often irreversible, disabilities associated with this disease, through better early diagnostic expertise.

3.2 Established rheumatoid arthritis

Joint pain is the universal characteristic in RA patients, but the long-standing disease has several features, easily recognizable by a trained rheumatologist, but often misdiagnosed by other specialists. The key to the recognition of the clinical and physical findings of RA is the capability to recognize the outcome of the synovial proliferation and inflammation [66]. As was already stated before, RA can affect any peripheral joints, with predilection on the small joints of the hands and feet, followed by the elbow, shoulder, ankle or knee.

3.2.1 Hand and wrist

Hand and wrist involvement with secondary deformity is a typical feature of late RA [67, 68]. If in the eRA, the physical findings are not extensive, in the late disease one can identify an entire panel of changes. The late, irreversible and most prevalent changes in hands include "swan-neck" and "boutonnière" deformities, along with metacarpophalangeal joints (MCP) swelling, subluxation and "ulnar drift," or ulnar deviation (**Figure 1**). Swelling of the MCP and wrists joints, together with atrophy of the intrinsic muscles of the hand, leads to the aspect of the hand like "two-humped camel's back," while the ulnar deviation makes it similar to the "mole's paw." Persistent inflammation adjacent to ulnar styloid, together with the laxity of the radioulnar ligament leads to a movement of the styloid under the examiner's pressure, similar to the "piano key" [68].

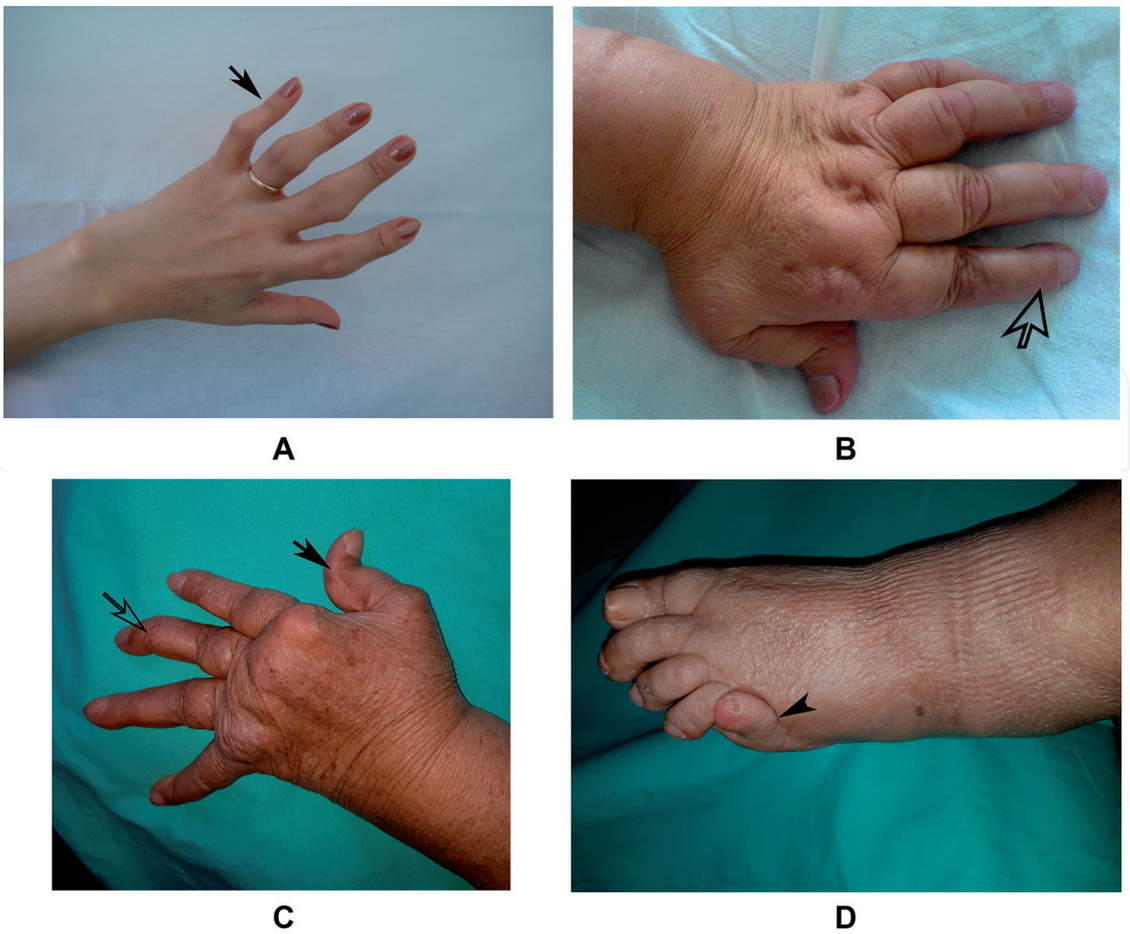

Figure 1.
Images of the small joints of the hands and feet, showing boutonnière - arrow (A and C), swan-neck – Empty arrow (B and C) and hammer toes deformities – arrowhead (D).

The boutonnière deformity presumes the flexion of the proximal interphalangeal (PIP) joint and extension of the distal interphalangeal (DIP) joint [69], whereas the swan-neck, by contrast, means hyperextension of the PIP and flexion of the DIP [68, 70]. The cause of the boutonnière deformity is the lesion of the central slip of the extensor tendon, secondary to tenosynovitis and PIP swelling, with the lateral and volar displacement and conversion of the lateral bands of the extensor tendon, into flexors of the PIP joint. In time, shortening of the tendon leads to hyperextension of the DIP joints. If the DIP swelling is disrupting the extensor tendons, the joints will be forced to remain flexed (due to the action of the only remaining tendons, the flexors). Besides, if the bulging of the PIP is volar, the lateral bands subluxate dorsally, generating hyperextension in the PIP joint and the aspect of the swan-neck deformity.

The involvement of the thumb results in severe functional impairment, due to the loss of the grip between the index finger and the tip of the thumb. The most prevalent pathological aspect of the thumb in RA is one of a "flails," followed by the boutonnière deformity, which is the same as described before, just one joint back proximally [66].

Extensor tenosynovitis might lead to tendon ruptures, especially at the level of the 6th compartment of extensors, while flexor tendon involvement includes besides thickening of the tendon sheet that could generate either "trigger finger" or a carpal tunnel syndrome [66].

It is not uncommon that the same hand develops different deformities simultaneously leading to a major impact on hand function and subsequently on the ability to perform daily life activities [70].

3.2.2 The elbow

The elbow is often involved both early and in longstanding rheumatoid arthritis. Because of its unique role in maneuvering and positioning the hand in space, the loss of normal motion and stability, or increased pain with the use of this joint are all significant sources of impairment in patients with RA [71]. Synovitis of the elbow joint can be identified by palpation between the olecranon and the epicondyles, especially the lateral one. Olecranon bursitis is a common finding in patients with RA but should be differentiated from the one appearing in polyarticular gout. To mention, in RA it tends to be more frequently bilateral [66].

3.2.3 The shoulder involvement

The shoulder joint is a complex joint and because of its deep location it is difficult to confirm accurately the joint effusion, or the rotator cuff tears only by physical examination, therefore shoulder lesions are often under diagnosed [72]. When involved, it might generate limitation of motion in all planes, with suggestive secondary scapulothoracic movement, or "shoulder pad" sign. The pain generated by joint effusion, subacromial subdeltoid bursitis, or rotator cuff tendon tears is often referred into the deltoid muscle. The fluid inside the biceps tendon sheet is not uncommon [72].

3.2.4 The knee joints

Knee joint synovitis is a frequent finding in patients with RA, anterior swelling being easily detectable through clinical examination, by the "bulge sign" or the ballottement of the patella with the index finger downwards, into the fluid. The Baker cyst is a benign fluctuant swelling of the gastrocnemius-semimembranosus bursa in the popliteal fossa at the back of the knee [73], resulted after severe effusion at the level of the knee joint. Hip joint involvement is associated with pain over the greater trochanter, probably due to bursitis and pain elicited by Patrick's test, or Flexion-Abduction-External Rotation maneuver (FABER) [74].

3.2.5 The ankle involvement

The ankle is an important weight-bearing joint, with a lot of structures involved in RA. Synovitis is common at the level of the tibiotalar subtalar and talonavicular joints, with a high impact on the patient's quality of life [75]. Tenosynovitis of the medial or lateral compartments is increasing the functional impairment. The forefoot comes with specific changes, including calluses under the metatarsal heads and secondary ulcerations, or joint deformities leading to the "hammertoes" aspect (**Figure 1**), resembling the piano hammer [66].

3.2.6 Other types of involvement

Bilateral pain, tenderness, swelling and limitation of jaw movements might be the result of temporomandibular joint involvement and due to these symptoms, patients experience limitations in their daily activities, such as eating, speaking and swallowing.

The involvement of the cervical spine is the most serious skeletal manifestation in patients with RA. Instabilities of the upper cervical spine can lead to headache, neck pain, paresthesias, weakness, signs of vertebrobasilar insufficiency or neurological complications such as bowel and bladder sphincter impairment [66].

3.2.7 Extraarticular features of RA

Most frequent extraarticular features of RA are represented by the *rheumatoid nodules*, with subcutaneous disposition on the extensor surfaces and joints at sites of chronic mechanical irritation and typical clinical characteristics [76, 77]. The diagnosis requires sometimes biopsy to differentiate them from gouty tophi but need no specific treatment unless they are causing pain, interference in mechanical function, nerve compression, or other important local phenomena. It is uncommon to find nodules within the first year from the disease onset, whereas it is more like a longstanding disease feature. To note, that patients with rheumatoid nodules are at an increased risk of developing other severe extraarticular manifestation. Association of HLA-DRB1*04 gene and smoking were found to be important predictors for the extraarticular disease [77].

Hematological abnormalities are not uncommon, especially anemia of different causes, such as chronic inflammatory disease, through hepcidin intervention and blockage of iron inside macrophages, or secondary to the gastrointestinal complication of the anti-inflammatory treatment or loss of folic acid during methotrexate therapy. Thrombocytopenia is uncommon, usually drug-induced. More frequently, RA patients manifest thrombocytosis of unknown cause, but correlated with disease activity and involved joint count. Lymphadenopathy is frequent in active RA, with a benign histological pattern, usually located in axillary, inguinal or epitrochlear areas. The lymph nodes are usually not painful and mobile [76].

Felty's syndrome represents the association of RA with splenomegaly and leukopenia (neutropenia) and usually occurs in seropositive patients with longstanding, deforming disease with rheumatoid nodules present. Some of those patients may also present thrombocytopenia and extremity ulcerations (lower leg) and hyperpigmentation of the skin, and are positive for antinuclear antibodies. To mention an increased risk of opportunistic infections, due to neutropenia [78].

Hepatic involvement is non-specific and minimal, related mostly to treat adverse effects, with an increase of liver enzymes that should decrease with discontinuation of the incriminated drug. On the other hand, in up to 65% of patients with Felty's syndrome, there are liver abnormalities, from portal fibrosis and abnormal lobular architecture to nodular regenerative hyperplasia [77, 78].

Pulmonary complications of RA are frequent, with men being more often affected than women and include pleural disease, in up to 50% in autopsies studies, parenchymal peripheral pulmonary asymptomatic nodules (PPP nodules), that can measure up to 8 cm in diameter, diffuse interstitial pulmonary fibrosis, or bronchiolitis obliterans organizing pneumonia (BOOP). Pulmonary nodules and pneumoconiosis appear in patients with RA and extensive exposure to coal dust (Caplan's syndrome), silica and asbestos. The RA- associated interstitial pneumonitis should be distinguished from the one generated by the methotrexate toxicity, the last one usually having a subacute onset, with low radiographic evidence of fibrosis, but rapid symptom progression. Inflammation of the cricoarytenoid joint might lead to other respiratory complications – upper airways obstruction [76, 79].

Heart disease presumes all cardiac structures involvement by intricate complex mechanisms of nodule formation, vasculitis of the coronary arteries, amyloidosis, serositis, valvulitis or fibrosis. Pericarditis is the most common cardiac feature of heart involvement, usually asymptomatic [80, 81]. Myocardial disease secondary to granulomatous lesions similar to rheumatoid nodules can lead to arrhythmia. Valvular granulomatous lesions might generate dysfunctionalities at the level of the mitral and aortic valves.

Rheumatoid vasculitis is a panarteritis, with mononuclear cells infiltrate and fibrinoid necrosis, which leads to clinical manifestations such as peripheral

neuropathy, palpable purpura or visceral infarcts. It is frequently associated with increased RF, erosive disease and rheumatoid nodules [80].

Other extraarticular manifestations of RA include *neurological impairment*, secondary to mononeuritis multiplex, to nerve compression by synovial proliferation (carpal tunnel syndrome) or to atlantoaxial subluxation; *eye involvement* includes keratoconjunctivitis sicca, episcleritis or scleromalacia perforans (secondary to a perforating rheumatoid nodule). Glucocorticoids might cause glaucoma and cataracts and chloroquine derivates cause retinopathy; the gastrointestinal disease can be secondary to mesenteric or hepatic vasculitis or associated with anti-inflammatory treatment [77].

Amyloidosis might complicate RA in up to 0.7% of patients with longstanding disease, leading to a poor outcome, with only 58% survival rates at 4 years [76].

Bone involvement is also frequent in rheumatoid arthritis patients, secondary to osteoclastic hyperactivity and or osteoblastic hypoactivity, in patients with impaired moving, local effect of proinflammatory cytokines or to the adverse effect of glucocorticoids [82].

Muscle atrophy is frequent, especially near affected joints. Inflammatory myositis or glucocorticoid myopathy (usually with the use of higher doses) might be present in patients with RA [76, 77].

4. Rheumatoid arthritis: imaging

Recent advances in the imaging field and therapeutic possibilities are changing the outcome in RA. Still, conventional radiology (CR) represents the main imaging method for rheumatoid arthritis patients' evaluation, in daily practice. The treat to target approach has brought into attention the new methods, ultrasonography (US) and magnetic resonance imaging (MRI), as more sensitive and specific imaging modalities. In this way, CR remains a method for identifying old and late changes, lesions that already happened, while US and MRI are the methods for identifying acute inflammatory lesions and details of small structural changes. Other methods, such as arthrography, computer tomography (CT) or scintigraphy remain suitable for complex cases and will not be subject to our paper [77].

Conventional radiology, a cheap and widely available method shows a wide spectrum of changes at the level of the peripheral joints, including hands, wrists, feet, and ankles or even larger joints (knee, shoulder, elbow), depending on the disease duration. Thus, imaging of any joint disorder, including rheumatoid arthritis should start with this method [77].

Peripheral joint involvement shows typical radiographic changes in rheumatoid arthritis including soft tissue swelling related to joint effusion or synovitis, juxta-articular osteoporosis, joint space narrowing and the late disease changes, bone erosions, and ankylosis. To note, the fact that joint space narrowing (JSN) is a good indicator for hyaline cartilage loss, as the articular space is mainly composed of the two-cartilage thickness sum, normally about 2 mm [83]. A comparison with adjacent or contralateral joints might clarify narrowing. Erosions occur earliest at the level of the carpal bones, especially pisiform or triquetrum, at the level of the ulnar styloid and second metacarpophalangeal (MCP) joint, in the bare area (metacarpal head, with no cartilage) [84]. Studies showed that up to 30% of the patients do not develop erosions in the first 2 years from disease onset, but still, most of the patients do, a fact that led to the expert recommendation of repeating CR every 6–12 months in eRA and every 1–2 years in late disease [85].

To quantify lesions and for a better follow-up of the disease, Sharp proposed a scoring system of erosions and JSN of hands [86]. The modified Sharp score, proposed by Van der Heijde, included feet, for a total of 16 areas evaluated for erosions and 15 for

JSN in each hand and 6 areas for erosions and six for JSN in each foot [87]. Radiographic progression can redefine remission, as clinically quiet joints often progress.

CR of the spine might show some abnormalities, especially in the cervical segment, which is involved in more than half of the patient [85]. The most frequent finding in this area is atlantoaxial subluxation and basilar invagination [88, 89], both identified best in a lateral radiograph, with the flexed neck. For the diagnosis of atlantoaxial subluxation, one should measure the distance between the anterior arch of C1 and anterior aspect of the dens of C2. Expected values in normal subjects should not exceed 3 mm in adults and 5 mm in children. The distance higher than those cutoffs lead to a diagnosis of subluxation and the ones higher than 8 mm require surgical intervention. Basilar invagination diagnosis should be confirmed by MRI or CT [88].

US was recently included by EULAR recommendations on the use of imaging, between the techniques with a potential role in RA diagnosis and management [90, 91]. The reflection of ultrasound waves by body structures generates US images of those structures in the greyscale (GS) [92]. Adding the Doppler technique to the examination, we obtain information on the blood flow inside structures. The higher the ultrasound frequency, the higher the detail on the image, but lower penetrance. In reverse, the lower the frequency, the higher penetrance, but with a low-quality image. Therefore, the use of appropriate probe frequencies is required for an optimal US evaluation. The higher frequency transducers (e.g. 10–18 MHz) are mandatory for superficial structures, such as small joints of the hands and feet and ligaments and tendons, whereas lower frequency probes (e.g. 5–12 MHz) are useful for deeper joints, such as hip, knee or shoulder [90].

For most of the joints, US allows visualization of most features of rheumatoid arthritis, including joint effusion, synovial hypertrophy, bursitis, tenosynovitis or bone erosions, being more sensitive than clinical examination for depicting subclinical synovitis and other inflammatory (**Figure 2**), acute changes and more sensitive than CR for detection of bony structural changes, like erosions [93, 94].

The outcome measurement in the rheumatology group (OMERACT), under the EULAR umbrella, developed definitions for all the US findings in rheumatology, which should be confirmed in two perpendicular planes. Thus, effusion is defined as abnormal hypoechoic or anechoic intraarticular material, that can be displaced and compressed, with no Doppler signal, whereas synovial hypertrophy or proliferation is defined as abnormal hypoechoic intraarticular tissue that is not displaceable and compressible but may exhibit Doppler signal [95].

Other inflammatory, acute, feature of RA is tenosynovitis, identified by the US as hypoechoic or anechoic thickened tissue with or without fluid within the tendon sheath, which is seen in two perpendicular planes and which may exhibit Doppler signal (**Figure 3**) [95].

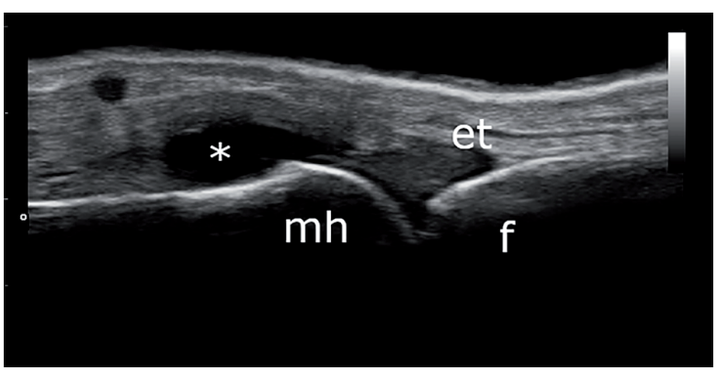

Figure 2.
US images showing - synovitis of MCP joint (asterisk – synovitis, mh – metacarpal head, f – phalanx, et – extensor tendon). Original image, from the personal archive (FLORIN VREJU).

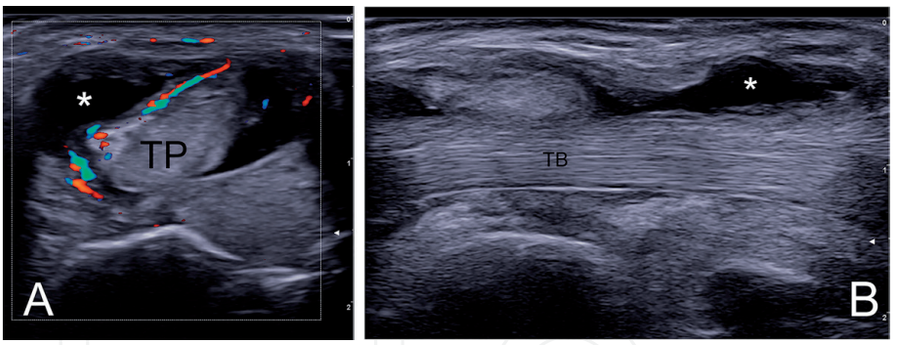

Figure 3.
US images showing - tenosynovitis of the tibialis posterior (asterisk – tenosynovitis) in transverse, with Doppler activity (A) and longitudinal scan (B).

4.1 Original image, from personal archive (FLORIN VREJU)

Since the US is more and more used in daily practice both for diagnosis and monitoring disease, a scoring system for synovitis became mandatory. The most used is the one proposed by Szkudlarek et al. [96] that scored fluid as follows: grade 0 – no effusion, grade 1 – minimal amount of fluid, grade 2 – moderate (no distension of the joint capsule) and grade 3 – extensive fluid collection (with distension of the joint capsule). The synovial hypertrophy was scored as grade 0 – none, grade 1 – minimal synovial thickening, grade 2 – synovial thickening bulging over the line linking top of bone cortical (no extension along bone diaphysis), grade 3 – synovial thickening bulging over the line, with extension to at list one of the bone diaphysis. Semiquantitative grading included grade 0 – no flow, grade 1 – single vessel signal, grade 2 – Doppler signal in less than half of the area of synovium and grade 3 – Doppler signal over more than half of the synovial area (**Figure 4**). Recently was developed a new combined score, Global OMERACT – EULAR Sonography Scoring (GLOESS), which considered the higher score of GS or power Doppler (PD) as the score for the joint [97].

The most characteristic US finding in RA is bone erosion, defined as an intraarticular step-down discontinuity of the bone surface that is visible in two perpendicular planes [95]. Scoring system for erosions according to Szkudlarek et al. defined grade 0 as normal bone cortical, grade 1 as bone irregularities, but without defect in two perpendicular planes, grade 2 – the defect is seen in two perpendicular planes, grade 3 – extensive bone destruction [96]. A more accurate grading score for erosions was the one based on irregularity size: grade 0 – no erosions, grade 1 – erosion <1 mm, grade 2 – small erosion between 1 and 1.9 mm, grade 3 – moderate erosion, between 2 and 4 mm, grade 4 – dimensions higher than 4 mm [98].

Validity of the method and sensitivity to change were primarily demonstrated for all US findings by Terslev et al. [99, 100], thus making it an important imaging method in the management of RA, along with other studies which confirmed predicting value in the treatment response [101, 102], and the role in discriminating between clinical and imaging, real remission [93, 103, 104].

However, even if the diagnosis is enhanced and not made only by the US and even if it is highly operator dependent, ultrasonography offers a cheap and dynamic possibility for monitoring the disease activity and progression and for assessing the persistence of subclinical inflammation in RA [92, 93].

Magnetic resonance imaging represents a favored and favorite imaging method in inflammatory joint diseases, as it allows evaluation of all the structures involved in those pathologies, being able to depict synovitis, tenosynovitis, erosions and more than this, the bone marrow edema, a feature that remains hidden to the

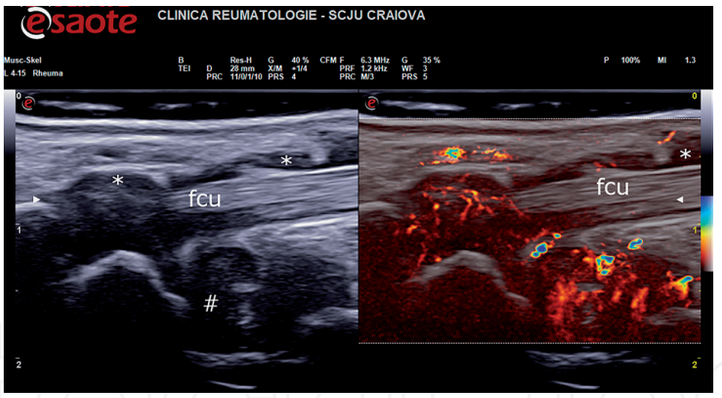

Figure 4.
US images showing - tenosynovitis of flexor carpi ulnaris and wrist synovitis, with Doppler signal present (asterisk – tenosynovitis, fcu – flexor carpi ulnaris, # – wrist synovitis).

US. MRI sequences that can be useful in RA patients include T1-weighted (T1w), favored by short imaging times and good anatomical details, T2-weighted (T2w) and short tau inversion recovery (STIR), both good for depicting inflammation, such as bone marrow edema or synovitis [105]. Adding intravenous contrast agent, like paramagnetic gadolinium (Gd) to T1w sequences allows us to visualize detailed structural lesions and, at the same time, the tissue vascularity and perfusion, inflamed synovium being easily recognizable. It is always advisable to use two sequences in parallel, to compare high signals in the water-sensitive (WS) one (T2w or STIR) with high-resolution details in the fat sensitive one (T1w). Thus, one can identify active erosions, by a hyperintense signal in WS sequences and hypointense signals in the T1w image [105].

As a conclusion, MRI allows identification of synovitis, tenosynovitis, and erosions and proves to be an important tool in the diagnosis, in the disease activity monitoring and treatment response. However, even if it brings complete information on the peripheral joints, the use of MRI in RA patients in clinical practice remains lower in comparison to US and CR, due to issues related to availability, cost, and duration of an examination. More than this, it cannot offer a dynamic assessment of structures [77].

5. Rheumatoid arthritis: pharmacotherapy

According to guidelines, the therapeutic approach for RA patients includes an early start of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), followed by biologic DMARDs (bDMARDs) and targeted synthetic DMARDs, aimed at a low disease activity or remission.

Regarding csDMARDs, Methotrexate (MTX) remains the first therapeutic choice, due to its immunomodulatory and immunosuppressive action, efficacy and sustained effect; it is administered orally or subcutaneous, with doses starting from 7.5–10 mg weekly up to 20–25 mg/week, In case of MTX intolerance, leflunomide (10/20 mg/day) or sulfasalazine (2–3 g/day) should be considered as therapeutic agents [106]. Treatment monitoring requires CBC, ALT, AST and creatinine evaluation at baseline, every 2–4 weeks for the first 3 months, every 8–12 weeks for the next 3–6 months and every 12 weeks after. Screening for hepatitis B and C should be performed before initiating the treatment. An increase over three times of hepatic enzymes requires treatment interruption [106].

If the therapeutic target is not achieved with csDMARD therapy, bDMARDs or tsDMARDs should represent the next approach (**Figure 5**) [106].

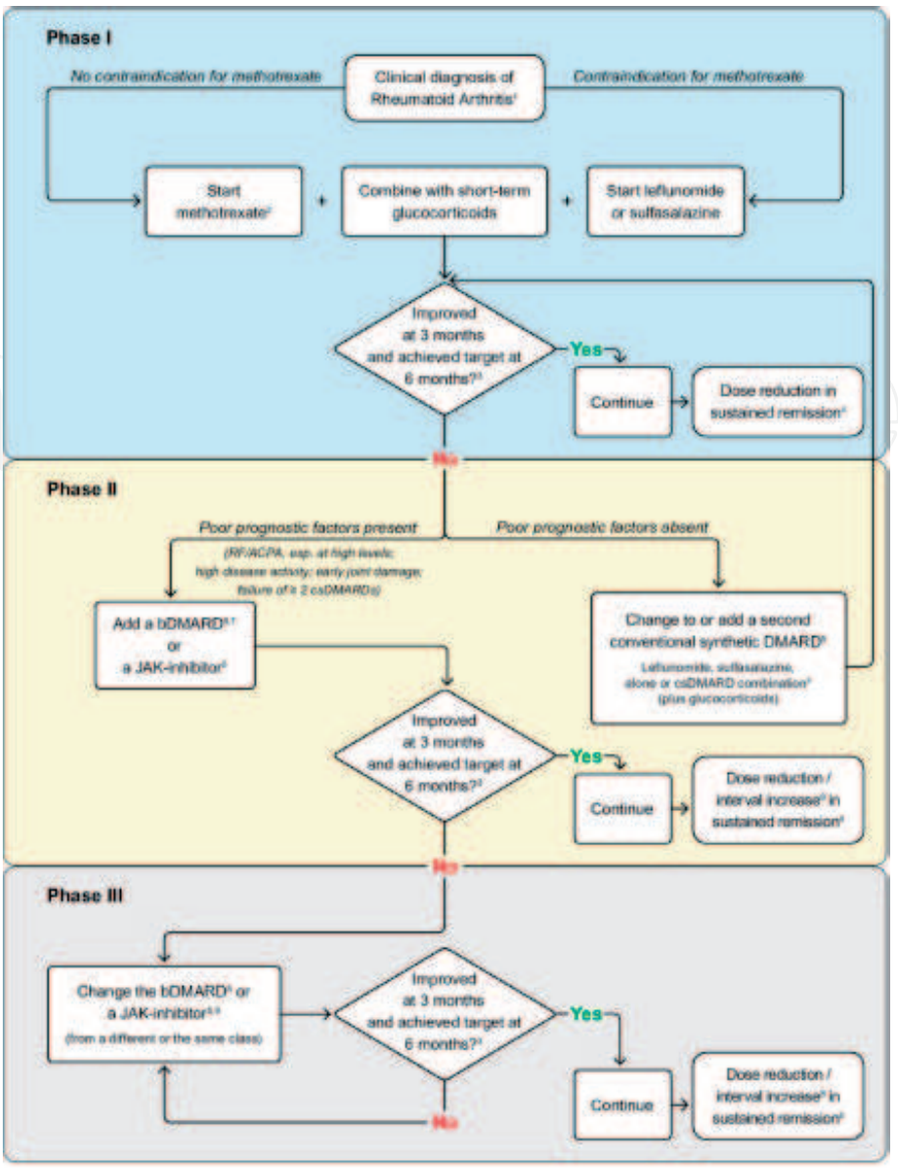

Figure 5.
EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs [106].

5.1 Biologic agents

Rheumatoid inflammation is initiated and maintained through immunological pathways when activated T and B cells produce cytotoxins – directly toxic to tissues – and cytokines such as TNF and interleukins (IL-1 and IL-6) – which provide further amplifies the interaction between pro-inflammatory cells [107, 108]. Biologic bDMARDs are licensed for the treatment of moderate-to-severe RA and target specific T and B-cell activation by [107, 109]:

1. Inhibiting TNF (with excessive production in the synovial fluid in RA) and reducing the progression of joint damage:

   - Adalimumab,
   - Certolizumab,
   - Etanercept,

- Golimumab,
- Infliximab

2. Binding of the CD80/86 receptor and preventing co-stimulation interaction between T cells:
   - Abatacept
3. Blocking the IL-1 receptor:
   - Anakinra
4. Blocking the IL-6 receptor and presenting a better safety profile:
   - Tocilizumab
5. Producing B-cell depletion and reducing the accumulation of bone damaging oxygen-free radicals:
   - Rituximab

Early use of bDMARDs can improve patient outcomes, reduce the symptoms of RA and modify the course of the disease, leading to remissions that can last several years [110].

Biosimilars are highly similar molecules with equivalent therapeutic effect to bDMARDs, also prescribed in RA, to reduce treatment costs because they are authorized by comparing randomized controlled trial data [109]. Biologic agents may be effective when DMARDs therapy fails to bring improvement of the physical function, but they present higher costs due to their complex manufacturing process [107, 109]. Biologic agents are genetically derived from living human or animal cells as whole monoclonal antibodies or as a specific fragment of an antibody called fusion protein [109].

Therefore, their protein structure predisposes patients to increased risk for infection, reactivation of latent tuberculosis, development of lupus-type reaction (mostly characterized by rashes, leukopenia, and thrombocytopenia) and vasculitis [107, 109, 111].

Pre-existing airway disease and interstitial lung disease have shown worsening symptoms and increased mortality after administering biological RA treatment [111].

Therapy monitoring: all patients should perform tuberculin skin testing or interferon-gamma release assay (IGRA) blood test before commencing anti-rheumatic treatment with biologic agents. Pre-existing airway disease and interstitial lung disease have shown worsening symptoms and increased mortality after administering biological RA treatment [110]. Neurological complications similar to multiple sclerosis symptoms and demyelinating disorders have also been associated with bDMARDs treatment and regular monitoring for new skin cancer is necessary regarding all patients receiving biologic agents [111]. Patients should not receive live vaccines during treatment, except for pneumococcal, influenza and hepatitis B which are killed vaccines [107, 109, 112]. Neurological complications similar to multiple sclerosis symptoms and demyelinating disorders have also been associated with bDMARDs treatment and regular monitoring for new skin cancer is necessary regarding all patients receiving biologic agents.

The bDMARDs have different pharmacokinetics properties and dosage, but similar adverse reactions and contraindications for the TNF inhibitors (TNFi). All TNFi increases cardiac mortality in RA patients with associated congestive heart failure (class III/IV and an ejection fraction of 50% or less) [107, 109]. Lymphoproliferative cancers, especially in children and adolescents, have been reported after using

TNFi, therefore the US Food and Drug Administration (FDA) added a black box warning product labeling. Patients are recommended to use appropriate skin protection. TNFi does not increase the risk of congenital malformation and is classified as pregnancy category B (no documented human toxicity) [110, 113]. However, due to the intense placental transfer of Ig in the third trimester, TNFi may increase the risk of neonatal bacterial and fungal infections. The lowest risk appears in etanercept and certolizumab, which are preferred for administration [113].

All in all, the following screening tests should be performed before initiating bDMARDs therapy:

1. Full infection history and screen, chest radiographs, tuberculin skin test, IGRA, asses risk factors for HIV, hepatitis B and C screening to exclude the presence of bacterial or viral infection;

2. Full blood count, urinalysis;

3. Check vaccination status;

4. Check the family/patient history of demyelinating disease or malignancy;

5. Review cardiac function;

6. Antibody profile assessment: anti-nuclear antibodies (ANA) and deoxyribonucleic acid (DNA).

5.1.1 Adalimumab

Adalimumab is a TNFi, fully humanized IgG1 monoclonal antibody (MAb), with a lower risk than animal-derived agents of generating immune responses such as injection-site reactions to anaphylaxis. It neutralizes the biological function of TNF, therefore it is recommended in patients with moderate-to-severe active RA, in association with methotrexate (MTX), as 40 mg subcutaneous injection or as monotherapy, with a 40 mg increase dosage once a week if the patient presents low rates of disease response. Pharmacokinetic properties: the average absolute bioavailability following a single 40 mg dose was 64%, with a terminal phase half-life of approximately 2 weeks. Pharmaceutical forms: premixed syringes or injection pens containing 40 mg, which is administered every 14 days. Therapy monitoring and specific screening commune to all bDMARDS: during treatment and 6 months after stopping. Concomitant administration of adalimumab with other bDMARDs (etanercept, anakinra, abatacept) is not recommended based upon the increased risk for infections and other potential pharmacological interactions. FKB327, a biosimilar agent, presented pharmacokinetic equivalence and similar pharmacodynamic properties to adalimumab, with minor differences due to formulation buffers, but not clinically relevant [109, 114, 115]. To highlight their safety of administration in patients with RA, biosimilars are mentioned as highly similar molecules with equivalent therapeutic effect to bDMARDs [109]. Biosimilars are prescribed to reduce treatment costs because they are authorized by comparing randomized controlled trial data [109].

5.1.2 Etanercept

Etanercept is a recombinant human soluble TNF-α receptor, produced in Chinese hamster ovary cells. It was the first TNFi approved by FDA in November 1998 as an immune-suppressant for RA treatment. Other indications for

etanercept are: juvenile idiopathic arthritis, spondyloarthritis, and plaque psoriasis. Pharmacokinetic properties: slow absorption and elimination, bioavailability 76%, the long half-life of 70 hours, and the presence of renal or hepatic impairment should not require dosage modification. Dosage: subcutaneous injection, 25 mg twice weekly or 50 mg once weekly. In 2018, its first biosimilar SB-4 also received approval and was developed as a single-use pre-filled syringe available at 25 and 50 mg. SB-4 lacks l-arginine and latex in the needle shield, which may explain the lower risk of injection site reactions in SB-4 treated patients. The most common adverse events are upper respiratory tract infections, nasopharyngitis, and hepatobiliary disorders. Neurological events have rarely been reported [109, 116, 117].

5.1.3 Golimumab

Golimumab, another human MAb, prevents TNF-α binding to its receptors, and it must be administered in combination with MTX in case of failure or intolerance to other TNFi. Pharmacokinetic properties: absolute bioavailability 77%, the terminal half-life of 18 days, passage through placenta and breast milk. Dosage: the starting recommended dosage is 50 mg monthly, by subcutaneous injection, with a visible clinical response after 12–14 weeks of treatment. Treatment should be discontinued if no response appears after administering four doses of 100 mg. Precautions and adverse reactions are similar to other TNFi [107, 109, 118].

5.1.4 Certolizumab

Certolizumab pegol is a recombinant human MAb bound to polyethylene glycol which increases its half-life to approximately 14 days and reduces the risk of antibody-dependent cell-mediated cytotoxicity. It is indicated in associations with MTX for the treatment of moderate-to-severe RA in adult patients, with a recommended starting dose of 400 mg (as 2 subcutaneous injections of 200 mg each in 1 day) at weeks 0, 2 and 4, followed by 200 mg every 2 weeks as a maintenance dosage. Treatment should be discontinued if there is no response after 12 weeks of treatment. Due to its reduced placental transfer, certolizumab is one of the safest biologic agents for use in pregnancy and can be given during all trimesters [107, 109, 113].

5.1.5 Infliximab

Adverse reactions are mostly observed in chimeric biologic agents, such as *infliximab* (which contain only 75% human antibodies), due to the development of neutralizing antibodies also associated with decreased therapeutic effect. Therefore, infliximab, a chimeric human-murine TNFi, which contains combined portions of mouse and human IgG1, must be administered with a low-oral-dose of MTX or prednisone to prevent adverse reactions. Dosage: it is the only monoclonal antibody administered only by intravenous infusion, at a dose of 3 mg/kg at weeks 0, 2 and 6, and maintenance infusions at 8 weeks. A specific and acute infusion reaction presents as fever, pruritus, chills, and rash, after 2 hours of receiving the drug, however, anaphylactic shock rarely appears. Prior 30–60 minutes to infliximab infusion, cetirizine 0.5 mg/kg or hydrocortisone 4 mg/kg and paracetamol 15 mg/kg are necessary to avoid infusion reactions. Lupus-like-syndrome and vasculitis have also been reported. Blood tests should be performed to evaluate the eventual drop of infliximab plasmatic concentration which indicates the appearance of neutralizing antibodies [107–109].

5.1.6 Abatacept

Abatacept is a fusion protein and a non-TNFi biologic medicine, which modulates lymphocyte responses and inflammation by blocking a co-stimulatory signal for T-cell activity. It is always recommended to be used with MTX in highly active RA in patients without positive response in prior treatment with MTX or in patients who have a contraindication preventing them from receiving rituximab, another non-TNFi biologic agent. Pharmacokinetic properties: bioavailability 78%, the terminal half-life of 14 days, placental crossing, but no transfer through breast milk. Dosage: it can be administered as intravenous infusion depending on patient weight: 500 mg <60 kg, 750 mg <100 kg, 1000 mg > 100 kg, every 2 weeks for two initial doses and then every 4 weeks. Abatacept presents better persistence rates over TNFi, even though it is a second line biologic agent [119, 120]. Alternatively, it can be given by the subcutaneous injection of 125 mg once a week. Common adverse reactions include headaches, nasopharyngitis and upper respiratory tract infections, dizziness, back pain, hypertension, dyspepsia, urinary tract infections, rash. Several studies have shown that abatacept is associated with presents a better prognosis than other biologic agents in patients with RA and interstitial lung disease [111]. Precautions should nonetheless be taken in patients older than 65 years, due to the increased number of reported malignancy cases [107, 108].

5.1.7 Rituximab

Rituximab binds to CD20, a protein expressed on B lymphocytes and affects B and T-cell interaction and cytokine production, delaying bone and tissue damage. B-cell recovery takes several months, therefore rituximab has a prolonged effect which allows intermittent therapy based on the reactivation of arthritis symptoms. Dosage: clinical response is usually achieved within 16–24 weeks and both rituximab and its biosimilar are administered in association with MTX for better therapeutic outcomes. The first dose is 1000 mg by intravenous infusion followed by a second dose of 1000 mg after 2 weeks, associated with intravenous methylprednisolone to prevent infusion reactions. The risk of infusion reactions decreases after every administration. Paracetamol and antihistamines may also bring benefits to atopic patients. Rituximab is preferred to be administered to patients with a history of malignancies, due to the fact that rituximab has not been associated with an increased risk of cancer. Contraindications for rituximab refer especially to severe active infections and severe heart failure [107, 109].

5.1.8 Tocilizumab

Tocilizumab binds to membrane receptors specific to IL-6 and therefore inhibits IL-6 which is involved in multiple regulation mechanisms of the immune response, hematopoiesis, and bone metabolism. In RA, IL-6 is responsible for raised platelet count, protein and auto-antibody overproduction, induction of osteoclasts, development of inflammation and joint destruction. Tocilizumab is licensed as a treatment for RA, in association or not with MTX and in patients following other DMARDs failure or intolerance to them. It represents the only therapy that has shown superiority over MTX monotherapy and other DMARDs, although the association with other antirheumatic drugs prolonged retention of tocilizumab [107, 109]. Furthermore, a retrospective observational study in 2019 has shown that tocilizumab and etanercept were the most persistent drugs, referring to retention rate and drug survival, with a median retention duration of 30.9 months. This study demonstrates a higher efficacy specific to tocilizumab [121]. Pharmacokinetic

properties: half-life is maintained between 6 and 18 days, depending on concentration and administration rhythm. Due to its mechanism of action, tocilizumab stimulates the action of cytochrome P450, especially CYP1A2, CYP2C9, CYP2C19, and CYP3A4, involved in the metabolism of many other drugs such as statins, warfarin, benzodiazepines, oral contraceptives, calcium channel blockers, theophylline, phenytoin. Tocilizumab increases the need for a higher dosage if associated with these other classes of medicines. Patients receiving tocilizumab will present a reduction in plasmatic neutrophils and platelets, but also a growth in plasmatic lipid levels; treatment should not be initiated in patients with an absolute neutrophil count less than 2×10^9 L and patients should have their cholesterol levels checked 4–8 weeks after initiating treatment with tocilizumab [107, 109, 122]. Further cautions should be taken in patients with aminotransaminase levels greater than 1.5 times the upper limit. Dosage: it can be administered as a subcutaneous injection once a week with a dosage of 162 mg or as an intravenous infusion with a dosage of 8 mg/kg/every 4 weeks, with a maximum of 800 mg per infusion [107, 109, 122].

Supplementary precautions should be taken in pregnancy and administration of rituximab, tocilizumab, and abatacept, due to their limited safety documentation when compared with TNFi [113].

5.1.9 Anakinra

Anakinra is less effective than other biologics, therefore it is not normally recommended, although patients with refractory disease can follow and benefit from this treatment. Failure of treatment in RA patients can be defined as a lack of response in 3 to 6 months after commencing therapy or as a loss of response after a first improvement was registered. Anakinra is a human IL-1 receptor antagonist, given as a subcutaneous injection in combination with weekly MTX. Dosage: 100 mg/per day, administered at approximately the same time each day. Topical glucocorticoids can avoid injectional reactions and are recommended. Specific adverse effects: rashes, urticaria, the elevation of hepatic enzyme levels, reproductive toxicity and a higher risk for serious infections and pulmonary events than other biologic agents, especially when associated with other TNF-antagonists [107, 109, 123].

5.2 Targeted synthetic DMARDs-JAK inhibitors (JAKi)

The multiple cytokines involved in the RA pathogenesis signal through Janus kinase/signal transduction and activator of transcription pathway (JAK-STAT). JAK represents intracellular tyrosine kinases associated with several cytokine receptors. JAK family includes JAK1, JAK2, JAK3, and TYK2 that are paired with specific receptors. Depending on the structure of their receptors, cytokines can be classified in [124]:

1. Type 1 receptors:
   - *γ chain* (IL-2, IL-7, IL-9, IL-15);
   - *gp 130 family* (IL-6, IL-11, oncostatin M-OSM, leukemia inhibitory factor-LIF),
   - *p40 subunit* (IL-12, IL-23)
   - and *β chain cytokines receptors* (IL-3, IL-5, GM-CSF).
2. Type 2 receptors include IL-10 and TNF families.

Recently, RA therapeutic research has focused on intracellular pathways and with advances in technology and disease knowledge, more targeted therapies were developed. JAKi represents an attractive therapeutic resource for patients with active moderate/severe RA, due to their oral bioavailability [124, 125].

Currently, there are two JAKi approved for RA treatment, associated with MTX or as monotherapy: *tofacitinib* (selective for JAK1 and JAK3) and *baricitinib* (selective for JAK1 and JAK2). Also, other agents are undergoing clinical studies: *upadacitinib* and *filgotinib* (selective for JAK1, 74-fold selectivity for the first agent and 28-fold for the second one), *peficitinib* (selective for JAK1 and JAK2) and *decernotinib* (JAK3 selective) [124–127].

5.2.1 Tofacitinib

Tofacitinib, the first oral JAKi approved for RA treatment, is a targeted small synthetic molecule, a reversible competitive inhibitor that binds to ATP binding site of the kinase domain of JAK. It selectively inhibits signaling through cytokine receptors associated with JAK3 and JAK1. Regarding its pharmacologic properties, it has a pharmacokinetic profile directly related to dose, with a half-life of approximately 3 hours. It is metabolized by the liver, via cytochrome P450, primary, and cytochrome P2C19, secondary, and eliminated renal. It is recommended for patients with moderate to severe RA, associated with MTX or in monotherapy, in doses of 5 mg twice a day [126]. Therapy monitoring: complete blood count should be performed at the initiation, 4–8 weeks after and every 3 months afterward. Lipid profile should be evaluated 4–8 weeks after initiation and according to hyperlipidemia guidelines if it is the case. Liver enzymes should be periodically monitored. The recommendations for treatment interruption are presented in **Table 1**.

5.2.2 Baricitinib

As well as *baricitinib*, it should be used carefully in patients with risk factors for deep vein thrombosis (DVT) or pulmonary embolism (PE) (old age, obesity, history of DVT or PE, surgery or immobilization). It is not recommended in case of pregnancy, lactation or children; it is also important to administer with caution in patients over 75 years [127]. Baricitinib, the second agent approved for the treatment

	Monitoring	**Action**
Lipid	4–8/12 weeks after treatment initiation and afterward according to hyperlipidemia guidelines	Management according to hyperlipidemia guidelines
Absolute neutrophil count (ANC)	Before initiation and afterward according to routine patient evaluation	Treatment interruption if ANC is $<1 \times 10^9$cells/L; may be restarted once ANC is above this value
Absolute lymphocyte count (ALC)		Treatment interruption if ANC is $<0.5 \times 10^9$cells/L; may be restarted once ANC is above this value
Hemoglobin (Hb)		Treatment interruption if Hb is <8 g/dL and may be restarted once Hb is above this value
Hepatic aminotransferases		Temporary interruption if drug-induced liver injury is suspected

Table 1.
Monitoring tofacitinib and baricitinib treatment [128].

of RA is a competitive ATP kinase inhibitor, selective inhibitor of JAK1 and JAK2 (100-fold selectivity over JAK3), that reduces immune cell functions by targeting several cytokines (IL-6, IL-12, IL-23, IFNs, and GM-CSF) and growth factor stimulation. By presenting less affinity for JAK3 it may be associated with decreased immunosuppressive effects [128]. After oral administration is very fast absorbed, with a maximum plasmatic concentration of about 90 minutes and a half-life of 14 hours that allows once a day administration. It does not have a significant liver metabolization and is excreted in the urine, mostly unchanged. It is recommended to reduce the dose in case of renal insufficiency, for patients with a creatinine clearance between 30 and 60 mL/minute, and is contraindicated to be administered when the clearance is under 30 mL/minute. It is administered in doses of 4 mg/day. Doses of 2 mg/day should be considered for patients over 75 years, with a history of infections or in case of persistent remission [129]. Safety and side effects: Before therapy initiation, all patients should be tested for latent tuberculosis and viral hepatitis and also baseline analyses must include absolute lymphocyte count (ALC), absolute neutrophil count (ANC) and hemoglobin. Laboratory changes that may be observed are represented by decreased hemoglobin and neutrophils, increased hepatic enzymes, creatinine, low-density, and high-density lipoprotein. Patients monitoring is presented in **Table 1**. During treatment, there were reported cases of tuberculosis reactivation, herpes zoster, malignancy and thrombosis [127].

5.2.3 Upadacitinib

Upadacitinib is an under investigation oral JAKi, with a higher selectivity for JAK1, which provided favorable efficacy, safety, and tolerability in the studies conducted so far. Similar to tofacitinib and baricitinib, demonstrated inhibition of radiographic progression in RA patients.

5.2.4 Figlotinib

Filgotinib presents a selectivity of almost 30-fold for JAK1 versus JAK2, with dose-dependent inhibition of Th1-Th2 [124, 130]. The most frequent side effects reported for JAK1 selective inhibitors are represented by nausea, cephalalgia, respiratory and urinary infections, dose-related neutropenia and an increase in serum levels for creatinine and hepatic enzymes [127].

6. Conclusions

The extensive research of the last two decades has concerned the diagnosis and individual prognosis of patients with RA and also the elaboration of personal treatment strategies.

Case management requires a continuous evaluation of the risk/benefit ratio of the therapy, so that the results are optimal and with minimal adverse effects and complications, including infections.

Also, anticipating a balance between the risks of comorbidities and the benefits of treatment is a management strategy that must be taken into account.

Conflict of interest

The authors declare no conflict of interest.

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