Article:
Di Matteo, A., Bathon, J.M. and Emery, P. orcid.org/0000-0002-7429-8482 (2023) Rheumatoid arthritis. The Lancet, 402. 10416. pp. 2019-2033. ISSN 0140-6736

Rheumatoid arthritis

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Summary

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune inflammatory disease that mainly affects the joints and peri-articular soft tissues.

In this seminar, we will provide an overview of the main aspects of RA. Epidemiology and recent advances in the understanding of the RA pathogenesis will be reviewed. We will discuss the clinical manifestations of RA, classification criteria, and the value of imaging in the diagnostic work-up of the disease.

The advent of new medications and the accumulated scientific evidence demand a continuous updating regarding the diagnosis and the management, including therapy, of RA. An increasing number of patients are now able to achieve disease remission. This major improvement in the outcome of RA patients has been determined by a combination of different factors (early diagnosis, 'window of opportunity', 'treat-to-target strategy', advent of targeted-disease modifying anti-rheumatic drugs, combination therapy), which will be illustrated in the current seminar.

The two most influential societies for Rheumatology worldwide (i.e. American College of Rheumatology and European Alliance of Associations for Rheumatology) recently updated their recommendations for the management of RA, which were be discussed. Furthermore, current controversies (i.e. the role of glucocorticoids in the management of RA, safety profile of JAK-inhibitors) and outstanding research questions, including precision medicine approach, prevention and cure of RA will be highlighted.

Bullet points

- Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that primarily affects the joints.
- RA is associated with disability, work-loss, reduced quality of life and premature death.
- RA affects 0.25-1% of the population worldwide, mainly women and individuals >40 years old.
- The pathogenesis of RA involves a complex interplay between genetic (e.g. shared epitope) and environmental risk factors (e.g. cigarette smoking).
- The production of autoantibodies (e.g. anti-CCP and rheumatoid factor) is a distinguishing feature of RA.
- These antibodies can precede the onset of the disease by several years; increasing evidence supports the mucosal area (lung, oral, gut) as the initial site of autoantibody production.
- The 'rheumatoid pannus' represents the hallmark sign of RA, which, if left untreated, invades and destroys the adjacent articular and periarticular structures, leading to irreversible joint damage.
- RA typically affects the small joints of the hands and feet in a symmetrical fashion.
- Several extra-articular manifestations may occur, especially in patients with long-standing disease (e.g. rheumatoid nodules, serositis, vasculitis, interstitial lung disease).
- The diagnosis of RA remains clinical, with many rheumatologists relying on the fulfillment of the 2010 ACR/EULAR classification criteria for confirmation.
- Imaging, in particular ultrasound, magnetic resonance imaging and conventional radiography, are adjunctive in the diagnostic work-up of RA.
- Three categories of disease modifying anti-rheumatic drugs (DMARDs) are used in RA: 1) conventional synthetic DMARDs (csDMARDs); 2) biologic (b)DMARDs; 3) targeted synthetic (ts)DMARDs.
- Several randomized controlled trials have shown a greater efficacy of combination with a b/tsDMARD plus a csDMARD versus a b/tsDMARD or csDMARD alone; however, biomarkers that could identify the most effective cs/b/tsDMARD for an individual patient are lacking.
- ACR and EULAR have recently updated their guidelines/recommendations for the management of RA.
- In these recommendations, initiating treatment as soon as diagnosed, and a 'treat to target' strategy (i.e. frequent follow-up of patients with treatment escalation if a target of disease remission, or low disease activity, is not achieved) have been confirmed as cardinal principles of RA management.
- While EULAR strongly recommends the use of short-term GCs as 'bridging therapy', when initiating or changing a DMARDs, with tapering and discontinuation as rapidly and clinically feasible, the ACR cautioned that GCs should not be systematically prescribed.
- The safety of Janus Kinase inhibitors has been questioned as a result of the Oral Surveillance study, which demonstrated an increased risk of major adverse cardiovascular events and malignancy with tofacitinib (especially in RA patients >65 years old and smokers) in comparison with TNF inhibitors.
- The advances in the diagnosis and management of RA have led to a dramatic improvement of the long-term outcomes in most RA patients in comparison with 20 years ago.
- An increasing number of RA patients are now able to achieve a status of disease remission.
- Patients in remission for 6 months can often taper therapy successfully without flaring; predictors of successful tapering are emerging.
- Drug-free remission, which is effectively a cure, remains a more challenging goal, with most patients experiencing a flare when DMARD therapy is discontinued.
- At the other end of the spectrum, there are those with persistently 'active' RA who have failed multiple cs/b/tsDMARDs ('Difficult to Treat RA'), which represent an ongoing therapeutic challenge.
- A precision medicine approach to treatment of RA is currently lacking. However, studies focused on characterizing specific cellular and molecular phenotypes within the RA synovium that will predict responsiveness to existing and/or future DMARDs are underway.

- Despite the development of clinical synovitis being widely accepted as the beginning of RA, increasing evidence suggest that this is preceded by a complex 'preclinical phase', which is characterized by a series of 'subclinical' pathological events (i.e. autoimmunity and inflammation).
- Multiple trials using DMARDs in the 'preclinical' phase (before the onset of clinical synovitis) have been carried out in recent years in 'at-risk' individuals. These studies have successfully improved signs and symptoms and have delayed progression to RA but have yet to demonstrate prevention.

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease that primarily affects the joints. RA is associated with progressive disability, premature death, and high socioeconomic costs (1,2). The prevalence of RA varies significantly around the globe, ranging from 0.25% to 1% in different populations worldwide (3). RA can affect individuals of any age, showing an increased incidence in people >40 years old. Women are affected two-three times more frequently than men (4).

Search strategy and selection criteria

The terms “rheumatoid arthritis” combined with “epidemiology”, “pathogenesis”, “clinical manifestations” “diagnosis”, “classification”, “management”, “therapy”, “prediction” and “prevention”, were searched on MEDLINE. References of selected articles were considered for the identification of relevant data. Recent ACR and EULAR guidelines/recommendations for the management of RA (as well as systematic literature reviews relevant to this topic) were reviewed. We prioritized articles that were published in the past 5 years but also included impactful older publications.

Disease susceptibility and pathogenesis

The pathogenesis of RA is complex and not fully understood (5,6). Genetic predisposition plays a key role, with first degree relatives of RA patients carrying a 2-to-5-fold higher risk of developing the disease compared to the general population (7). Multiple alleles have been associated with an increased risk of RA. The strongest evidence supports the role of HLA-DRB1 gene, and in particular a key sequence of five amino acid sequence motif in residues 70–74 of the HLA-DRβ chain, the so called ‘shared epitope’ (8,9). Several non-major histocompatibility complex genes have been linked with RA (e.g. PTPN22, CTLA4, PADI4), but their individual contribution is modest compared to the HLA region (10,11). Recent large-scale genome-wide association studies have identified numerous genetic mechanisms/loci associated with RA, such as TNIP2, WISP1 and TNFRSF11A (12).

Epigenetic factors, such as DNA methylation and histone acetylation, also contribute to RA pathogenesis (13). In genetically predisposed individuals, environmental risk factors, such as smoking (i.e. the strongest environmental risk factor for RA), dust exposure, viruses, obesity, low socioeconomic status and changes in the lung, gut and oral microbiome, have been implicated in the so called ‘break of tolerance’ (i.e. production of autoantibodies and generation of pro-inflammatory cytokines), which appear to be responsible for disease initiation and perpetuation (14-16). Conversely, a moderate alcohol intake seems to be protective (17). A recent study has shown an increasing incidence of rheumatoid factor (RF) negative RA in comparison with previous decades (18). However, the precise interplay between genetic and environmental risk factors and how this interaction leads eventually to development of the disease have not been fully elucidated.

The production of autoantibodies and the presence of auto-reactive T cells in blood and synovial structures are distinguishing features of RA. Anti-citrullinated protein antibodies (ACPA) and, to a lesser extent, RF have shown the strongest association with RA (19,20). Other autoantibodies have been linked to RA, including peptidyl arginine deiminase-4 antibodies, carbamylated proteins antibodies and collagen type II antibodies (21,22).

It is now accepted that RA-related autoimmunity precedes the onset of clinical disease by up to several years (23). Recent observations suggest that, in at least some patients, the initial site of autoantibody generation is distant from the joint, specifically the mucosae of the periodontium, gut or lung (24). This initial phase of localized mucosal autoimmunity (IgA-related) would be then followed by transition to systemic autoimmunity (IgG-related) and expansion of ACPAs number and specificities, leading to a complex pro-inflammatory immune response and eventually disease initiation and perpetuation (25).

Among the different RA-related autoantibodies, ACPAs and in particular the anti-cyclic citrullinated peptide (CCP) antibodies have shown the highest specificity for RA (26). ACPAs have an important diagnostic role, but also a potential prognostic value, as their presence has been associated with radiographic progression, extra-articular manifestations, and response to treatment (27).

From a histological point of view, the 'rheumatoid pannus' represents the hallmark sign of RA. This pannus demonstrates hyperplasia of the normal synovial tissue, neovascularization, and a heterogeneous inflammatory cell infiltrate of activated T-cells (CD4+ and CD8+), B-cells, immunoglobulin producing plasma cells, macrophages, fibroblasts, neutrophils and dendritic cells (28,29). If left untreated, this highly aggressive pannus invades adjacent structures leading to progressive and irreversible damage of bone, cartilage, tendons and ligaments. Activated osteoclasts, and also chondrocytes, play a direct role in the development of joint structural damage (30). Several mediators have been identified in the interaction between the cells involved in this 'inflammatory network', such as TNF, IL-6, IL-1 and TGF-β (31).

Clinical manifestations

The clinical presentation of RA in most patients is an insidious and gradual onset of joint pain and swelling, which may start with one or a few joints but usually develops into a symmetrical polyarthritis (32). The wrists, small joints of the hands and feet are the most affected joints. Any synovial joint including large joints, such as shoulders, elbows, knees and ankles, can also be involved. Early morning stiffness lasting 30 minutes or longer, fatigue and weakness are common features. In patients with severe systemic inflammation, such as those with markedly elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), anorexia, weight loss and low-grade fever may occur.

In the early phases of RA, joint function is mainly impaired by the stiffness (or 'gelling') and pain, which are secondary to the active inflammatory process in the joints and peri-articular soft tissues, such as tendons, including the recently described peritendinitis of the interossei (33). If not properly treated with disease modifying anti-rheumatic drugs (DMARDs), this inflammatory process progresses to the development of irreversible joint damage, with consequent loss of function (Figure 1).

Extra-articular manifestations occur in about 40% of RA patients, especially those with long-standing disease (34,35). Subcutaneous nodules, also known as rheumatoid nodules, are mainly observed in patients with positive anti-CCP antibodies and/or RF, and are exacerbated by smoking. Other relatively common extra-articular manifestations are haematological abnormalities (e.g. anaemia, thrombocytosis and lymphadenopathy) and interstitial lung disease, while less common and rare manifestations include vasculitis, neuropathy, serositis, glomerulonephritis, inflammatory eye involvement, Felty syndrome, myopathy and amyloidosis. The prevalence of many of these extra-articular manifestations has decreased over time, presumed to be due to better and earlier treatment of inflammation.

Diagnosis and classification of rheumatoid arthritis

To date, no diagnostic criteria exist for RA. In routine practice, many rheumatologists rely on the fulfillment of the ACR/EULAR classification criteria for RA, which in 2010 replaced the previous 1987 ACR criteria (36,37).

The entry criterion is ≥1 clinically swollen joint. Other types of arthritis, such as crystal arthritis, reactive arthritis and connective tissue diseases must be excluded to apply these criteria. Main domains of these criteria are joint distribution (large joints vs small joints), serological status (positive ACPA and/or RF), acute phase reactants and duration of symptoms. In 2014, a systematic literature review showed a pooled sensitivity of 0.82 (95% CI 0.79-0.84) and specificity of 0.61 (95% CI 0.59-0.64) for the 2010 ACR/EULAR classification criteria (38).

Imaging is increasingly used in clinical practice to confirm inflammation and identify early structural damage. Ultrasound (US), magnetic resonance imaging (MRI) and conventional radiography are useful when the

diagnosis of RA is in question. US has been proven sensitive and accurate for the detection of synovial hypertrophy and pathological vascularization (i.e. power Doppler signal) in the joints and tendons of RA patients (39).

MRI can detect synovitis, tenosynovitis and osteitis, which is a potential predictor of the development of bone erosions (40). Conventional radiography remains the first-line imaging test for the detection of joint damage according to EULAR (41). US and MRI represent promising tools for the assessment of structural joint damage due to their higher sensitivity compared to conventional radiography (42) (Figure 2). The value of imaging in the follow-up of RA patients has not been clearly established, with some recent studies failing to show the additional value of US over clinical measures in the treatment decision making of RA patients (43,44).

Treatment

The prompt initiation of DMARD therapy within a few weeks or months of disease onset when an intervention has a disproportionate long-term impact has been proven crucial to improve the prognosis and long-term outcomes in RA (45). The precise timing for this 'window of opportunity' has not yet been defined, but is assumed to be 3 months; nevertheless, there is unequivocal evidence showing that initiation of DMARD therapy early in the course of the disease decreases structural damage and its progression and improves physical functioning compared to delayed treatment (46).

As shown in Table 1, three categories of DMARDs constitute the therapeutic armamentarium of RA: 1) conventional synthetic (cs)DMARDs, which are small-molecular weight synthetic drugs (small chemical drugs) with unclear anti-inflammatory mechanisms; 2) biologic (b)DMARDs, which are mostly monoclonal antibodies or, less often, soluble receptor constructs, that specifically target an individual molecule; 3) targeted synthetic (ts)DMARDs, which target specific enzymes within cells.

Amongst the csDMARDs, methotrexate (MTX) and, to a lesser extent, sulfasalazine (SSZ), leflunomide and hydroxychloroquine (HCQ) are those most commonly used in RA. MTX is traditionally regarded as the 'anchor drug' in RA (47).

The advent of bDMARDs has dramatically changed the natural history of the disease in the majority of RA patients (48). Multiple bDMARDs with different mechanisms of actions have been developed, ranging from direct inhibition of the cytokines TNF (TNFi) and interleukin-6 receptor antagonism (IL-6ra) to blockade of T-cell co-stimulation and B cell depletion. The safety profile of the bDMARDs has now been established and has been outlined in Table 1, with most of these drugs sharing an increasing risk of infections as the most common side effect. In addition, tsDMARDs inhibiting the Janus kinase (JAKi) pathways are also licensed for the treatment of RA. Several randomized controlled trials (RCTs) demonstrated a greater efficacy of combination with b/tsDMARD plus csDMARD versus a b/tsDMARD or csDMARD alone (49,50). One action of MTX is to reduce the development of anti-drug antibodies, particularly against chimeric antibodies (51). Certain less immunogenic monoclonal antibodies, such as some TNFi or IL-6 inhibitors, are licensed as monotherapy (52).

For some of the bDMARDs originators for which patents have expired, less expensive biosimilars have been developed and approved as effective and safe options, equivalent to the bio-originators.

The ACR and EULAR recommendations for the management of rheumatoid arthritis

The two most influential organizations for Rheumatology worldwide, namely ACR and EULAR, recently developed (in 2021 and 2022, respectively) updated versions of recommendations/guidelines for the management of RA (53,54).

Both ACR and EULAR highlight the importance of the 'window of opportunity' according to which DMARDs should be started as soon as the diagnosis of RA is made, and the 'treat to target' strategy, which consists in

a ‘tight control’ with regular follow-up of patients (1 to 3 months according to EULAR) and prompt treatment escalation if disease remission (or low disease activity if remission is not feasible) is not achieved.

The first-line therapy should be a csDMARD (i.e. mostly MTX), because of the lack of evidence supporting the higher efficacy of bDMARDs for all patients, in comparison with MTX, and costs.

While the EULAR recommendations suggest using MTX in all newly diagnosed RA patients (unless contraindicated), the ACR considers the possibility of different csDMARDs according to the patient disease activity. In DMARD-naïve patients with moderate to high disease activity, MTX is strongly recommended over other csDMARDs, such as HCQ or SSZ. In contrast, in those with low disease activity, HCQ is conditionally recommended over other csDMARDs because of its tolerability and safety profile. The ability to predict MTX response at baseline would improve management, and there are some positive developments in this area that could alter management, which a proof-of-concept study nearing completion should clarify (55).

In patients with inadequate response to a csDMARD, risk-stratification is clinically sound, although the evidence for treating patients according to prognostic markers is limited. EULAR recommends the use of another csDMARDs in patients without poor prognostic factors, such as autoantibodies, high disease activity, bone erosion or failure of two csDMARDs. Conversely, in those with these poor prognostic factors, a bDMARD (or a tsDMARD in selected populations) should be added. The ACR does not provide any specific indication regarding the sequence of these medications in patients with persistently active RA despite csDMARD therapy, but recommends the addition of a b/tsDMARD over triple therapy (i.e. MTX, SSZ and HCQ). Importantly, local regulations vary, with mandatory failure of two different csDMARDs required in some countries, such as the UK, before starting a bDMARD.

- *Is there still a role for glucocorticoids in the management of rheumatoid arthritis?*

GCs have traditionally represented a cornerstone in the management of RA.

Given their availability in different doses and formulations (i.e. oral, parenteral, or intra-articular) and rapid onset of anti-inflammatory activity, GCs are commonly used as a ‘bridging therapy’ when DMARD therapy is initiated, for treating flares and, in some patients, as a long-term maintenance therapy (56).

Multiple studies have demonstrated the ability of GCs to improve disease activity and functional status in RA patients, and potentially delay the evolution of radiographic joint damage (like DMARDs) (57,58). The NORD-STAR trial, which included 812 treatment naïve RA patients with disease duration <2 years, demonstrated a non-inferiority of csDMARDs plus GCs compared to certolizumab pegol+MTX and tocilizumab+MTX, while abatacept+MTX was statistically superior (59). In addition, NORDSTAR showed clinical similarity between csDMARD+GC therapy and any bDMARD+MTX treatment, with high rates of stringent remission by CDAI at 24 weeks (>40%) for all these therapies. Other clinical trials have shown similar efficacy of combination between MTX plus GCs vs MTX plus a bDMARD (60).

GCs have a well-known risk profile of side effects, especially if exposure to high doses is protracted (61).

In a multicentric RCT (GLORIA study), 451 patients with established RA and age >65 years were randomized to receive prednisolone 5 mg/day or placebo for 2 years (62). RA patients who received prednisolone achieved better disease activity outcomes and showed less radiographic progression than those receiving placebo. In the former group, there was a higher incidence of side effects compared to placebo, but these were mainly non severe infections. However, because it is the cumulative dose of GCs that has been mainly associated with increased mortality, longer term observation would be needed to discern the safety profile of GCs in this susceptible (i.e. >65 years old and active RA) population.

The position of ACR and EULAR regarding the use of GCs in the management of RA is slightly divergent (53,54). While EULAR strongly recommends the use of short-term GCs as ‘bridging therapy’, when initiating or

changing a DMARDs, with tapering and discontinuation as rapidly as clinically feasible (ideally within 3 months), the ACR cautioned that GCs should not be systematically prescribed. They however, acknowledge the conditionality of this statement given the need at times to alleviate patients' symptoms prior to the onset of action of DMARDs (or in case of a flare). Intramuscular steroid is commonly used as being effective for minimum dose with little rebound on steroid withdrawal, as suggested by EULAR.

- *The use of JAKi in rheumatoid arthritis patients*

Among the available treatment options for RA, JAKi represent the newest class of drugs. JAKi are small, targeted molecules which act through inhibition of a family of protein kinases (including JAK 1, JAK 2, JAK 3, and tyrosine kinase 2), thus blocking production of multiple cytokines implicated in the pathogenesis of RA with a different mechanism of action compared to bDMARDs (63). Unlike bDMARDs, JAKi are orally administered. Known side effects are an increase both in reactivation of Herpes Zoster and in venous thromboembolism (VTE) (64,65). The efficacy, both in improvement in clinical signs/symptoms and in the inhibition of progression of structural joint damage, and safety of JAKi in RA patients have been documented in clinical trials (64,65). In contrast to most bDMARDs, JAKi have proven higher efficacy than MTX monotherapy and have shown superiority to bDMARDs when both combined with MTX (66-69).

Indeed, both EULAR in 2019 (70) (before the most recently updated 2022 recommendations) and ACR latest guidelines recommended that JAKi could be used as first-line advanced therapy, in patients who do not achieve the treatment target despite csDMARD therapy.

An unexpected twist in the plot occurred after the publication of the results of the ORAL Surveillance in 2022 (71). In this randomized, open-label, post-authorization, phase 3b-4 safety end-point trial, the incidence of major adverse cardiovascular events (MACE) and cancer (excluding non-melanoma skin cancer) was compared between tofacinitib (5 mg twice daily, which is the approved dose for RA, or 10 mg twice daily as per treatment for ulcerative colitis) vs adalimumab or etanercept in more than 4000 patients ≥50 years of age with active moderate-to-severe RA despite MTX treatment, who had ≥1 one cardiovascular (CV) risk factor. In this study, MACE and cancers occurred more frequently in patients taking tofacitinib (combined dose) than in those on TNFi, with a hazard ratio (HR) of 1.33 (95%CI 0.91-1.94) for MACE and 1.48 (95% CI 1.04-2.09) for cancers. In addition, during the trial, the investigators reduced the dose of tofacitinib from 10 mg twice daily to 5 mg twice daily after the observation of a higher incidence of pulmonary embolism and mortality in patients receiving tofacitinib 10 mg twice daily in comparison with those receiving a TNFi.

The results of the ORAL Surveillance triggered an immediate response by the Food and Drug Administration (FDA), which produced a warning (Drug Safety communication) regarding the increased risk of serious heart-related events, cancer, blood clots, and death for JAKi (72). In this document, the FDA stated these drugs should be reserved to patients who have had an inadequate response or intolerance to ≥1 TNFi, thus downgrading JAKi to second line among advanced therapies. A similar document was subsequently published by the European Medicine Agency (EMA) (73).

In contrast to the previous recommendations in 2019, the new EULAR recommendations suggest using JAKi only in those patients without CV risk factors, such as age >65 years, previous/current smoking, diabetes, obesity, hypertension, predisposing conditions for thromboembolic events, and malignancy (54). Therefore, despite retaining the placement of JAKi as first-line therapy after csDMARDs in these latest EULAR recommendations, the safety profile will limit the use of these medications to a selected population, <65 years old and without CV risk factors.

Several important questions concerning the safety of JAKi and therefore their use in RA patients remain unanswered. Whether the risk profile which emerged in the ORAL Surveillance would be applicable to more selective JAKi (JAK1 or JAK 1/2) than tofacitinib (a pan JAKi) or in RA patients without predisposing CV risk factors needs to be established. Recent observational studies including a large number of RA patients have

provided reassuring data on the safety profile of baricitinib and tofacitinib regarding the risk of MACE, VTE and malignancy (with the exception of non-melanoma skin cancer), when compared to TNFi (74,75). A post-hoc analysis of the ORAL Surveillance study showed that RA patients without history of atherosclerotic CV disease did not show an increased incidence of MACE when exposed to tofacitinib 5 mg twice a daily in comparison with TNFi (76).

In addition, in a very recent post hoc analysis of the ORAL Surveillance, a subpopulation with higher risk of MACE and malignancies was identified based by the presence of age (≥65 years) and smoking (ever smoked), with no significant risk in those without the risk factors, providing useful information on the risk assessment and decision-making on treatment with tofacitinib in RA patients (77). Interestingly, in a nationwide cohort from Sweden including more 27000 RA patients, treated with JAKi, TNFi or other bDMARDs, therapy with IL-6ra showed a non-significant increased VTE risk in comparison with TNFi, especially in males (78).

Remission in rheumatoid arthritis

The improvement in outcome of RA patients is reflected in various registries worldwide. An increasing number of RA patients are now able to achieve disease remission (79,80).

Various composite indices are used in RA to define states of disease activity (including remission) and response to treatment. The most used is the Disease Activity Index (DAS), which uses a complex mathematical formula including as variables the number of tender and swollen joints out of 28, inflammatory markers (CRP or ESR) and the patient assessment of global health status (81,82). Other composite indices are the Clinical Disease Activity Index (CDAI) and the Simple Disease Activity Index (SDAI) for RA (83,84). Recently, the ACR and EULAR have developed stringent remission criteria (ACR/EULAR Boolean criteria), in which the included variables [tender joint count, swollen joint count, patient global assessment (PGA), CRP] must all have a value of ≤1 (revised to ≤2 for PGA) (85).

Both ACR and EULAR considered the opportunity of tapering therapy in patients with sustained (≥6 months) clinical remission (EULAR) and/or low disease activity (ACR) (53,54). ACR takes into account the high risk of flares that follows therapy discontinuation, with a potential negative impact on a patient's quality of life and function, and conditionally recommend DMARD continuation at their current dose over therapy tapering (86). If tapering is to be considered, both societies recommend a gradual tapering (i.e. dose reduction or interval increase) over abrupt drug interruption.

Indeed, a large proportion of patients will experience a flare when their treatment with DMARDs is tapered or discontinued (87,88). This is mitigated by the fact that disease control is usually recaptured (about 90% of patients) when treatment is resumed (89).

The observation of frequent disease reactivation following therapy reduction or discontinuation has raised the hypothesis that the achievement of a threshold of disease remission according to the routinely used disease activity indices might not be sufficient to define a status of 'true' disease remission. Some studies have demonstrated the presence of US sub-clinical synovitis in patients in clinical remission, and this could arguably explain the radiographic progression observed in some RA patients with no apparent clinically 'active' disease (90,91).

Recently, the concept of 'multi-dimension' remission has emerged, which is based on the following levels of remission: 1) clinical (i.e. absence of clinical signs of inflammation); 2) serological and imaging; 3) immunological (i.e. disappearance of autoantibodies) (92). While the achievement of a clinical, serological and imaging remission might represent an obtainable goal with the current RA therapeutic strategies, immunological remission has been observed infrequently in RA patients, including those in sustained drug-free remission (93). An alternative immunological remission, based on normalization of T-cell subsets, proposed by Gul et al. may be more practical (94).

Objective biomarkers that can reliably predict the future risk of disease relapse are lacking (95). A shorter disease duration, early remission induction with use of bDMARDs, absence of radiographic damage and low disease activity have been associated with successful therapy tapering in RA patients in clinical remission (96-98). On the other hand, abnormal T-cell subsets, US sub-clinical inflammation and inflammatory markers have been associated with disease relapse after therapy reduction or discontinuation (99-101).

Challenges and future directions

- *Difficult to treat rheumatoid arthritis*

One of the most challenging issues in RA is management of patients with persistent 'active' disease (including those achieving low disease activity), despite successive trials of cs/b/and tsDMARDs with varying mechanisms of action (i.e. ≥2 b/tsDMARDs with different mechanisms of actions according to EULAR). This group of patients with multi-drug resistant RA, who has been recently termed 'Difficult to Treat RA' (D2TRA) by EULAR, represents an ongoing therapeutic challenge (102,103).

The prevalence of D2TRA reached 6% in a recent UK registry, however this appears to be higher when cs-DMARDs (which are not accepted as criteria for D2TRA in the EULAR definitions) are also considered (104,105).

In RA patients, and especially in this group of D2TRA, the correct identification of persistent active disease (and the distinction from joint pain/swelling from other causes, such as damage, osteoarthritis, or chronic non-articular pain) is crucial to guide pharmacological and non-pharmacological interventions. Indeed, continuous cycling of further DMARD therapy might be unnecessary in those without definitive evidence of an ongoing inflammatory joint process.

Two categories of patients with D2TRA have been recently proposed: 1) RA patients with persistent inflammatory refractory RA (PIRRA), defined as the presence of unequivocal signs of ongoing inflammation (US inflammation and/or abnormal inflammatory markers); 2) RA patients in whom symptoms persist despite the absence of discernible inflammation (non-inflammatory refractory RA, NIRRA) (Figure 4) (106). Despite this intriguing hypothesis, future investigations will have to clarify whether patients with PIRRA have different genetic/epigenetic mechanisms and immune pathways, which contribute to the immunopathogenesis of refractory inflammation in comparison with NIRRA, and therefore a different prognosis, long-term outcomes and response to therapy. In addition, novel approaches in which dual therapies, or bi-valent antibodies, are utilized to simultaneously inhibit two different molecular pathways are current under consideration, but risk of infection may be a limiting factor (107).

- *Precision medicine approach*

In those patients with insufficient response to MTX, which occurs in up to 50%, and poor prognostic factors, treatment escalation to b/tsDMARD should be undertaken. The answer to the question "which patients will respond to which type of treatment?" remains unclear as several meta-analysis and head-to-head clinical trials have failed to clearly demonstrate a higher efficacy of any of the bDMARDs (some positive results have been published for tsDMARDs) over the others when combined with MTX (108).

Therefore, the decision of which bDMARD to start is currently arbitrary and mainly based on cost. However, a few additional considerations include patients' comorbidities and preferences, including frequency or route of administration, and, to a lesser extent, the presence of some biomarkers that have been inconsistently associated with better response following specific therapy, such as positive RA auto-antibodies for abatacept, rituximab, and TNFi responses, or increased CRP for IL-6ra response (109,110).

In those where b/tsDMARDs therapy is commenced, there are three possible outcomes, provided that the drug is well tolerated: 1) good response (ideally disease remission); 2) no response after 3-6 months of

therapy (primary non-response); 3) initial good response, which is then followed by loss of response (secondary non-response) (111).

This poses the relevant question whether, in non-responders to one bDMARD, an agent with a different mechanism of action versus a second agent with the same mode of action should be used. The scientific evidence is inconclusive, even though some studies have demonstrated that using a drug with the same mechanism of action can be associated with positive outcomes (112,113). Drug immunogenicity (i.e. development of anti-drug antibodies) has been regarded as one of the mechanisms responsible for therapeutic failure of bDMARDs, secondary non-response (114). An important aspect to consider is that the response rate to bDMARDs decreases with multiple drug failure (115).

Recently, attention has turned to investigation and characterization of prominent cellular and molecular pathways and patterns within RA synovia across an array of patients, utilizing US-guided synovial biopsy techniques (5). Indeed, a number of specific effector cell states in RA synovia have been identified as potential targets for therapy development, including MERTK+ macrophages, NOTCH3+ synovial fibroblasts, CD11c+ autoimmune-associated B cells, PD-1hi peripheral helper T (TPH) cells, and others (116-118). Moreover in a recent clinical trial comparing an anti-CD20 antibody (rituximab) to an anti-IL-6ra (tocilizumab), patients with a low or absent synovial B cell molecular signature had lower responses to rituximab than to tocilizumab (119,120). Although still in early stages, these strategies offer excitement and hope that a precision medicine approach in RA, in which a DMARD is selected based upon the synovial characteristics of each patient's tissue, may be forthcoming in the near future.

- *Prediction and prevention of rheumatoid arthritis*

The development of clinical synovitis is widely accepted as the beginning of RA. Despite the considerable advances in the treatment and management of RA, it is evident that once the disease develops there is no cure for most patients. Indeed, long-term therapy is usually required, with important implications on patient's quality of life and ability to work, and socioeconomic costs.

The detection in the stored serum of RA patients of RA-related autoantibodies, particularly the relatively specific anti-CCP, years before the development of clinically evident disease, has represented a milestone in the understanding of 'pre-clinical' RA (121-123). The concept of an 'RA continuum' has emerged. As shown in Figure 5, in this 'continuum' clinical synovitis is not the beginning of the disease (as per traditional view) but the culmination of a whole series of mainly 'sub-clinical' pathological events, such as autoimmunity and inflammation.

Lessons from the early arthritis paradigm have demonstrated that it is possible to modify the natural history of the disease and improve patients' long-term outcome. This has raised the hypothesis that the initiation of a treatment in the early stages of the 'RA continuum', before the development of clinically evident disease, might prevent, or at least delay, the onset of RA in individuals 'at-risk' (124,125).

In clinical trials on RA prevention, where individuals 'at-risk' are offered anti-rheumatic treatments, an accurate risk stratification is of paramount importance, especially to avoid over-treatment of those who will never develop the disease. In recent years, several research groups worldwide have built models for optimum risk prediction, which variably combine genetic, clinical, serological, and imaging risk factors for RA development (126,127). A very recent paper studied an extensive pre-RA population and provided scores for whom to refer from primary care, and whom would be appropriate for intervention in secondary care (128).

Clearly, the most impactful intervention in RA would be its prevention. Multiple trials on RA prevention based on the use of drugs have been completed recently, while others are actively enrolling (129).

The first study, ADJUST, demonstrated that abatacept therapy for 6 months could delay the onset of RA in undifferentiated arthritis, whilst reducing anti-CCP levels and reducing erosions (130).

In a RCT, 83 patients with arthralgia and positive anti-CCP antibody or RF received two intramuscular injections of 100 mg dexamethasone (at baseline and 6 weeks) or placebo (131). Patients receiving dexamethasone showed a significant and sustained reduction of autoantibodies (the primary end point) in comparison with the placebo group. However, the rate of progression to RA was similar in the two groups (20% vs 21%, respectively) over 26 months.

In the PRAIRI Trial, 81 individuals with positive anti-CCP antibodies and RF with either MRI/US evidence of inflammation or increased CRP were randomized to receive a single dose of rituximab (1000 mg + 100 mg methylprednisolone premedication) or placebo (132). In individuals receiving rituximab, there was a significant delay in the development of RA (12 months) compared to the placebo group, even though the rates of RA development after a follow-up of 29 months did not differ between the two groups (34% vs 40, respectively).

In a recent RCT, 236 individuals with clinically suspect arthralgia and MRI-detected subclinical joint inflammation were randomly assigned to 12-months therapy of oral MTX (up to 25 mg/week) plus a single intramuscular steroid injection (n=119), or placebo (n=117) (133). This RCT failed to demonstrate the ability of MTX versus placebo to reduce the rate of progression to RA after 2 years, although improvement in symptoms and MRI features was superior in the MTX group.

Other studies have shown the potential ability of abatacept to suppress sub-clinical synovitis on MRI in ACPA positive 'at-risk' individuals with MRI signs of inflammation (134). The preliminary results of another recently completed trial, Arthritis Prevention In the Pre-clinical Phase of Rheumatoid Arthritis with Abatacept (APPIPPRA), which started in 2014, showed a reduction in the development of RA over two years in individuals 'at-risk' treated with abatacept (135). On the other hand, an interim analysis of the stop-RA trial, which included 144 CCP3 positive individuals with or without arthralgia and imaging inflammation, failed to demonstrate the ability of HCQ to prevent the development of inflammatory arthritis in comparison with placebo; therefore, the trial was stopped before its expected conclusion (136).

A potential interpretation for these studies is that an earlier stage in the 'RA continuum' (i.e. before the development of subclinical joint disease) might be the correct target for prevention (137,138). On the other hand, not all patients with arthralgia and subclinical joint disease progress to RA (139), those that do, have other risk factors present (140).

The pivotal mechanisms implicated in progressing from subclinical to clinical disease are poorly understood, and targets for interventions not been definitively identified. What is also clear is that 'pre-clinical' RA, however defined, has a considerable morbidity which responds to treatment, guidelines for management are in development.

Conclusions

The management and outcomes of RA patients have drastically improved in the last two decades. The recommendations for managing RA are changing rapidly, due to newly developed therapies and evolving scientific evidence. In this seminar, the new ACR and EULAR recommendations are discussed. The controversies regarding the use of GCs have been highlighted, as well as the uncertainty around JAKi, and approaches to tapering therapy in those in remission outlined. There is a clear a need for reliable biomarkers for diagnosis, prognosis and especially for therapy, due to a not irrelevant proportion of patients not responding to multiple b/tsDMARDs. New areas of research have been illustrated, including D2TRA, 'precision medicine', and attempts to delay/prevent arthritis.

Conflict of interest statement

ADM and JMB declare no conflict of interest. PE has received grants from Lilly and Samsung. He has received consulting fees from BMS, Boehringer-Ingelheim, Lilly, Novartis and payment and honoraria from Galapagos, Lilly and Novartis. He has also received support for attending meetings and/or travel from Lilly and has participated on a Data Safety Monitoring Board or Advisory Board with AstraZeneca.

Contributors section

All authors discussed and agreed on the structure of the seminar. They equally contributed in the search of the papers. ADM prepared the images and tables and wrote the first draft of the manuscript, which was critically reviewed by JMB and PE. All authors have seen and approved of the final version of the manuscript.

References

1. Aletaha D, Smolen JS. Diagnosis and Management of Rheumatoid Arthritis: A Review. JAMA. 2018 Oct 2;320:1360-1372
2. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet. 2016;22;388:2023-2038.
3. Finckh A, Gilbert B, Hodkinson B, et al. Global epidemiology of rheumatoid arthritis. Nat Rev Rheumatol. 2022;18:591-602.
4. Scott IC, Whittle R, Bailey J, et al. Rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis epidemiology in England from 2004 to 2020: An observational study using primary care electronic health record data. Lancet Reg Health Eur. 2022;10;23:100519.
5. Gravallese EM, Firestein GS. Rheumatoid Arthritis - Common Origins, Divergent Mechanisms. N Engl J Med. 2023;9;388:529-542
6. Alivernini S, Firestein GS, McInnes IB. The pathogenesis of rheumatoid arthritis. Immunity. 2022;13;55:2255-2270.
7. Hemminki K, Li X, Sundquist J, Sundquist K. Familial associations of rheumatoid arthritis with autoimmune diseases and related conditions. Arthritis Rheum. 2009;60:661-8.
8. Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. Arthritis Rheum. 1987;30:1205-13.
9. Wouters F, Maurits MP, van Boheemen L, et al. Determining in which pre-arthritis stage HLA-shared epitope alleles and smoking exert their effect on the development of rheumatoid arthritis. Ann Rheum Dis. 2022;81:48-55.
10. Karlson EW, Chibnik LB, Cui J, et al. Associations between human leukocyte antigen, PTPN22, CTLA4 genotypes and rheumatoid arthritis phenotypes of autoantibody status, age at diagnosis and erosions in a large cohort study. Ann Rheum Dis. 2008;67:358-63.
11. Plenge RM, Padyukov L, Remmers EF, et al. Replication of putative candidate-gene associations with rheumatoid arthritis in >4,000 samples from North America and Sweden: association of susceptibility with PTPN22, CTLA4, and PADI4. Am J Hum Genet. 2005;77:1044-60.
12. Ishigaki K, Sakaue S, Terao C, et al. Multi-ancestry genome-wide association analyses identify novel genetic mechanisms in rheumatoid arthritis. Nat Genet. 2022;54:1640-1651.

13. Nemtsova MV, Zaletaev DV, Bure IV, et al. Epigenetic Changes in the Pathogenesis of Rheumatoid Arthritis. Front Genet. 2019;14;10:570.
14. Conrad N, Misra S, Verbakel JY, et al. Incidence, prevalence, and co-occurrence of autoimmune disorders over time and by age, sex, and socioeconomic status: a population-based cohort study of 22 million individuals in the UK. Lancet. 2023;3:1878-1890.
15. Sugiyama D, Nishimura K, Tamaki K, et al. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis. 2010;69:70-81.
16. Deane KD, Demoruelle MK, Kelmenson LB, et al. Genetic and environmental risk factors for rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2017;31:3-18.
17. Di Giuseppe D, Alfredsson L, Bottai M, et al. Long term alcohol intake and risk of rheumatoid arthritis in women: a population based cohort study. BMJ. 2012;10;345:e4230.
18. Myasoedova E, Davis J, Matteson EL, et al. Is the epidemiology of rheumatoid arthritis changing? Results from a population-based incidence study, 1985-2014. Ann Rheum Dis. 2020;79:440-444.
19. van Venrooij WJ, van Beers JJ, Pruijn GJ. Anti-CCP antibodies: the past, the present and the future. Nat Rev Rheumatol. 2011;7;7:391-8.
20. Bas S, Genevay S, Meyer O, et al. Anti–cyclic citrullinated peptide antibodies, IgM and IgA rheumatoid factors in the diagnosis and prognosis of rheumatoid arthritis. Rheumatology. 2003;42:677-680.
21. Shi J, van de Stadt LA, Levarht EW, et al. Anti-carbamylated protein (anti-CarP) antibodies precede the onset of rheumatoid arthritis. Ann Rheum Dis. 2014;73:780-783.
22. Shi J, van Steenbergen HW, van Nies JA, et al. The specificity of anti-carbamylated protein antibodies for rheumatoid arthritis in a setting of early arthritis. Arthritis Res Ther. 2015;17:339.
23. Mankia K, Emery P. Preclinical Rheumatoid Arthritis: Progress Toward Prevention. Arthritis Rheumatol. 2016;68:779-88.
24. Zhang X, Zhang D, Jia H, et al. The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. Nat Med. 2015;21:895-905.
25. Holers VM, Demoruelle MK, Kuhn KA, et al. Rheumatoid arthritis and the mucosal origins hypothesis: protection turns to destruction. Nat Rev Rheumatol. 2018;14:542-557.
26. Nishimura K, Sugiyama D, Kogata Y, et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. Ann Intern Med. 2007;5;146:797-808.
27. van den Broek M, Dirven L, Klarenbeek NB, et al. The association of treatment response and joint damage with ACPA-status in recent-onset RA: a subanalysis of the 8-year follow-up of the BeSt study. Ann Rheum Dis. 2012;71:245-8.
28. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011;8;365:2205-19.

29. Choy E. Understanding the dynamics: pathways involved in the pathogenesis of rheumatoid arthritis. Rheumatology (Oxford). 2012;51 Suppl 5:v3-11.
30. Guo Q, Wang Y, Xu D, Nossent J, et al. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. Bone Res. 2018;27;6:15.
31. Feldmann M, Maini SR. Role of cytokines in rheumatoid arthritis: an education in pathophysiology and therapeutics. Immunol Rev. 2008; 223:7-19
32. Smolen JS, Aletaha D, Barton A, et al. Rheumatoid arthritis. Nat Rev Dis Primers. 2018;8;4:18001.
33. Mankia K, D'Agostino MA, Rowbotham E, et al. MRI inflammation of the hand interosseous tendons occurs in anti-CCP-positive at-risk individuals and may precede the development of clinical synovitis. Ann Rheum Dis. 2019;78:781-786.
34. Turesson C, O'Fallon WM, Crowson CS, et al. Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. Ann Rheum Dis. 2003;62:722-7.
35. Turesson C. Extra-articular rheumatoid arthritis. Curr Opin Rheumatol. 2013;25:360-6.
36. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62:2569-81.
37. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315-24.
38. Radner H, Neogi T, Smolen JS, Aletaha D. Performance of the 2010 ACR/EULAR classification criteria for rheumatoid arthritis: a systematic literature review. Ann Rheum Dis. 2014;73:114-23.
39. Di Matteo A, Mankia K, Azukizawa M, et al. The Role of Musculoskeletal Ultrasound in the Rheumatoid Arthritis Continuum. Curr Rheumatol Rep. 2020;19;22:41.
40. Schett G, Gravallese E. Bone erosion in rheumatoid arthritis: mechanisms, diagnosis and treatment. Nat Rev Rheumatol. 2012;8:656-64.
41. Colebatch AN, Edwards CJ, Østergaard M, et al. EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. Ann Rheum Dis. 2013;72:804-14.
42. Baillet A, Gaujoux-Viala C, Mouterde G, et al. Comparison of the efficacy of sonography, magnetic resonance imaging and conventional radiography for the detection of bone erosions in rheumatoid arthritis patients: a systematic review and meta-analysis. Rheumatology (Oxford). 2011;50:1137-47.
43. Haavardsholm EA, Aga A-B, Olsen IC, et al. Ultrasound in management of rheumatoid arthritis: ARCTIC randomised controlled strategy trial. BMJ. 2016;354:i4205.
44. Dale J, Stirling A, Zhang R, Purves D, et al. Targeting ultrasound remission in early rheumatoid arthritis: the results of the TaSER study, a randomised clinical trial. Ann Rheum Dis. 2016;75:1043–50.
45. Smolen JS, Aletaha D, Bijlsma JW, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2010;69:631–7.

46. Burgers LE, Raza K, van der Helm-van Mil AH. Window of opportunity in rheumatoid arthritis - definitions and supporting evidence: from old to new perspectives. RMD Open. 20193;5:e000870.
47. Pincus T, Yazici Y, Sokka T, et al. Methotrexate as the "anchor drug" for the treatment of early rheumatoid arthritis. Clin Exp Rheumatol. 2003;21(5 Suppl 31):S179-85.
48. Frisell T, Bower H, Morin M, et al; ARTIS Study group. Safety of biological and targeted synthetic disease-modifying antirheumatic drugs for rheumatoid arthritis as used in clinical practice: results from the ARTIS programme. Ann Rheum Dis. 2023;82:601-610.
49. Kerschbaumer A, Sepriano A, Bergstra SA, et al. Efficacy of synthetic and biological DMARDs: a systematic literature review informing the 2022 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2023;82:95-106.
50. Nam JL, Ramiro S, Gaujoux-Viala C, et al. Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2013 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2014;73:516-28.
51. Jani M, Barton A, Warren RB, et al. The role of DMARDs in reducing the immunogenicity of TNF inhibitors in chronic inflammatory diseases. Rheumatology (Oxford). 2014;53:213-22.
52. Emery P, Pope JE, Kruger K, et al. Efficacy of Monotherapy with Biologics and JAK Inhibitors for the Treatment of Rheumatoid Arthritis: A Systematic Review. Adv Ther. 2018;35:1535-1563.
53. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol. 2021;73:1108–23.
54. Smolen JS, Landewé RBM, Bergstra SA, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis. 2023;82:3-18.
55. Targeted Treatment Early With Etanercept + Methotrexate vs.T2T Care for DMARD-naïve Early RA Patients Based on naïve T-cell Stratification (TEEMS). https://clinicaltrials.gov/ct2/show/NCT03813771
56. Doumen M, Pazmino S, Bertrand D, et al. Glucocorticoids in rheumatoid arthritis: Balancing benefits and harm by leveraging the therapeutic window of opportunity. Joint Bone Spine. 2022 18;90:105491.
57. Graudal N, Jurgens G. Similar effects of disease-modifying antirheumatic drugs, glucocorticoids, and biologic agents on radiographic progression in rheumatoid arthritis: meta-analysis of 70 randomized placebo-controlled or drug-controlled studies, including 112 comparisons. Arthritis Rheum. 2010;62:2852-2863.
58. Wassenberg S, Rau R, Steinfeld P, et al. for the Low-Dose Prednisolone Therapy Study Group. Very low-dose prednisolone in early rheumatoid arthritis retards radiographic progression over two years: a multicenter, double-blind, placebo-controlled trial. Arthritis Rheum. 2005;52:3371-3380.

59. Hetland ML, Haavardsholm EA, Rudin A, et al; NORD-STAR study group. Active conventional treatment and three different biological treatments in early rheumatoid arthritis: phase IV investigator initiated, randomised, observer blinded clinical trial. BMJ. 2020;2;371:m4328.
60. Kerschbaumer A, Sepriano A, Smolen JS, et al. Efficacy of pharmacological treatment in rheumatoid arthritis: a systematic literature research informing the 2019 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis. 2020;79:744-759.
61. Hua C, Buttgereit F, Combe B. Glucocorticoids in rheumatoid arthritis: current status and future studies. RMD Open. 2020;6:e000536.
62. Boers M, Hartman L, Opris-Belinski D, et al; GLORIA Trial consortium. Low dose, add-on prednisolone in patients with rheumatoid arthritis aged 65+: the pragmatic randomised, double-blind placebo-controlled GLORIA trial. Ann Rheum Dis. 2022;81:925-936.
63. Nash P, Kerschbaumer A, Dörner T, et al. Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: a consensus statement. Ann Rheum Dis. 2021;80:71-87.
64. Wang F, Sun L, Wang S, et al. Efficacy and safety of tofacitinib, baricitinib, and upadacitinib for rheumatoid arthritis: a systematic review and meta-analysis. Mayo Clin Proc. 2020;95:1404-1419;
65. Kerschbaumer A, Smolen JS, Nash P, et al. Points to consider for the treatment of immunemediated inflammatory diseases with Janus kinase inhibitors: a systematic literature research. RMD Open. 2020;6:e001374.
66. Lee EB, Fleischmann R, Hall S, et al; ORAL Start Investigators. Tofacitinib versus methotrexate in rheumatoid arthritis. N Engl J Med. 2014;19;370(25):2377-86.
67. van Vollenhoven R, Takeuchi T, Pangan AL, et al. Efficacy and Safety of Upadacitinib Monotherapy in Methotrexate-Naive Patients With Moderately-to-Severely Active Rheumatoid Arthritis (SELECT-EARLY): A Multicenter, Multi-Country, Randomized, Double-Blind, Active Comparator-Controlled Trial. Arthritis Rheumatol. 2020;72:1607-1620.
68. Fleischmann R, Schiff M, van der Heijde D, et al. Baricitinib, Methotrexate, or Combination in Patients With Rheumatoid Arthritis and No or Limited Prior Disease-Modifying Antirheumatic Drug Treatment. Arthritis Rheumatol. 2017;69:506-517.
69. Taylor PC, Keystone EC, van der Heijde D, et al. Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis. N Engl J Med. 2017;16;376:652-662.
70. Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis 2020;79:685–99.
71. Ytterberg SR, Bhatt DL, Mikuls TR, et al; ORAL Surveillance Investigators. Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. N Engl J Med. 2022;27;386:316-326.

72. Food and Drug Administration of the United States. FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions, 2021. Available: https:// www fda gov/drugs/drug-safety-and-availability/fda-requires-warnings-aboutincreased-risk-serious-heart-related-events-cancer-blood-clots-and-death
73. European Medicines Agency. Xeljanz (tofacitinib): increased risk of major adverse cardiovascular events and malignancies with use of tofacitinib relative to TNF-alpha inhibitors, 2021. Available: https://www ema europa eu/en/medicines/dhpc/xeljanztofacitinib-increased-risk-major-adverse-cardiovascular-events-malignancies-usetofacitinib
74. Huss V, Bower H, Hellgren K et al; behalf of the ARTIS group. Cancer risks with JAKi and biological disease-modifying antirheumatic drugs in patients with rheumatoid arthritis or psoriatic arthritis: a national real-world cohort study. Ann Rheum Dis. 2023;82:911-919.
75. Hoisnard L, Pina Vegas L, Dray-Spira R, et al. Risk of major adverse cardiovascular and venous thromboembolism events in patients with rheumatoid arthritis exposed to JAK inhibitors versus adalimumab: a nationwide cohort study. Ann Rheum Dis. 2023;82:182-188.
76. Charles-Schoeman C, Buch MH, Dougados M, et al. Risk of major adverse cardiovascular events with tofacitinib versus tumour necrosis factor inhibitors in patients with rheumatoid arthritis with or without a history of atherosclerotic cardiovascular disease: a post hoc analysis from ORAL Surveillance. Ann Rheum Dis. 2023;82:119-129.
77. Kristensen LE, Danese S, Yndestad A, et al. Identification of two tofacitinib subpopulations with different relative risk versus TNF inhibitors: an analysis of the open label, randomised controlled study ORAL Surveillance. Ann Rheum Dis. 2023;82:901-910.
78. Molander V, Bower H, Frisell T, et al. Venous thromboembolism with JAK inhibitors and other immune-modulatory drugs: a Swedish comparative safety study among patients with rheumatoid arthritis. Ann Rheum Dis. 2023;82:189-197.
79. Einarsson JT, Willim M, Saxne T, et al. Secular trends of sustained remission in rheumatoid arthritis, a nationwide study in Sweden. Rheumatology (Oxford). 2020;1;59:205-212.
80. Aga AB, Lie E, Uhlig T, et al. Time trends in disease activity, response and remission rates in rheumatoid arthritis during the past decade: results from the NOR-DMARD study 2000-2010. Ann Rheum Dis. 2015;74:381-8.
81. van der Heijde DMFM, Van't Hof MA, van Riel PLCM, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann Rheum Dis. 1990;49:916-920.

82. Prevoo MLL, van't Hof MA, Kuper HH, van de Putte LBA, van Riel PLCM. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum1995; 38:44-48.
83. Aletaha D, Nell VPK, Stamm T, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: Validation of a clinical activity score. Arthritis Res;2005; 7:R796-R806.
84. Smolen JS, Breedveld FC, Schiff MH, et al. A Simplified Disease Activity Index for Rheumatoid Arthritis For Use In Clinical Practice. Rheumatology2003; 42:244-257.
85. Felson DT, Smolen JS, Wells G, et al. American college of rheumatology/european league against rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis2011; 70:404-413.
86. Smolen JS, Pedersen R, Jones H, et al. Impact of flare on radiographic progression after etanercept continuation, tapering or withdrawal in patients with rheumatoid arthritis. Rheumatology (Oxford). 2020;1;59:153-164.
87. Terslev L, Ostergaard M, Georgiadis S, et al. Flare during tapering of biological DMARDs in patients with rheumatoid arthritis in routine care: characteristics and predictors. RMD Open. 2022;8:e002796.
88. Amstad A, Papagiannoulis E, Scherer A, et al. Comparison of drug retention of TNF inhibitors, other biologics and JAK inhibitors in RA patients who discontinued JAK inhibitor therapy. Rheumatology (Oxford). 2022;23;62:89-97.
89. Schett G, Tanaka Y, Isaacs JD. Why remission is not enough: underlying disease mechanisms in RA that prevent cure. Nat Rev Rheumatol. 2021;17:135-144.
90. Brown AK, Quinn MA, Karim Z, et al. Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression. Arthritis Rheum. 2006;54:3761-73.
91. Brown AK, Conaghan PG, Karim Z, et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum. 2008;58:2958-67.
92. Schett G, Emery P, Tanaka Y, et al. Tapering biologic and conventional DMARD therapy in rheumatoid arthritis: Current evidence and future directions. Ann. Rheum. Dis. 2016;75:1428–1437.
93. Boeters DM, Burgers LE, Toes RE, et al. Does immunological remission, defined as disappearance of autoantibodies, occur with current treatment strategies? A long-term follow-up study in rheumatoid arthritis patients who achieved sustained DMARD-free status. Ann Rheum Dis. 2019;78:1497-1504.
94. Gul HL, Eugenio G, Rabin T, et al. Defining remission in rheumatoid arthritis: does it matter to the patient? A comparison of multi-dimensional remission criteria and patient reported outcomes. Rheumatology (Oxford). 2020;1;59:613-621.

95. Schlager L, Loiskandl M, Aletaha D, et al. Predictors of successful discontinuation of biologic and targeted synthetic DMARDs in patients with rheumatoid arthritis in remission or low disease activity: a systematic literature review. Rheumatology (Oxford). 2020;1;59(2):324-334.
96. Huizinga TW, Conaghan PG, Martin-Mola E, et al. Clinical and radiographic outcomes at 2 years and the effect of tocilizumab discontinuation following sustained remission in the second and third year of the ACT-RAY study. Ann Rheum Dis. 2015;74:35-43.
97. Ghiti Moghadam M, Vonkeman HE, Ten Klooster PM, et al; Dutch National POET Collaboration. Stopping Tumor Necrosis Factor Inhibitor Treatment in Patients With Established Rheumatoid Arthritis in Remission or With Stable Low Disease Activity: A Pragmatic Multicenter, Open-Label Randomized Controlled Trial. Arthritis Rheumatol. 2016;68:1810-7.
98. Bijlsma JWJ, Welsing PMJ, Woodworth TG, et al. Early rheumatoid arthritis treated with tocilizumab, methotrexate, or their combination (U-Act-Early): a multicentre, randomised, double-blind, double-dummy, strategy trial. Lancet. 2016;23;388:343-355.
99. Filippou G, Sakellariou G, Scirè CA, et al. The predictive role of ultrasound-detected tenosynovitis and joint synovitis for flare in patients with rheumatoid arthritis in stable remission. Results of an Italian multicentre study of the Italian Society for Rheumatology Group for Ultrasound: the STARTER study. Ann Rheum Dis. 2018;77:1283-1289.
100. Gul HL, Di Matteo A, Mankia K, et al. Can biomarkers predict successful tapering of conventional disease-modifying therapy in rheumatoid arthritis patients in stable remission? Clin Exp Rheumatol. 2023;41:126-136.
101. Burgoyne CH, Field SL, Brown AK, et al. Abnormal T cell differentiation persists in patients with rheumatoid arthritis in clinical remission and predicts relapse. Ann Rheum Dis. 2008;67:750-7.
102. Nagy G, Roodenrijs NMT, Welsing PM, et al. EULAR definition of difficult-to-treat rheumatoid arthritis. Ann Rheum Dis. 2021;80(1):31-35.
103. Nagy G, Roodenrijs NMT, Welsing PMJ, et al. EULAR points to consider for the management of difficult-to-treat rheumatoid arthritis. Ann Rheum Dis. 2022;81:20-33.
104. Kearsley-Fleet L, Davies R, De Cock D, et al; BSRBR-RA Contributors Group. Biologic refractory disease in rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Ann Rheum Dis. 2018;77:1405-1412.
105. Bécède M, Alasti F, Gessl I, et al. Risk profiling for a refractory course of rheumatoid arthritis. Semin Arthritis Rheum. 2019;49:211-217.
106. Buch MH, Eyre S, McGonagle D. Persistent inflammatory and non-inflammatory mechanisms in refractory rheumatoid arthritis. Nat Rev Rheumatol. 2021;17:17-33.

107. Boleto G, Kanagaratnam L, Dramé M, et al. Safety of combination therapy with two bDMARDs in patients with rheumatoid arthritis: A systematic review and meta-analysis. Semin Arthritis Rheum. 2019;49:35-42.

108. Landewé R, Smolen JS. Review of head-to-head study designs in rheumatoid arthritis. Semin Arthritis Rheum. 2016;46:279-285.

109. Isaacs JD, Cohen SB, Emery P, et al. Effect of baseline rheumatoid factor and anticitrullinated peptide antibody serotype on rituximab clinical response: a meta-analysis. Ann Rheum Dis. 2013;72:329-36.

110. Wang J, Devenport J, Low JM, et al. Relationship Between Baseline and Early Changes in C-Reactive Protein and Interleukin-6 Levels and Clinical Response to Tocilizumab in Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2016;68:882-5.

111. Vallejo-Yagüe E, Keystone EC, et al. Primary and secondary non-response: in need of operational definitions in observational studies. Ann Rheum Dis. 2021;80:961-964.

112. Smolen JS, Kay J, Doyle MK, et al; GO-AFTER study investigators. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet. 2009;18;374:210-21.

113. Emery P, van Hoogstraten H, Thangavelu K, et al. Subcutaneous Sarilumab in Patients With Rheumatoid Arthritis who Previously Received Subcutaneous Sarilumab or Intravenous Tocilizumab: An Open-Label Extension of a Randomized Clinical Trial. ACR Open Rheumatol. 2020;2:672-680.

114. Moots RJ, Xavier RM, Mok CC, et al. The impact of anti-drug antibodies on drug concentrations and clinical outcomes in rheumatoid arthritis patients treated with adalimumab, etanercept, or infliximab: Results from a multinational, real-world clinical practice, non-interventional study. PLoS One. 2017;27;12(4):e0175207.

115. Aletaha D, Maa JF, Chen S, et al. Effect of disease duration and prior disease-modifying antirheumatic drug use on treatment outcomes in patients with rheumatoid arthritis. Ann Rheum Dis. 2019;78:1609-1615.

116. Alivernini S, MacDonald L, Elmesmari A, et al. Distinct synovial tissue macrophage subsets regulate inflammation and remission in rheumatoid arthritis. Nat Med. 2020;26:1295-1306.

117. Wei K, Korsunsky I, Marshall JL, et al; Accelerating Medicines Partnership Rheumatoid Arthritis & Systemic Lupus Erythematosus (AMP RA/SLE) Consortium; Siebel CW, Buckley CD, Raychaudhuri S, Brenner MB. Notch signalling drives synovial fibroblast identity and arthritis pathology. Nature. 2020;582:259-264.

118. Zhang F, Wei K, Slowikowski K, et al; Accelerating Medicines Partnership Rheumatoid Arthritis and Systemic Lupus Erythematosus (AMP RA/SLE) Consortium; Boyce BF, DiCarlo E, Gravallese EM,

Gregersen PK, Moreland L, Firestein GS, Hacohen N, Nusbaum C, Lederer JA, Perlman H, Pitzalis C, Filer A, Holers VM, Bykerk VP, Donlin LT, Anolik JH, Brenner MB, Raychaudhuri S. Defining inflammatory cell states in rheumatoid arthritis joint synovial tissues by integrating single-cell transcriptomics and mass cytometry. Nat Immunol. 2019;20:928-942.

119. Humby F, Durez P, Buch MH, et al; R4RA collaborative group. Rituximab versus tocilizumab in anti-TNF inadequate responder patients with rheumatoid arthritis (R4RA): 16-week outcomes of a stratified, biopsy-driven, multicentre, open-label, phase 4 randomised controlled trial. Lancet. 2021;23;397(10271):305-317.

120. Rivellese F, Surace AEA, Goldmann K, et al; R4RA collaborative group. Rituximab versus tocilizumab in rheumatoid arthritis: synovial biopsy-based biomarker analysis of the phase 4 R4RA randomized trial. Nat Med. 2022;28:1256-1268.

121. del Puente A, Knowler WC, Pettitt DJ, et al. The incidence of rheumatoid arthritis is predicted by rheumatoid factor titer in a longitudinal population study. Arthritis Rheum. 1988;31:1239-1244.

122. Rantapaa-Dahlqvist S, de Jong BA, Berglin E, et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. Arthritis Rheum. 2003;48:2741-2749.

123. Nielen MM, van Schaardenburg D, Reesink HW, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. Arthritis Rheum. 2004;50:380-386.

124. Gerlag DM, Raza K, van Baarsen LG, et al. EULAR recommendations for terminology and research in individuals at risk of rheumatoid arthritis: report from the Study Group for Risk Factors for Rheumatoid Arthritis. Ann Rheum Dis. 2012;71:638-41.

125. Mankia K, Di Matteo A, Emery P. Prevention and cure: The major unmet needs in the management of rheumatoid arthritis. J Autoimmun. 2020;110:102399.

126. Mankia K, Siddle H, Di Matteo A, et al. A core set of risk factors in individuals at risk of rheumatoid arthritis: a systematic literature review informing the EULAR points to consider for conducting clinical trials and observational studies in individuals at risk of rheumatoid arthritis. RMD Open. 2021;7:e001768.

127. Mankia K, Siddle HJ, Kerschbaumer A, et al. EULAR points to consider for conducting clinical trials and observational studies in individuals at risk of rheumatoid arthritis. Ann Rheum Dis. 2021;80:1286-1298.

128. Duquenne L, Hensor EM, Garcia-Montoya L, et al. Predicting inflammatory arthritis in at-risk individuals: development of scores for risk stratification. Ann Intern Med. 2023. In press.

129. Van der Helm-van Mil AHM. Preventive interventions in individuals at risk for Rheumatoid Arthritis: State of the art and perspectives. Joint Bone Spine. 2023 15;90:105543.

130. Emery P, Durez P, Dougados M, et al. Impact of T-cell costimulation modulation in patients with undifferentiated inflammatory arthritis or very early rheumatoid arthritis: a clinical and imaging study of abatacept (the ADJUST trial). Ann Rheum Dis. 2010;69:510-6.

131. Bos WH, Dijkmans BA, Boers M, et al. Effect of dexamethasone on autoantibody levels and arthritis development in patients with arthralgia: a randomised trial. Annals of the rheumatic diseases. 2010;69:571–574.

132. Gerlag DM, Safy M, Maijer KI, et al. Effects of B-cell directed therapy on the preclinical stage of rheumatoid arthritis: the PRAIRI study. Ann Rheum Dis. 2019;78:179-185.

133. Krijbolder DI, Verstappen M, van Dijk BT, et al. Intervention with methotrexate in patients with arthralgia at risk of rheumatoid arthritis to reduce the development of persistent arthritis and its disease burden (TREAT EARLIER): a randomised, double-blind, placebo-controlled, proof-of-concept trial. Lancet. 2022;23;400:283-294.

134. Rech J, Ostergaard M, Tascilar K, et al. Abatacept Reverses Subclinical Arthritis in Patients with High-risk to Develop Rheumatoid Arthritis -results from the Randomized, Placebo-controlled ARIAA Study in RA-at Risk Patients [abstract]. Arthritis Rheumatol. 2021; 73 (suppl 9). https://acrabstracts.org/abstract/abatacept-reverses-subclinical-arthritis-in-patients-with-high-risk-to-develop-rheumatoid-arthritis-results-from-the-randomized-placebo-controlled-ariaa-study-in-ra-at-risk-patients/. Accessed May 5, 2023.

135. Cope A, Jasenecova M, Vasconcelos J, et al. OP0130 ABATACEPT IN INDIVIDUALS AT RISK OF DEVELOPING RHEUMATOID ARTHRITIS: RESULTS FROM THE ARTHRITIS PREVENTION IN THE PRE-CLINICAL PHASE OF RA WITH ABATACEPT (APIPPRA) TRIAL. Annals of the Rheumatic Diseases 2023;82:86.

136. Deane K, Striebich C, Feser M, et al. Hydroxychloroquine Does Not Prevent the Future Development of Rheumatoid Arthritis in a Population with Baseline High Levels of Antibodies to Citrullinated Protein Antigens and Absence of Inflammatory Arthritis: Interim Analysis of the StopRA Trial [abstract]. Arthritis Rheumatol. 2022; 74 (suppl 9). https://acrabstracts.org/abstract/hydroxychloroquine-does-not-prevent-the-future-development-of-rheumatoid-arthritis-in-a-population-with-baseline-high-levels-of-antibodies-to-citrullinated-protein-antigens-and-absence-of-inflammatory/. Accessed May 5, 2023.

137. Di Matteo A, Duquenne L, Cipolletta E, et al. Ultrasound subclinical synovitis in anti-CCP-positive at-risk individuals with musculoskeletal symptoms: an important and predictable stage in the rheumatoid arthritis continuum. Rheumatology (Oxford). 20223;61:3192-3200.

138. Di Matteo A, Mankia K, Duquenne L, et al. Third-Generation Anti-Cyclic Citrullinated Peptide Antibodies Improve Prediction of Clinical Arthritis in Individuals at Risk of Rheumatoid Arthritis. Arthritis Rheumatol. 2020;72:1820-1828.

139. Rogier C, Wouters F, van Boheemen L, et al. Subclinical synovitis in arthralgia: how often does it result in clinical arthritis? Reflecting on starting points for disease-modifying anti-rheumatic drug treatment. Rheumatology (Oxford). 2021;2;60:3872-3878.

140. Garcia-Montoya L, Duquenne L, Nam J, et al POS0947 SUBCLINICAL SYNOVITIS IN ANTI-CCP POSITIVE INDIVIDUALS AT-RISK OF RA: HOW LIKELY IS IT TO RESOLVE? Annals of the Rheumatic Diseases 2023;82:786.

Table 1. Main characteristics of glucocorticoids, csDMARDs, bDMARDs and tsDMARDs, which are currently approved for the treatment of rheumatoid arthritis (USA and Europe).

DMARD	Target	Route of administration (dose)	Adverse events	Management of RA
Glucocorticoids	Genomic and non-genomic pathways	Oral, IM, IV, IA (dose depends on the route of administration and clinical indication)	Depending on dose and duration of therapy. Most common adverse events: diabetes, hypertension, infections, GI diseases, skin atrophy, psychiatric, osteoporosis and ophthalmological diseases (cataract and glaucoma)	'Bridging therapy' when DMARD therapy is initiated or switched and treating flares. In some patients it is sometimes used as a long-term maintenance therapy (like a DMARD)
Conventional DMARDs				
Synthetic				First-line therapy in DMARDs naïve patients
• Methotrexate	Unknown	Oral, SC, IM (10-25 mg/week)	GI, increased liver enzymes, bone marrow suppression, stomatitis, hair loss, teratogenicity, interstitial pneumonitis	First choice among csDMARDs
• Sulfasalazine	Unknown	Oral (2-3 g/day)	GI, skin rash, temporary oligospermia, drug induced SLE	Combination therapy with MTX (or monotherapy if MTX is contraindicated)
• Leflunomide	Dihydroorotate dehydrogenase	Oral (20 mg/day)	GI, increased liver enzymes, leukopenia, hypertension, teratogenicity	Monotherapy if MTX is contraindicated (combination therapy with MTX uncommon)
• Hydroxychloroquine	Unknown	Oral (200-400 mg/day)	GI, skin rash, retinopathy	Combination therapy with MTX (or monotherapy if MTX is contraindicated in patients with low disease activity)
Targeted			GI, infections, colonic perforation, increased CK levels, TB/HZ reactivation, cytopenia, increased risk of VTE, lipids abnormalities	In patients who failed ≥1 csDMARDs, after ≥1 TNFi failure (ACR) or as first-line therapy (EULAR) in selected populations*. Might have some advantages in monotherapy compared to others bDMARDs
• Tofacitinib	JAK 1,2,3	Oral (10 mg/day)	Possible increased risk of MACE and neoplasm (especially in smokers and >65 years)	
• Baricitinib	JAK 1,2	Oral (2-4 mg/day)		
• Upatacitinib	JAK 1 (2)	Oral (15 mg/day)		
• Filgotinib	JAK 1	Oral (200 mg/day)		
Biologic DMARDs				First-line therapy in patients who failed ≥1 csDMARD
TNFi			Infections, TB reactivation, cytopenia, drug induced SLE, NMSC, demyelinating syndromes,	Commonly used as first-line therapy among bDMARDs

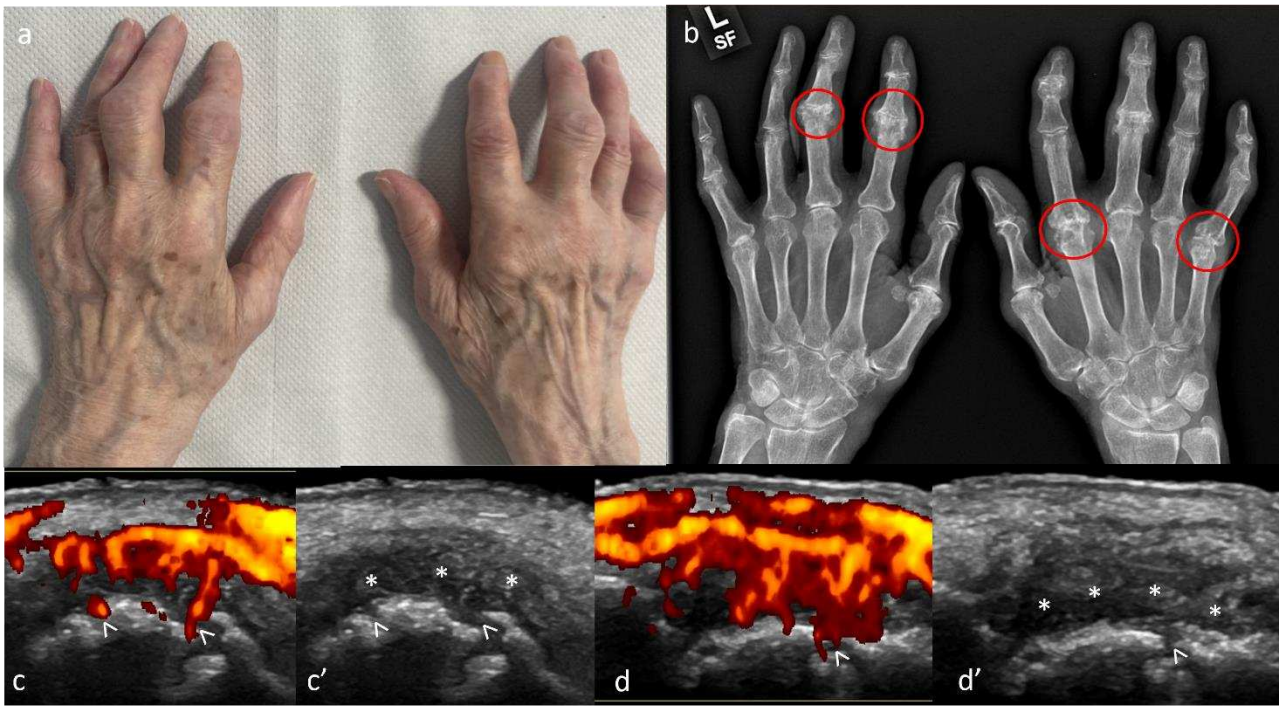
			congestive heart failure, infusion/injections related reactions	
• Adalimumab	TNF	SC (40 mg/2 weeks)		
• Etanercept	TNF	SC (50 mg/week)		
• Golimumab	TNF	IV (2 mg/kg at week 0, 4 and every 8 weeks) SC (50 mg/4 weeks)		
• Certolizumab pegol	TNF	SC (400 mg at 0, 2 and 4, then 200 mg/2 weeks)		
• Infliximab	TNF	IV (3 mg/kg at week 0, 2 and 6 and every 8 weeks) SC (120 mg/2 weeks)		
Anti-B cell				In patients, who failed ≥1 csDMARD, usually after TNFi. ACR suggests use after inadequate response to TNFi or in patients with history of lymphoproliferative disorder
• Rituximab	CD20	IV (1-2 g/6 months)	Infusion reactions, reduced response to vaccines, infections, hepatitis B reactivation, PML	
Anti T-cell co-stimulation				First-line therapy in patients who failed ≥1 cs/bDMARD
• Abatacept	CD80-CD86 co-stimulation	IV (500-1000 mg depending on weight) SC (125 mg/week)	Infections, infusion/injections site reaction, reduced response to vaccines, TB reactivation, leukopenia	
Anti-IL6			Infections, colonic perforation, lipid abnormalities, cytopenia, liver enzyme elevations, infusion/injections related reactions	First-line therapy in patients who failed ≥1 csDMARD. Might have some advantages in comparison with b-DMARDs in monotherapy
• Tocilizumab	IL-6 receptor	IV (4-8 mg/kg/4 weeks – max 800 mg) SC: 162 mg/week		
• Sarilumab	IL-6 receptor	SC (150-200 mg/2 weeks)		

*: Risk factors for cardiovascular events and malignancies to consider before prescribing a JAKi: age >65 years, previous or current smoking, diabetes, obesity, hypertension, current or previous malignancy (other than NMSC), risk factors for thromboembolic events (history of myocardial infarction or heart failure, history of blood clots or inherited disorders of coagulation, combined contraceptives/hormonal replacement therapy, immobility, undergoing major surgery).

Abbreviations. **ACR**: American College of Rheumatology; **b**: biologic; **CK:** creatinine kinase; **cs**: conventional synthetic; **DMARD**: disease modifying anti-rheumatic drug; **EULAR:** European Alliance of Association for Rheumatology; **GI**: gastrointestinal; **HZ**: Herpes Zoster; **IA**: intra-articular; **IL**: interleukin; **IM**: intramuscular; **IV**: intravenous; **JAKi**: Janus kinase inhibitors; **LDA**: low disease activity; **MACE**: major adverse cardiovascular events; **MTX**: methotrexate; **NMSC**: non-melanoma skin cancer; **PML**: progressive multifocal leukoencephalopathy; **RA**: rheumatoid arthritis; **SC**: subcutaneous; **SLE**: systemic lupus erythematosus; **TNFi**: TNF inhibitors; **TB**: tuberculosis; **USA**: United States of America; **ts**: targeted synthetic; **VTE**: venous thromboembolism.

Anakinra is approved for the treatment of RA in USA and Europe, however clinical trials showed modest therapeutic effects in RA (drug not mentioned in EULAR/ACR recommendations)

Figure 1. Long-standing rheumatoid arthritis.



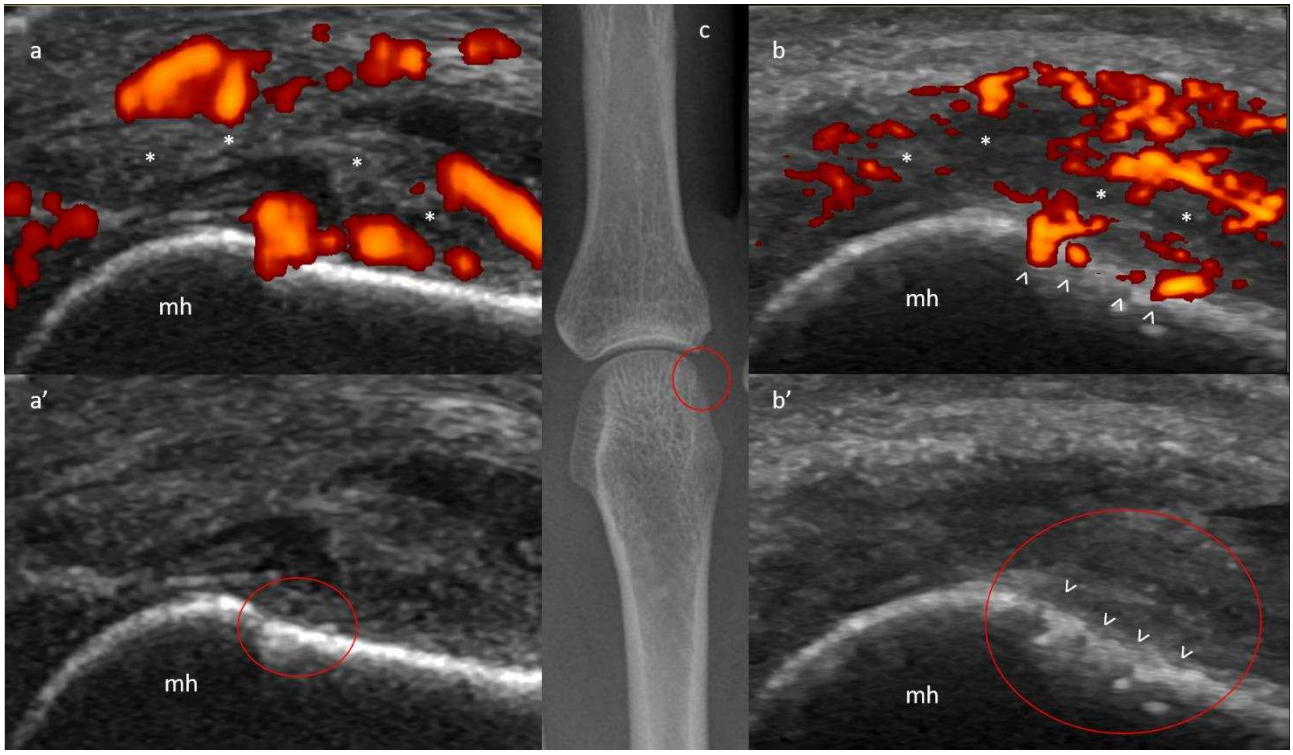
Legend. In Figure a, polyarticular synovitis and joint deformities are illustrated in the hands of a patient with long-standing RA (>20 years disease duration).

In Figure b, x-rays show diffuse structural damage (severe cartilage loss and bone erosions in multiple MCP and PIP joints bilaterally), with complete loss of the normal joint architecture (i.e. ulnar deviation, joint subluxation, multiple bone erosions) in the MCPs and PIPs circles in red.

A longitudinal US scan of the medial aspect of the 2nd right MCP joint (c, c') and 2nd left MCP joint (d, d') demonstrates diffuse synovial hypertrophy (asterisks) and large bone erosions (arrowheads) in the metacarpal head filled with power Doppler signal (intra-synovial red spots) indicating 'active' synovitis ('hot' bone erosions).

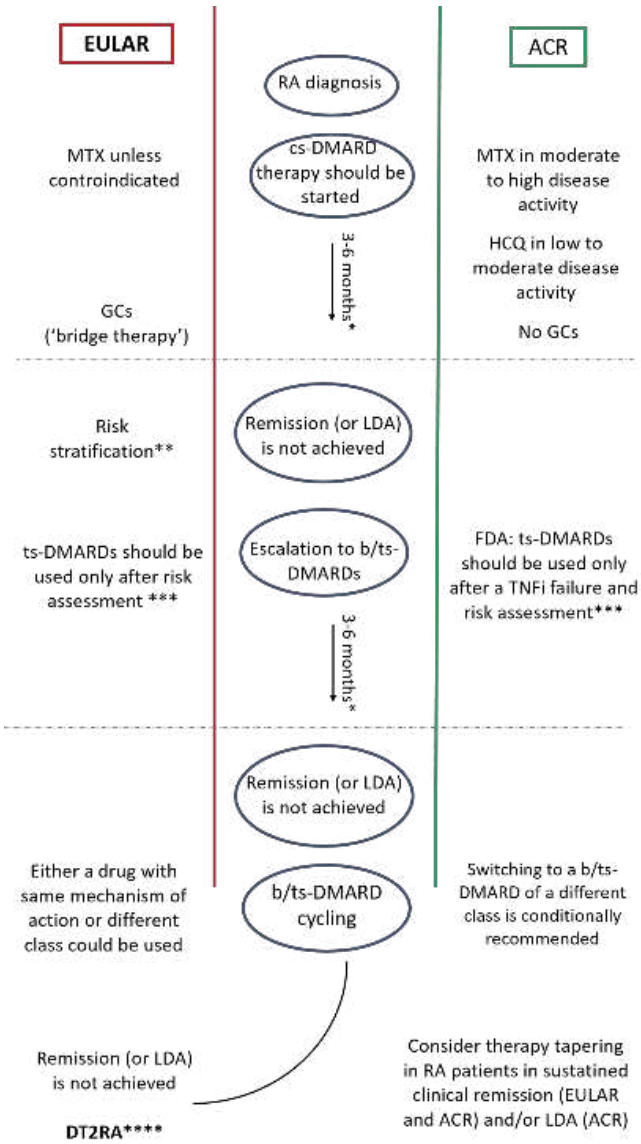
Acronyms. **MCP**: metacarpophalangeal; **PIP**: proximal interphalangeal; **RA:** rheumatoid arthritis; **US:** ultrasound.

Figure 2. Conventional radiography and ultrasound findings in 'early' rheumatoid arthritis.



Legend. Longitudinal ultrasound scans (a, a', b, b') and x-rays (c) of the right 3rd MCP joint in a patient with 'early' rheumatoid arthritis (disease duration 16 week).
The US images, which were obtained using a 15 MHz (a, a') and 18 MHz (b, b') probe, show synovial hypertrophy (asterisks) and diffuse power Doppler signal (red spots) indicating 'active' inflammation.
High frequency probes (i.e. 18 MHz probe) provide a detailed morphological evaluation of the superficial structures. In this patient, loss of sharpness of the bony cortex suggestive for a pre-erosive change can be appreciated in figure b' (arrowheads). The presence of highly vascularized synovial hypertrophy (asterisks and red spots) in close contact with the bone surface (arrowheads) is shown in Figure b.
No abnormality was reported in the x-rays of this patient (c).
Abbreviations. **MCP**: metacarpophalangeal; **mh**: metacarpal head; **US:** ultrasound.

Figure 3. The therapeutic management of rheumatoid arthritis according to ACR and EULAR guidelines/recommendations.



Legend.

*: Treatment target: remission (according to the ACR-EULAR definition) or low disease activity at 6 months. According to EULAR, therapy should be adapted if 50% improvement is not achieved at 3 months.

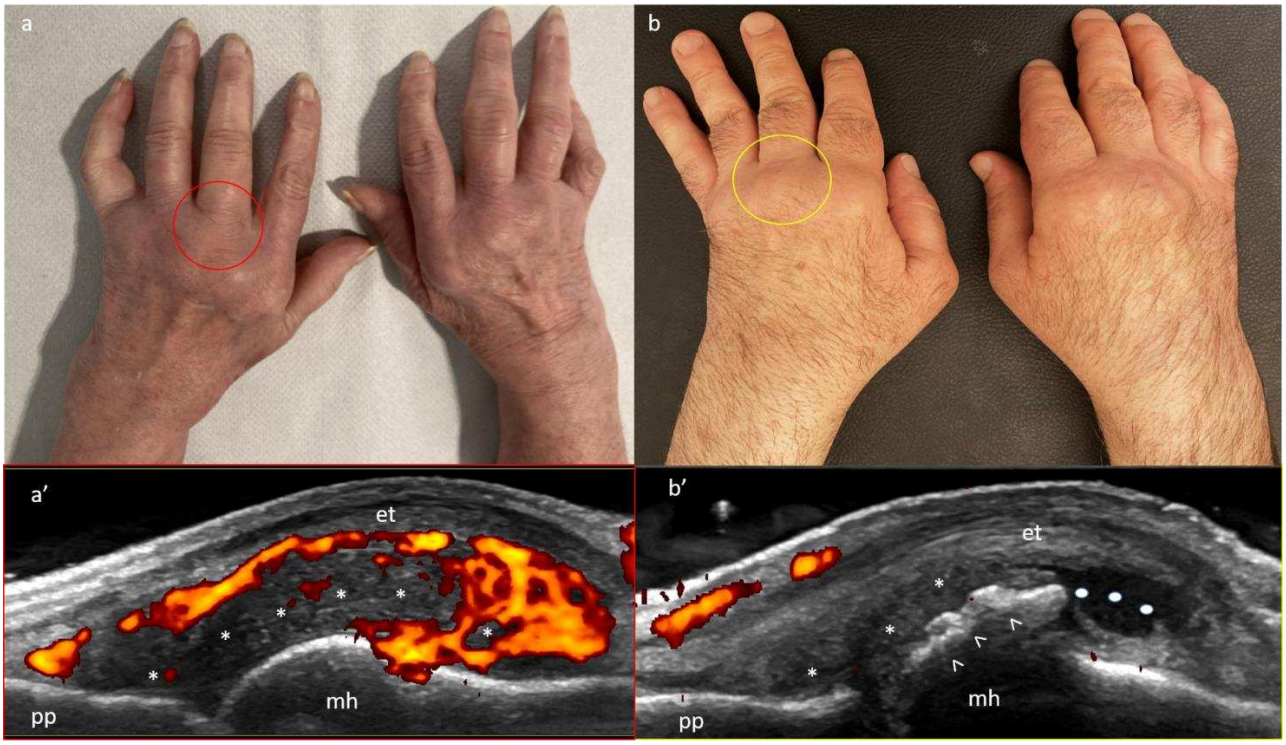
**: In presence of poor prognostic factor (autoantibodies, high disease activity, bone erosion or failure of two csDMARDs), a b/tsDMARD should be added. Otherwise, another csDMARD should be considered.

***: Risk factors for cardiovascular events and malignancies to consider before prescribing a JAKi: age >65 years, previous or current smoking, diabetes, obesity, hypertension, current or previous malignancy (other than NMSC), risk factors for thromboembolic events (history of myocardial infarction or heart failure, history of blood clots or inherited disorders of coagulation, combined contraceptives/hormonal replacement therapy, immobility, undergoing major surgery).

****: In patients with D2TRA, after failure of a ≥2 b/tsDMARD (particularly TNFi), a b/tsDMARD with a different target (i.e. mechanism of action) should be considered.

Abbreviations. **ACR**: American College of Rheumatology; **b**: biologic; **cs**: conventional synthetic; **DMARD**: disease modifying anti-rheumatic drugs; **DT2RA**: difficult to treat rheumatoid arthritis; **EULAR:** European Alliance of Associations for Rheumatology; **FDA**: food and drug administration; **GCs**: glucocorticoids; **HCQ**: hydroxychloroquine; **JAKi**: Janus kinase inhibitors; **LDA**: low disease activity; **MTX**: methotrexate; **NMSC**: non-melanoma skin cancer; **RA**: rheumatoid arthritis; **TNFi**: Tumor Necrosis Factor inhibitors; **ts**: targeted synthetic.

Figure 4. Difficult to treat rheumatoid arthritis patients with different sonographic scenarios.



Legend. This mosaic shows different ultrasound (US) scenarios (a', b') in two patients with D2TRA. Both these patients had failed at ≥1 csDMARD and ≥2 bDMARDs with different mechanisms of action and had a DAS-28 CRP >3.2 and reduced quality of life related to RA disease activity at the time of the clinical visit. None of these two patients was on glucocorticoids.

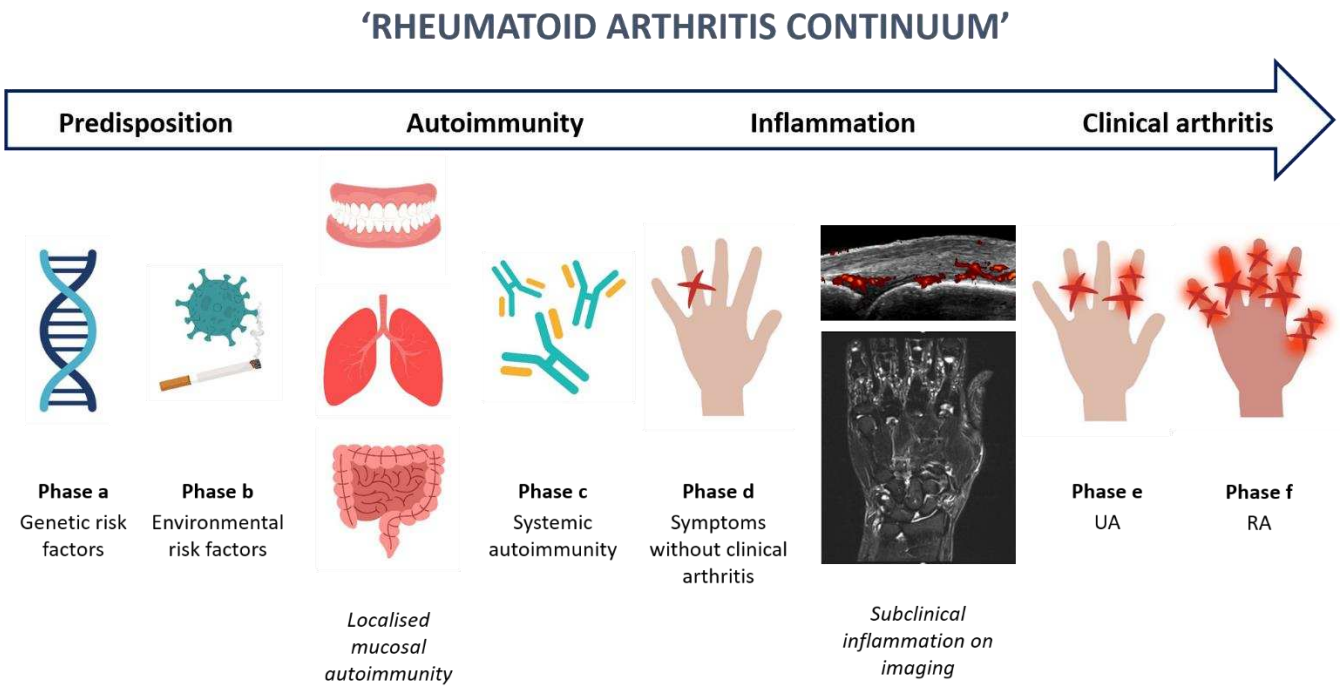
The MCP joints circled in red (Figure a) and yellow (Figure b) were judged as swollen (and painful) on clinical examination. In both patients, intra-articular synovial hypertrophy could be appreciated (asterisks) on US (a',b').

While in Figure a' there is evidence of diffuse power Doppler signal (red spots) indicating 'active' inflammation, the US features in Figure b' suggest advanced structural damage (arrowheads), mainly involving the metacarpal head (joint subluxation and multiple bone erosions). In addition, no power Doppler signal is detectable in Figure b' but an area of joint effusion (white dots), which (together with the bony deformity involving the metacarpal head) could be responsible for the clinical swelling.

The presence of power Doppler signal could indicate a persistent inflammatory process (and therefore be useful to define PIRRA). On the other hand, the chronic joint damage rather than 'active' inflammation could explain the clinical signs and symptoms of the patient represented in Figure b' (NIRRA). However, further studies are needed to define the prognostic value and implications of the different US abnormalities in this D2TRA population.

Abbreviations. **CRP**: C-reactive protein; **cs:** conventional synthetic; **DAS-28**: disease activity score using 28 joints; **DMARD**: disease modifying anti-rheumatic drug; **D2TRA**: difficult to treat rheumatoid arthritis **et**: extensor tendon; **MCP**: metacarpophalangeal; **mh**: metacarpal head; **NIRRA**: non-inflammatory refractory rheumatoid arthritis; **PIP**: proximal interphalangeal; **PIRRA:** persistent inflammatory refractory rheumatoid arthritis**; pp**: proximal phalanx; **US**: ultrasound.

Figure 5. The 'rheumatoid arthritis continuum': an overview of the rheumatoid arthritis pre-clinical phase.



Legend. Six stages along the 'RA continuum' were defined in 2012 by the EULAR Committee on Investigative Rheumatology (Gerlag et al. reference 124): genetic risk factors for RA (phase A), environmental risk factors for RA (phase B), systemic autoimmunity associated with RA (phase C), musculoskeletal symptoms without clinical arthritis (phase D), unclassified arthritis (phase E) and RA (phase F).

These phases do not occur necessarily in all patients (i.e. seronegative RA), or in the same order in all patients. Increasing evidence suggests that systemic autoimmunity is preceded by a phase of mucosal dysbiosis with localized production of RA-related antibody, mainly in the oral, lung or gut mucosa (*localized mucosal autoimmunity*). In addition, several studies have demonstrated that a great proportion of RA patients go through a stage of sub-clinical synovitis on imaging (US or MRI), which is, in at-risk individuals, associated with a great increase in the risk of progression to inflammatory arthritis (*subclinical inflammation on imaging*).

Abbreviations. **EULAR**: European Alliance of Associations for Rheumatology; **MRI**: magnetic resonance imaging; **RA**: rheumatoid arthritis; **UA**: undifferentiated arthritis; **US**: ultrasound.