EUROPEAN LEAGUE AGAINST RHEUMATISM RECOMMENDATIONS FOR EARLY ARTHRITIS: WHAT HAS CHANGED?

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CLINICAL PRACTICE GUIDELINES BEFORE BIOLOGICALS: 1996–2007

Rheumatoid arthritis (RA) is a chronic, disabling, inflammatory, autoimmune disease that affects approximatively 0.4–1.0% of the population. Immune dysregulations, synovial membrane hyperplasia, activation of proinflammatory cells, and release of cytokines, such as interleukin (IL)-1, IL-6, and tumour necrosis factor-alpha (TNF-α) are involved in the pathophysiological process. The first RA clinical practice guidelines were developed in 1996 by members of the American College of Rheumatology (ACR).[1] The authors underlined that optimal management requires early diagnosis and timely introduction of agents that reduce the probability of irreversible joint damage. The initial evaluation should document symptoms of active disease, functional status, objective evidence of disease activity, mechanical joint problems, the presence of extra-articular disease and comorbid conditions, as well as the presence of radiographic damage in selected involved joints. Baseline laboratory evaluations included complete blood cell count, platelet count, chemistry profile, immunoglobulin (Ig)M-rheumatoid factor (IgM-RF), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).

The aggressiveness of the treatment was defined according to poor prognosis associated with early age at onset, high IgM-RF, active inflammation, and presence of extra-articular manifestations. The initial drug treatment involved non-steroidal anti-inflammatory drugs (NSAID), e.g., aspirin or ibuprofen, to reduce joint pain and swelling; however, NSAID do not alter the course of the disease nor prevent joint destruction. Patients whose disease remains active despite NSAID were candidates for disease-modifying antirheumatic drugs (DMARD), the most widely used being methotrexate (MTX). The timing was recognised as an important factor; i.e., the initiation of DMARD should not be delayed beyond 3 months for any patient with an established diagnosis. Early RA was not mentioned, but the goal was to intervene in the disease before joints are damaged. These guidelines were followed by an update in 2002;[2] the authors of the guidelines insisted that a specialised rheumatologist should estimate the progression of disease and determine a prognosis. The Arthritis Impact Measurement Scale and the Health Assessment Questionnaire were identified as valid evaluation tools for functional status. The ACR established a scale of improvement, depending whether there has been a 20–70% improvement. A scoring system was established as an outcome measure for radiographic progression. At that time, newly proposed therapies were infliximab (a chimeric IgG1 monoclonal antibody against TNF-α) and etanercept (a soluble TNF receptor protein, binding soluble TNF-α), in combination with MTX; both drugs were shown to be beneficial in improving clinical symptoms.[3,4] Anakinra (a human recombinant form of IL-1 receptor antagonist) also was evaluated.[5] Due to the new agents incurring higher costs, longitudinal studies were necessary to justify their use.

In 2006, guidelines were published by the British Society for Rheumatology (BSR) specifically focussing on early cases and the first 2 years of therapy.[6] Again, the authors recommended to establish patients with RA on DMARD therapy as soon as possible. DMARD therapies should be prescribed as part of an aggressive package of

care, incorporating escalating doses, intra-articular steroid injections, parenteral MTX, and combination therapy, rather than sequential monotherapy, progressing to biologic (e.g., anti-TNF-α) therapy, when required.

The European League Against Rheumatism (EULAR) recommendations for the management of early arthritis were published first in 2007,[7] with updates every 3 years.[8-10] In 2007, anti-cyclic citrullinated peptide/anti-citrullinated protein antibody (anti-CCP/ACPA) positivity was added to the diagnosis criteria. Simultaneously, the authors claimed that early diagnosis was complicated due to the absence of specific tests. Nowadays, we know that anti-CCP/ACPA precedes the clinical onset of RA by years and are initially produced at extra-articular sites.[11] The committee recommended that patients presenting with arthritis of more than one joint be referred to a rheumatologist, ideally within 6 weeks after the onset of symptoms.[7] Another recommendation was to use new techniques to detect synovitis, including magnetic resonance imaging (MRI). Factors predicting persistent and erosive disease should be measured, including the number of swollen and tender joints, inflammation parameters (CRP and ESR), levels of IgM-RF and anti-CCP/ACPA, and radiographic erosions. IgA-RF has also been mentioned as a sign of poor prognosis, but *HLA-DRB1* genotyping was regarded as less suitable. Most importantly, the authors recommended to begin aggressive DMARD therapies as early as possible, even if the patients did not yet fulfil established classification criteria for RA. This was an important paradigm change. Among patients with recent onset polyarthritis, those who received DMARD treatment early had a better outcome with regard to radiographic progression, function, and ability to work, than those in whom DMARD treatment was delayed by a few months.

CLINICAL PRACTICE GUIDELINES AFTER BIOLOGICALS: 2010–2016

The primary reason for discontinuation of traditional DMARD, such as MTX, were adverse effects. First clinical studies with biologicals (IL-1 receptor antagonist and anti-TNF-α therapies) emerged 1998–2003. However, as with traditional DMARD, many patients (20–40%) who were treated with TNF-α antagonists did not respond to treatment or were unable to sustain the response over time. Alternatives, such as abatacept (which inhibits macrophage/T cell interactions),[12] were developed and clinically tested from 2005–2006 in RA patients with an inadequate response to MTX and/or anti-TNF.[13] In 2010, 15 recommendations were developed by a EULAR committee, regarding patients in whom synthetic DMARD and anti-TNF-α therapies have failed.[8] Meanwhile, other alternative biological therapies came on the market, in particular tocilizumab, a humanised monoclonal antibody against the IL-6 receptor,[14] and rituximab, a monoclonal antibody that targets CD20+ B cells.[15] These biologicals are expensive; however, they may enable the lowering of short and long-term indirect costs of disease.[8] Again, the authors insisted that treatment with synthetic DMARD, such as MTX has to be started as soon as possible. Biologicals are kept in reserve for when patients present with poor prognosis factors and respond insufficiently to synthetic DMARD; at first, a TNF-α inhibitor in combination with MTX should be used. Patients with RA, for whom a first TNF-α inhibitor has failed, should receive another biological, such as tocilizumab, rituximab, or abatacept. In cases of refractory severe RA or contraindication to MTX and/or biological agents, the following synthetic DMARD were suggested: azathioprine, ciclosporin A, or, in exceptional circumstances, cyclophosphamide. Intensive medication strategies should be considered in every patient. Anti-malarial drugs (e.g., hydroxychloroquine) and anakinra were not recommended because, while effective in RA, their efficacy is lower than that of other agents in their class.

The 2010 ACR/EULAR classification criteria for RA included at least one joint with definite clinical synovitis (swelling), not better explained by another disease, and a scoring system with the number and type of joints, serology (IgM-RF and ACPA), acute-phase reactants (CRP and ESR), and duration of symptoms. In fact, these criteria were designed to be applied in early arthritis and possibly contributed to a certain degree of uncertainty in the diagnosis of RA.

A further update of these EULAR recommendations came out in 2013.[9] Briefly, the EULAR committee underlined that all TNF-α inhibitors, tocilizumab, abatacept, and, under certain circumstances, rituximab, were essentially considered to have similar efficacy and safety. If the first biological DMARD strategy fails, any other biological DMARD may be used. The recommendations also addressed tofacitinib (Janus kinase inhibitor)

as a targeted synthetic DMARD, which was recommended, where licensed, after use of at least one biological DMARD.[16]

THE 2016 UPDATE OF THE EULAR RECOMMENDATIONS

The most persuasive argument that RA has multiple pathways to the same phenotype is the diversity of responses to highly specific biological DMARD.[17] Thus, it will be important in future to better categorise patient subpopulations. The authors of the 2016 update of the EULAR recommendations mentioned that identifying the underlying disease is difficult, particularly at early stages.[10] The hypothetical subgroups of early arthritis are frequently clinically undifferentiated and can develop into established RA or another definite arthropathy, remain undifferentiated, or resolve spontaneously. The challenge with early arthritis is the difficulty in knowing what it might become, which produces some tension between the risks of over-treating and under-treating. In recent years, research on early arthritis has been a major focus. After defining the target population and formulating a definition of management, the 2016 committee selected research questions to serve as the basis for a systematic literature review. Clinical examination is still the method of choice for detecting synovitis, which may be confirmed by ultrasonography. The authors focussed on clinical examination and downplayed the role of MRI, as well as the use of biomarkers in making an appropriate diagnosis.

Multiple studies that claim greater sensitivity for MRI or ultrasound have not convinced the committee, since the drawback of using these diagnostic techniques is reduced specificity. In the opinion of the committee members, all evidence for drug treatment should be based on clinically detecting arthritis. In cases of undifferentiated arthritis, if a definite diagnosis cannot be reached, risks factors for persistent and/or erosive disease should be considered in management decisions. Compared with previous recommendations, the authors, even more so than before, focussed on early referral and early DMARD treatment for those who need it, since this may improve outcomes. A recent study validated this concept for anti-TNF-α therapies.[18] MTX remains the anchor drug and, unless contraindicated, should be part of the first line of treatment in patients at risk of persistent disease. NSAID should be used at the minimum effective dose for the shortest time possible, after evaluation of gastrointestinal, renal, and cardiovascular risks; this also includes the new specific cyclooxygenase-2 inhibitors. The authors put a warning on careless and unlimited glucocorticoid use, since new evidence points to side effects of long-term use. All these therapies are accompanied by some risk, particularly around infection or toxicity, and, as such, rheumatologists have to exercise caution in when to intercede and with which agent. Hydroxychloroquine, which is a drug rheumatologists often use when there is some degree of uncertainty,[19] remains excluded from the recommendations. The 2016 revision further enshrines treat-to-target as the principle that should guide clinical decisions, which is taken to mean treatment in spite of absence of inflammatory disease activity. The guidelines include additional emphasis on outcomes monitoring, which might mark a change in usual practice for some clinicians. Disease activity should be more tightly assessed, at least every 1–3 months, until the treatment target has been reached. Dynamic exercises and occupational therapy should be considered as adjuncts to drug treatment. Based on epidemiological evidence, the authors added words on prevention of arthritis: stop smoking,[20] good dental care,[21] and avoid obesity.[22] This last revision underlined that treatment is more than providing drugs; health professionals are key in providing education and, more than before, communication with the patient as a partner rather than as a recipient of care was emphasised. The updated recommendations are largely consistent with the standards of care for managing these patients in other parts of the world.

POINT OF VIEW OF A RESEARCHER

There are many positive points to take from these recommendations, such as treating early RA as aggressively and as soon as possible, tightly monitoring the disease activity, and avoiding detrimental environmental factors that also emphasise the relevance of epigenetic research in the field.[23] The aim for coming years, according to the 2016 updated EULAR recommendations,[10] is to cure the disease. This sounds very optimistic, but let us explore this possibility in the eyes of a researcher.

Many methods exist to induce arthritis in animals and RA can similarly also have multiple aetiologies, reflecting the concept that it is probably not a

single disease but a syndrome.[17] This predicts large, inter-individual variations in the response to therapies and limits the significance of large genetic studies with undifferentiated cohorts.[24] Thus, it will be essential to better define the patient subgroups, not only as early or established RA but also according to the pathological mechanisms. In the clinic, the use of biomarkers in the diagnosis of RA was reduced to a minimum.

From a clinician's point of view, this appears logical, since according to the 2010 ACR/EULAR classification criteria as mentioned above no more than the assessment of symmetric polyarthritis, signs of inflammation (CRP and/or ESR), and autoantibodies (IgM-RF and/or anti-CCP/ACPA) are needed; however, to achieve personalised medicine, this is insufficient. As mentioned previously, not all RA patients respond to current biologic therapies and responses are not always maintained.[25] The change from one biological DMARD to the others, as suggested in the recommendations, is time intensive and costly. To identify patient subgroups, large cohorts, specific biomarkers, and multicentre association studies, including responders and non-responders to given therapies, are needed. HLA genotyping and searches for defined polymorphisms have to be reconsidered. To be able to differentiate anti-TNF-α responders from non-responders, biomarkers, such as serum IgA-RF (associated with a poor prognosis)[26] and cartilage oligomeric matrix protein (associated with cartilage destruction),[27] have to be reintroduced. Other new markers, such as autoantibodies against carbamylated peptides, have to be evaluated in large clinical settings.[28] Early MRI erosion progression is a valid measure of structural damage that can be used in clinical trials, but is not routinely used outside of a clinical trial setting.[29] Simultaneously, the pathophysiological mechanisms have to be differentially identified. Certain disease forms are more driven by the adaptive immune system than others and respond better to abatacept and, as such, these patients better match the definition of autoimmunity than others in which a chronic inflammatory process is ongoing. The hallmarks of RA include not only inflammation and immune dysfunctions, but also synovial tissue hyperplasia and aggressive synovial fibroblasts, i.e., the effectors of joint destruction. The current DMARD mainly target inflammation and may relieve pain; the other components of the disease, however, are only dampened indirectly, if at all. MTX as a cytostatic agent might limit synovial hyperplasia, and anti-TNF-α therapies might reduce, but not abolish, the aggressive behaviour of RA synovial fibroblasts. No DMARD directly targets these cells, and, as long as this is the case, no real cure of the disease is possible. RA synovial fibroblasts are intrinsically activated due to biochemical and epigenetic modifications.[30] They slowly but persistently continue to destroy cartilage and bone, even in the absence of TNF-α. Indeed, hip and knee joints with moderate-to-advanced pre-existing damage resulted in radiographic progression, even after TNF-α-blocking therapies.[31] Conversely, other patients showed repair of their arthritic hip joints,[32] demonstrating again the disease's heterogeneity. In addition, for hands, the response to therapy could be different.[33]

Epigenetic therapies,[23,30,34] in addition to the proposed DMARD, need to be clinically evaluated. Again, it can be predicted that only a subgroup of patients will respond.[30] In fact, the chronicity of the disease might be related to positive feedback loops that allows biostability, i.e., a more stable cellular differentiation and memory. This can occur at different cellular levels and involves chromatin changes. To cure the disease, such feedback loops have to be disrupted. The aim will, therefore, be to interfere with the mechanisms that lead to chronicity and to offer patients a personalised therapy, thereby fulfilling the goal of the 2016 EULAR committee: curing the disease.

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