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Abstract: Rheumatoid arthritis is a chronic inflammatory joint disease, leading to cartilage and bone damage as well as disability. Early diagnosis is key to optimal therapeutic success with well characterized risk factors for bad outcome, such as high disease activity, presence of autoantibodies and early damage. Treatment algorithms involve measuring disease activity with composite indices, applying a treatment-to-target strategy, and conventional as well as novel biologic and non-biologic disease modifying antirheumatic drugs. Once the treatment target of stringent remission or at least low disease activity is maintained, dose reduction or interval increases should be attempted. While today prospects are good for the majority of patients, many do not respond to current therapies and, therefore, new therapies are needed and partly on the horizon. In this Seminar we elude to current insights into genetics and etiology, pathophysiology, epidemiology, assessment, therapeutic agents and strategies as well as unmet needs of rheumatoid arthritis.

Seminar: Rheumatoid Arthritis

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JS wrote the first versions of the introduction, the sections on treatment strategies, therapies, tapering, adverse events, failed therapies and open questions and contributed to all other parts of the manuscript.
DA performed the search and wrote the first versions of the sections on epidemiology, differential diagnosis and assessment and contributed to all other parts of the manuscript.
IMcI wrote the first versions of the sections on genetics and pathophysiology, contributed to all other parts of the manuscript and amended language aspects.
All authors performed several rounds of amendments and also had a face-to-face meeting to finalise the manuscript.

Summary

Rheumatoid arthritis is a chronic inflammatory joint disease, leading to cartilage and bone damage as well as disability. Early diagnosis is key to optimal therapeutic success with well characterized risk factors for bad outcome, such as high disease activity, presence of autoantibodies and early damage. Treatment algorithms involve measuring disease activity with composite indices, applying a treatment-to-target strategy, and conventional as well as novel biologic and non-biologic disease modifying antirheumatic drugs. Once the treatment target of stringent remission or at least low disease activity is maintained, dose reduction or interval increases should be attempted. While today prospects are good for the majority of patients, many do not respond to current therapies and, therefore, new therapies are needed and partly on the horizon. In this Seminar we elude to current insights into genetics and etiology, pathophysiology, epidemiology, assessment, therapeutic agents and strategies as well as unmet needs of rheumatoid arthritis.

Rheumatoid arthritis (RA) is one of the most prevalent chronic inflammatory diseases. It primarily involves the joints, but should be considered a syndrome that includes extra-articular manifestations, such as rheumatoid nodules, pulmonary involvement or vasculitis, as well as systemic comorbidities, particularly affecting the vasculature and metabolism. A therapeutic revolution in the treatment of RA in the last decade that includes advent of novel therapeutics, introducing therapy earlier and application of effective treatment strategies, has transformed outcomes such that long term damage and functional decline have been significantly reduced and systemic features diminished.

In this seminar, we will highlight recent insights into the epidemiology of RA; diagnostic and differential diagnostic approaches; etiology and pathophysiology; the current state of clinical treatment targets, disease assessment and follow up; established, new and evolving treatment approaches; therapeutic strategies and their outcomes and controversies; and future prospects and open questions. Importantly, despite remarkable progress, our pathogenetic insights are still limited, exemplified by the frequent failure of novel molecular therapeutic entities. There is still a considerable unmet need in RA – deep remission is not the norm, nor is it typically sustained.

Search strategy and selection criteria

We searched Medline using the terms "rheumatoid arthritis" in conjunction with "diagnosis", "classification", "epidemiology" and "pathogenesis". For treatment, we used the systematic literature searches that were done for the development of the 2013 update of the EULAR Management Recommendations and the treat-to-target recommendations,[1-4] and updated the respective searches to extend through Oct 2015 and to include terms on novel therapeutic mode of actions and the term "treatment strategy". We considered all reports that were identified by this search or during the review of reference lists of individual papers. Selection of included articles was based on our personal judgement of relevance within the scope of the present Seminar.

Epidemiology and genetics

RA carries a significant burden, for both the individual and society.[5-10] The individual burden is a direct consequence of musculoskeletal deficits, with attendant decline in physical function and quality of life and cumulative co-morbid risk.[11] The socio-economic burden, aside from major direct medical costs, is a consequence of functional disability and ensuing reduced work capacity and societal participation.[12] As a

chronic disease, RA confers exponential burden over time; in turn efforts to establish the diagnosis early (to initiate treatment promptly) and design novel treatment strategies (to meticulously control inflammation and reduce or prevent consequent damage) are paramount.

RA has an incidence of 0.5% to 1%, with an apparent decline from North to South and from urban to rural areas.[13-15] Consistently reported risk factors for developing RA and increased disease severity include smoking and lower socioeconomic status,[16-19] which – in addition to different genetic backgrounds – may partly explain the above observations. A positive family history increases the risk of RA ~3-5 fold; concordance rates in twins are elevated implicating genetic factors in pathogenesis.[14;20] The heritability of RA is debated, currently estimated to be between 40-65% for seropositive disease, but lower (20%) for seronegative RA.[21;22] This has provoked intense genetic study in search of pathogenetic clues, clinical endotypes and prognostic biomarkers. Modern genetic technologies combined with large well-characterized clinical cohorts have considerably advanced our understanding. Genome wide (SNP) association, Immunochip and next-generation sequencing studies, have now characterized >100 loci associated with RA risk, the large majority of which implicate immunity (Figure 1), most of which furthermore are common across distinct geographical populations, and some of which are shared with other chronic inflammatory diseases.[23] The HLA (particularly HLA-DRB1) remains the dominant influence, strongly implicating (self) peptide binding in pathogenesis.[24-26] Disease associated alleles share common amino acid sequences in the peptide-binding groove referred to as the 'shared epitope'.[27] Moreover, some HLA genotypes particularly associate with more aggressive erosive disease and with higher all cause mortality pointing to a critical, quantitatively relevant functional impact of peptide binding.[28;29] The HLA also accounts exclusively for the remarkable gene environmental interaction between smoking and RA risk, although this is not consistently observed and further studies may be needed.[30-35] Other genetic loci likely contribute smaller functional effects that are presumably singly or cumulatively mediated[35] e.g. via altered co-stimulatory pathways (e.g. CD28, CD40), cytokine signaling, lymphocyte

receptor activation threshold (e.g. PTPN22) and innate immune activation (Figure 1). Intriguing familial aggregation studies suggest that known genetic and environmental factors as yet explain only a small part of aggregation and much more remains to be elucidated in this area. The increased risk for RA in patients with the HLA-DRB1 shared epitope is also linked with seropositivity for autoantibodies against citrullinated peptides (ACPA) and immunoglobulin G (rheumatoid factor, RF), autoantibodies that are characteristic for many patients with RA (~80% with established disease, ~50% with early disease). It is by virtue of this immunologic association that the shared epitope is also linked with progression of joint damage. The shared epitope has only poor association with ACPA and or RF negative RA patients.[36]

Epigenetics are considered to contribute to pathogenesis, likely by integrating environmental and genetic effects.[37] At the population level, a recent epigenome wide association study identified ten differentially methylated positions that could promote genetic risk in RA[38] – more studies are underway. Studies at the cellular level have been highly informative; altered histone acetylation and DNA methylation can significantly influence the inflammatory, matrix regulatory and invasive properties of synovial fibroblasts, and some leukocyte populations[37]. As such, pathways that regulate the epigenome e.g. histone deacetylases, bromodomains, represent exciting novel therapeutic targets. MicroRNAs represent a further level of epigenetic regulation by targeting and removing mRNA thereby fine-tuning cellular responses.[39;40] Many microRNAs have now been identified as key regulators of lymphocytes, macrophages and synovial fibroblasts, in the context of animal arthritis models or human RA studies, e.g. miR146a or miR155[40] – whether microRNAs will offer therapeutic utility beyond biomarker or pathway identification is unclear.[37]

Pathophysiology of RA

RA is pathologically heterogeneous – seropositive RA, characterized by the presence of autoantibodies, has been most thoroughly investigated. The detection of autoimmune responses to citrullinated self-

proteins represents a major advance.[41;42] ACPAs recognize citrullinated residues on many self-proteins including vimentin, α-enolase, fibronectin, fibrinogen, type II collagen. The tissue origin of such reactivity is uncertain but may arise at mucosal sites. The lung is an attractive candidate originator tissue, commensurate with a role for smoking in RA, the detection of pulmonary CT abnormalities in early disease and the presence of shared citrullinated peptides in lung and synovial tissue biopsies (Figure 2).[43;44] Circulating ACPAs may be detected in low titre and with limited specificity up to 10 years prior to diagnosis – so called 'pre-RA'.[45] Over time their concentration and epitope diversity increases, as do serum cytokine and chemokine levels, especially prior to onset of articular involvement. ACPAs can be of IgG, IgA or IgM isotype, indicative of T cell help, are of low avidity but with high tissue penetration, and have altered glycosylation status that confers enhanced effector functional properties. ACPA producing B cells are identified in the synovium and, using high sensitivity methods, in the circulation.[46;47] ACPAs may be directly pathogenic via macrophage activation (e.g. by TLR binding or FcR engagement), or by osteoclast activation via immune complex formation and Fc-rceptor engagement or possibly membrane cit-vimentin binding,[48] possibly promoting bone loss, even prior to onset of synovitis. Their concentrations decrease with effective therapeutics but patients usually do not become ACPA seronegative, contrasting with RF.[49] More recently anti-carbamylated peptide autoantibodies have also been identified[50] - more autospecificities may emerge with improved detection methodologies. RF has been shown to be more directly involved in macrophage activation and induction of cytokine activation than ACPA. Possibly ACPA form immune complexes that interact with RF, thus potentiating the effect on the inflammatory and destructive response.[51;52] Less is known of the T cell response that supports the foregoing. Clonal T cell expansions are detected in early RA synovitis.[53] Using HLA-DRB1*0401 tetramers, elevated numbers of Th1 cells have been found circulating in RA particularly in early disease.[54] Whether T cells must exhibit obligate citrullinated peptide specificity or indeed precisely where and when they contribute to emerging autoimmunity remains uncertain. Lymph node biopsies in early RA suggest T cell

activation distant from the synovium.[55] Recent elegant studies e.g. suggest that the RA-protective *HLA-DRB1*13* allele contains a peptide that deletes cit-vinculin specific, autoreactive T cells that could otherwise react to microbial peptides via molecular mimicry and promote ACPA production.[56]

RA has long been associated with infectious triggers e.g *Proteus*, *E.coli*, EBV, generally via molecular mimicry models that have not been fulfilled upon closer scrutiny. RA is associated with periodontal disease although the causality and functional nature of the relationship remains ill defined.[57] One hypothesis proposes that *P. gingivalis*, by virtue of endogenous peptidyl-arginine-deiminase (PADI) 4 expression, can promote aberrant citrullination and provoke local breach of tolerance to citrullinated peptides.[58] In common with many autoimmune diseases, there is now considerable interest in the impact of the microbiome on RA risk and progression (Figure 2).[59;60] Animal models of arthritis, e.g. KRN, collagen-induced arthritis, IL-1Ra-deficient arthritis, all point to a critical role for the gut microbiome in the development of disease.[59] Various explanatory mechanisms are proposed including facilitation of type 17 immune responses, or exposure to microbial-derived innate activators, arising from microbial population changes and/or altered mucosal permeability.[59] Initial human studies have identified gastrointestinal dysbiosis, particularly in early RA.[61] Remarkably, in a recent study, common microbial population alterations were detected in oral, salivary and gastrointestinal sites, that were associated with CRP, ACPA status and were further altered by DMARD therapy.[62] The mechanisms underpinning such observations remain to be elucidated and their importance requires exploration.

The major clinical characteristic of RA is joint swelling reflecting inflammation in the synovial membrane as a consequence of the events discussed above. It comprises leukocyte infiltration of a normally relatively sparsely populated synovial compartment (Figure 3). The cellular composition of RA synovitis includes features of innate (e.g. monocytes, dendritic cells, mast cells, innate lymphoid cells) and

adaptive (e.g. T helper cell [Th] 1, Th17, B cells, plasmablasts and plasma cells) immunity, together with a robust tissue response whereby synovial fibroblasts accumulate and assume an aggressive inflammatory, matrix regulatory and invasive phenotype, that together with enhanced chondrocyte catabolism and osteoclastogenesis, promote articular destruction.[63;64] Original studies did not reveal particularly remarkable cellular differences between early and established disease synovium. However with the advent of US-guided micro techniques, detailed molecular, particularly transcriptomic analyses, suggest that myeloid, lymphocytic and fibroid dominant synovial subtypes may exist that could be of therapeutic significance; confirmatory studies are.[65] This inflammatory milieu is regulated in turn by a complex cytokine and chemokine network – clinical interventions clearly demonstrate that of these, tumour necrosis factor (TNF), interleukin (IL)-6 and likely granulocyte-monocyte colony stimulating factor (GM-CSF) are hierarchically critical, while others, such as IL-1 and various lymphokines may be less important.[66] Cytokines and chemokines lead to the induction or aggravation of the inflammatory response by activating endothelial cells and attracting immune cells to accumulate within the synovial compartment. Activated fibroblasts in conjunction with the accumulated activated T- and B-cells as well as monocyte/macrophages ultimately trigger osteoclast generation via engagement of receptor activator of nuclear factor kappa B ligand (RANKL), expressed on T-cells, B-cells and fibroblasts, with its receptor RANK on macrophages, dendritic cells and pre-osteoclasts. Bony erosions ensue, arising from the “bare area” at the junction between cartilage, periosteal synovial membrane insertion and bone. Cartilage undergoes damage by the evolution of catabolic effects in chrondrocytes after their stimulation by cytokines. Cytokines bind cognate receptors to trigger various intracellular signal transduction events, which are the actual intermediaries between the different extracellular events and the activation of an array of genes that lead to or aggravate inflammation (Figure 3). Many of these cells and molecules have been tested as therapeutic targets, with some success, allowing for dramatic advances in treatment of RA and subsequently other chronic inflammatory diseases. Thus, whereas the pathogenetic events

initiating and thereafter mediating chronicity of the synovial lesion are not yet fully understood, there have been remarkable recent insights arising from genetic, epidemiologic, translational biological and therapeutic studies.

Taken together, RA likely arises from multiple 'hits' whereby an initial combination of environmental, lifestyle and stochastic insults occurring in a genetically predisposed, epigenetically modified individual, leads to breach of immunological tolerance. This manifests as the emergence of low titre autoantibodies (primarily ACPAs and subsequently RF), circulating cytokines and metabolic disturbance, often occurring considerably prior to the development of clinically evident articular disease. A further trigger, perhaps infectious, facilitated particularly by HLA class II associated pathways, drives the expansion of T cell mediated autoimmunity, and thereafter, articular localization via currently obscure mechanisms (e.g. neurologic, vascular, biomechanical). This critical transition to chronic (non-resolving) synovitis is characterised by leukocyte and stromal cell dysregulation and wider co-morbidity affecting vascular, cardiac, bone and neurologic tissues. Importantly, this transition must occur quite early, since treatment of very early, clinically incipient but overt RA usually does not reverse arthritis and since synovial infiltration by inflammatory cells may occur before clinical signs and symptoms.[67] Therefore, diagnosis of pre-clinical RA becomes a target and focus of research activities[68;69] to be able to employ preventive therapy and the term "window of opportunity" increasingly refers to preventive aspects rather than interferences with early but clinically already manifest disease.

Diagnostic approach and differential diagnosis

No diagnostic criteria exist for RA. The typical patient presents tender and swollen joints of recent onset, morning stiffness, and abnormal laboratory tests, such as elevated C-reactive protein (CRP) levels or erythrocyte sedimentation rate. Unfortunately, this presentation is not at all specific for RA and there is

no pathognomonic finding for RA. Other causes of arthritis need to be considered, such as reactive arthritis, osteoarthritis, infectious arthritis (viral; bacterial, particularly Lyme disease depending on geographic region); some rarer autoimmune conditions, such as connective tissue diseases, may be considered if additional suggestive signs or symptoms are present (e.g. rash, mouth ulcers, alopecia, Raynaud's phenomenon, ANA, elevated muscle enzymes). In fact, in many patients no specific diagnosis can be made at first presentation, and the diagnosis of exclusion is "undifferentiated arthritis". This may be important, since (disease modifying) treatment is indicated and necessary for any type of chronic inflammatory arthritis, supported by periodic reassessment.

New classification criteria of RA have been developed and published in 2010.[70] Their purpose was to eliminate shortcomings of the former criteria, established by the American Rheumatism Association in 1987. Those were not any more helpful, since they included features of chronicity and poor prognosis (e.g. erosions) as well as low prevalence characteristics (e.g. nodules) - this was unfit to recognise early disease.[71] Briefly, the new criteria require a single clinically swollen joint as entry criterion in the absence of other diseases explaining the clinical symptoms. Thereafter, the classification criteria allow for sensitive assessment of extent of joint involvement (tender joints can be considered as "active joints"; imaging by ultrasound [US] or magnetic resonance [MRI] may also be used). Additional features are serological markers of the disease (RF and APCA), and (with smaller contribution) longer symptom duration and laboratory markers of systemic inflammation. Since publication, the criteria have been validated in numerous settings and offer 21% higher sensitivity than the 1987 criteria, at the cost of 16% lower specificity.[72] Note that classification is not synonymous with diagnosis. While diagnosis has the ultimate goal of being correct at the individual patient level, classification aims to maximise homogenous populations for study purposes, but can be used to support diagnosis.

Disease assessment and definition of treatment targets

Assessment of disease activity is critical to follow-up of RA patients because it drives adverse clinical outcomes, including joint damage, and poor physical function and quality of life.[73;74] Composite measures that include joint counts have been recommended for daily practice. The American College of Rheumatology (ACR) improvement criteria[75] differentiate placebo from active therapy and are widely used in clinical trials, but cannot be employed easily in practice. In contrast, the disease activity score (DAS) employing 28 joint counts,[76] the simplified and the clinical disease activity index (SDAI, CDAI)[77;78] provide continuous numerical scales reflecting disease activity (higher is worse).[79;80] While the DAS28 requires a computer, SDAI and CDAI are easy to calculate in routine practice (Table 1). Importantly, these measures can also classify disease activity states (high, moderate, low and remission). Other disease activity measures that do not include joint counts,[81] have also been developed but are not recommended because there is insufficient evidence that they can be used reliably across all patient populations and reflect all disease outcomes. There is an almost linear relationship between disease activity, particularly discrete disease activity states, and physical function or quality of life.[82;83] The relationship between disease activity and progression of joint damage is also essentially linear, even upon treatment with csDMARDs.[78;84-86]

Remission or low-disease activity have been established as treatment targets.[87;88] The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have recently developed new remission criteria[89], which are based on a Boolean approach and an index-based approach using the criteria of the SDAI and CDAI (Table 1).[90] Other definitions of remission (e.g. "DAS28 remission") should not now be used, since they are associated with progression of joint damage,[91] presence of

comorbidities,[92] and significant residual activity in many patients.[93;94] Moreover, they frequently result in high false positive response rates, particularly when drugs affecting the acute phase response are employed.[95] For example, a normal ESR of 15mm/h contributes almost 2 points to the DAS28 score, which has a cut-off for "remission" at 2.6, whilst 20 swollen joints contribute only 1.2 points, a score likewise provided by just 5 tender joints.[96;97] With the development of the new remission criteria, the definition of remission is now truly related to the virtual absence of residual inflammatory disease activity, as is required for such state,[89] leaving other definitions that allow for significant residual disease activity as better consistent with a state of low disease activity.[98]

Finally, it is important to evaluate the structural progression of disease. Treatment of RA should, in addition to symptom relief, prevent or halt structural changes and thereby minimize or reverse physical disability. In routine practice, structure progression is usually done semi-quantitatively, usually at intervals of approximately 1 year. Formal scoring of radiographs for progression of erosions and joint space narrowing, as performed in trials, is more accurate and sensitive.[99] Other imaging modalities are being increasingly used not only for diagnostic purposes, but also for follow up: MRI scans detect bone marrow edema as a potential area of (future) erosions,[100] and may differentiate overt synovitis (and tenosynovitis) from other – potentially non-inflammatory – causes of pain and swelling. Ultrasound can quantify the degree and extent of inflammatory synovitis by using gray scale and power Doppler measurements, respectively.[101] However, the relevance of detecting subclinical inflammation in patients in clinical remission, in order to decide on treatment reduction or escalation, is unclear[102-104] Notably, a large proportion of healthy persons may have detectable ultrasound and MRI signals of synovitis and vascularity.[105]

Physical function is typically assessed using the Health Assessment Questionnaire Disability Index (HAQ).[106] Newer computer assisted methods have not yet entered daily routine management.[107]

Functional assessments are typically performed at every clinical visit, although they may be done remotely from the clinic, since they are solely questionnaire based.

Treatment strategies

Since inflammation is at the apex of clinical events (driving damage, functional impairment, comorbidity), its reversal is the major therapeutic target – if inflammation subsides rapidly, damage or its progression are prevented and physical function maximally improved without further sequelae. By corollary, it is critical to determine disease activity regularly in pursuit of a desired clinical state (low disease activity or remission). Treatment of RA thus requires a strategic approach whereby regular disease activity assessment drives therapeutic adaptations or changes of drugs in accordance with such activity ("Treat to Target"; T2T).[89] Composite disease activity measures that include joint counts are preferred instruments in T2T approaches; measures of structure or function are sub-optimal in T2T approaches because they reflect the consequence of inflammation. In practice, if a state of low disease activity has been reached, or approximately 80% improvement in SDAI or CDAI is achieved by three months, then the likelihood of reaching the treatment target at 6 months from therapy initiation is very high[108]. If improvement is small at 3 months (Figure 4A), treatment should be adapted. Likewise, if the state of low disease activity (or remission) is not attained at 6 months, treatment should be re-evaluated.

The therapies

Disease modifying antirheumatic drugs (DMARDs) target inflammation and by definition must reduce structural damage progression. Non-steroidal anti-inflammatory drugs (NSAIDs), while reducing pain and stiffness and improving physical function, do not interfere with joint damage and, therefore, will not

affect the long-term sequelae of RA. Glucocorticoids, on the other hand, have rapid symptomatic and disease modifying effects, but carry significant long-term side effects.[109]

There are two major classes of DMARDs, namely synthetic (sDMARDs) and biological (bDMARDs); sDMARDs are defined as conventional synthetic (cs) or targeted synthetic (ts) DMARDs.[110] The former comprise methotrexate (MTX), sulphasalazine, leflunomide, gold salts and (hydroxy)chloroquine – their use has evolved empirically and their modes of action are still largely unknown. In contrast, tsDMARDs have been developed to modulate a particular target implicated in the generation of inflammation. Key exemplars include Janus kinase (Jak) inhibitors, such as tofacitinib or baricitinib.

cs DMARDs and glucocorticoids. According to EULAR recommendations for the management of RA,[87] treatment should be initiated with a csDMARD, ideally MTX, plus low dose glucocorticoids (Figure 4B). There is compelling evidence that this is the optimal approach. Firstly, clinical trials comparing MTX+glucocorticoids with combinations of MTX plus a biological agent have shown no significant difference in outcomes (Table 2);[111-113] secondly, comparing MTX+glucocorticoids with combinations of csDMARDs plus glucocorticoids revealed similar efficacy with less toxicity (Table 2).[114-117] Glucocorticoids are given at low to intermediate oral doses or parenterally as single intravenous or intramuscular applications. Low doses of glucocorticoids combined with MTX confer additive structural protection when compared with MTX alone.[118-120] Oral glucocorticoids should be tapered within 3 months, when csDMARD should have induced significant improvement.[121] With respect to the choice of a csDMARD, MTX is considered the anchor drug that also optimizes efficacy of bDMARDs.[122] However, it has not yet been conclusively shown that MTX is superior to other csDMARDs clinically or structurally; rather, comparisons with sulfasalazine or leflunomide revealed similar outcomes, but the doses of MTX in these studies were low compared with those used today.[114;114;115;115]

Table 2 summarizes the most recent data on csDMARD mono- and combination therapy. They suggest that combination of csDMARD has little place in the treatment armamentarium, since in comparison with MTX monotherapy there is no added efficacy at cost of more toxicity. Moreover, in comparison with biological agents used after MTX, csDMARD combination confers profound responses (e.g. ACR70) at only low frequencies.[123]

When the first treatment cycle fails, EULAR recommends stratifying for predictors of severe disease which comprise the presence of high disease activity despite the prior therapy; autoantibodies (ACPA or RF, especially at high titres); and early joint damage on radiography (Figure 4C). Patients exhibiting these risk factors should receive a bDMARD, whereas those without should receive another csDMARD again in combination with glucocorticoids.

bDMARDs. Biologic therapeutics comprise four different modes of action:[1] TNF-inhibition, IL-6 receptor inhibition, T-cell costimulation blockade and B-cell depletion (Table 3, yellow ovals in Figure 3 and Figure 5). A small proportion of patients may respond to inhibition of IL-1 pathways.[124] Among the TNF-inhibitors (TNFis), 5 compounds are currently approved, one for i.v. use (infliximab) and 4 for s.c. application (adalimumab, certolizumab pegol, etanercept, golimumab). Biosimilar infliximab is already available in Europe and a biosimilar etanercept has just been approved by the European Medicines Agency (Table 3). IL-6 inhibition is currently delivered by tocilizumab, a humanized monoclonal antibody directed at the IL-6 receptor; sarilumab, also an IL-6R inhibitor, has completed phase 3 trials. IL-6 itself is targeted by several monoclonal antibodies, including sirukumab and clazakizumab, both currently undergoing phase 3 trial. Abatacept is presently the only T-cell costimulation inhibitor; intriguingly its efficacy may reflect not only T cell targeting but also reverse licencing, and therefore inhibition of

myeloid cell activation,[125] and migration inhibition. [126]. Rituximab is the only monoclonal anti-CD20 antibody approved for the treatment of RA, but biosimilars are expected in the near future.

These mechanistically discrete therapies appear to convey similar efficacy.[1] Focusing on ACR70 response rates as a surrogate for achieving low disease activity, patients who are MTX naïve have the highest overall response rates (~40%) to bDMARDs in combination with MTX (Figure 5). However, embedded within these responders are those who would experience efficacy with MTX alone (20-25%). This formed one of the rationales for EULAR and more recently also ACR to recommend starting csDMARD treatment with MTX.[87;88] Importantly, despite the differences in the targets, when used in patients with active disease despite prior MTX treatment, all four major principles of targeted biological agents (added to MTX) arrive at ACR70 rates of ~20% , while those who have previously failed TNFis usually exhibit only about 10-15% ACR70 rates when exposed to another biological (Figure 5). These responses are seen irrespective of the bDMARD and thus even on another TNFi if patients failed a TNFi (Figure 4C).[1;127;128] This indicates that all these agents may ultimately mediate their efficacy by interfering with a common final pathway, namely proinflammatory cytokine production,[129] by either acting further upstream or directly at the cytokine level.

All bDMARDs exhibit enhanced efficacy when combined with MTX and presumably other csDMARDs.[130] Indeed, none of the bDMARDs, when employed as a monotherapy, has shown consistent clinical or functional superiority compared with MTX.[131-135] Progression of structural damage is inhibited more strongly than MTX monotherapy, albeit to a lesser extent than with the combination therapy. Moreover, MTX (plus glucocorticoids) conveys similar clinical, functional and structural efficacy as MTX plus biological agent (Table 2).[112;113;136] If a monotherapy of a bDMARD must be given because of intolerance of all csDMARDs, then tocilizumab would be the biologic of choice, since it has better efficacy than TNF-inhibitor monotherapy.[137]

tsDMARDs. The first ever approved tsDMARD is tofactinib, a pan-Jak inhibitor;[138] Jak inhibition interferes with signal transduction and thus cell activation elicited by IL-6, GM-CSF, interferons (type I and type II) and common gamma chain cytokines (like IL-2 or IL-15), but also erythropoietin.[139] Tofacitinib has hitherto been approved in the USA, Canada, Japan, and several other countries, but not yet in the European Union. The efficacy of tofacitinib plus MTX at the approved dose of 5mg bid appears to be similar to that of biological agents (Figure 5). In phase 3 clinical trials the Jak 1,2-inhibitor baricitinib appears to convey a similar range of efficacy as the bDMARDs and tofacitinib (Figure 5). Interestingly, however, in a very recent trial baricitinib elicited a superior clinical and functional, though not structural outcome compared with adalimumab;[140] moreover, the ~15% ACR70 response rate in patients who previously failed a TNFi was seen similarly in patients who failed multiple biologics.[141]

Tapering therapy.

Once the desired treatment target (LDA or remission) has been reached and sustained for some time (usually about 6 months), one should consider rationalisation of therapeutics. The first agent that should already have been withdrawn within about 3 months is glucocorticoid. Concerning biologic therapy, the risk of a flare upon halving dose or doubling the interval between doses is low, while upon complete withdrawal most patients will eventually flare, irrespective of the type of biologic.[142-146] Importantly, even if patients flare they usually respond very well again to the same agent. However it may not be considered ethical to let patients undergo the ordeal of a flare and also risk that some of them may not recapture the original response hence dose reduction should be the norm.[146]

Adverse event profiles.

The biologic agents and the tsDMARDs induce higher rates of adverse events than csDMARDs. In particular, the rates of serious infections are increased, although they decrease over time.[3;147] A special

risk relates to reactivation of tuberculosis,[148] although this has not been reported on rituximab. Rituximab would also be the drug of choice in patients with concomitant multiple sclerosis, since it has shown efficacy in this disease,[149] while TNF-inhibitors can elicit flares.[150] Patients with hepatitis B or C whose disease is well controlled with antiviral therapy, may be cautiously treated with biologics, whereby the risk is lower for hepatitis C. It is recommended to avoid biological agents (except rituximab) within 5 years after a malignancy has been cured, although registry data do not suggest increased risks.[151] On the other hand, with a history of lymphoma again rituximab or possibly also tocilizumab, which is used to treat Castleman's disease, would be drugs of choice. During pregnancy, the drug of choice is sulphasalazine, while MTX and leflunomide are contraindicated; also biologics are not recommended, although their detailed teratogenic risk is unknown.[152-154]

Targeted therapies that failed.

While results obtained from experimental models and/or ex-vivo data are helpful to drive hypotheses, the ultimate information on efficacy and safety of a treatment targeting specific molecules or cells has to come from clinical trials as a proof of concept. Over the years, many targeted therapies have failed to elicit any or at least clinically important responses (red ovals in Figure 3). Among these disappointing results are the effects of depletion of CD4-T-cells[155], the use of IL-10 as an anti-inflammatory principle,[156] or the inhibition of IL-17, IL-12 and IL-23 pathways.[157-159] Especially the results obtained by IL-17 and IL-23 inhibition are perplexing, since RA was believed to be a Th17 mediated disease.[160] Direct inhibition of IL-23, the pivotal cytokine leading to Th17 activation, and of IL-17A itself, were expected to constitute new therapeutic advances. Negative results were also obtained for p38 MAPK inhibition, which constitutes an important intracellular messenger protein for TNF- and IL-1 effects,[161;162] presumably by virtue of the redundancy of signal transduction events involved in signaling of this pivotal pathway. Inhibition of spleen tyrosine kinase (syk), a molecule involved in B-cell and Fc-gamma receptor signaling,

failed to reveal reproducible efficacy.[163] Thus, the negative as well as the positive results of clinical trials allow recognition of the level of importance of specific molecules and cells in the context of the inflammatory response in RA.

Open questions and unmet needs

Despite all the advances made over the last decade or two, many open issues remain to be resolved. Firstly,[164;165] we still do not understand the riddle of the similar efficacies of therapies targeting different molecules and we even do not know if profound responses are elicited by these agents in the same, totally different or somewhat overlapping patient populations. We do not yet have clinically useful endotypes nor biomarkers that can offer utility beyond acute phase reactants and the presence of autoantibodies. Secondly, it can still not be predicted who will respond best to which treatment; molecular analyses have failed to provide clues to answer this question,[166-169] although we firmly believe the predictors exist which would allow introducing precision medicine approaches also in rheumatology. Thirdly, given that remission or at least low disease activity are today's therapeutic goals for RA patients, a significant proportion of them does still not reach this target, implying that new therapies are still needed. Further, many patients lose responsiveness over time, and the reasons for this loss are not yet fully elucidated and might be due to immunogenicity, non-adherence or other factors. Fourthly, therapeutics are not delivered via a pathogenetically coherent protocol, that takes account of early dominant autoimmunity and later damage-related effector pathways; in this context, preventive treatment may be highly effective to interfere with the manifestation of RA, but we have no clues yet how to detect pre-RA or patients at risk. Finally, future therapeutics must deliver more predictable and better outcomes; Table 4 describes some potential approaches that are partly already addressed in early trials. The ultimate desire would be to develop causative therapies, but this will not be possible without deciphering the cause(s) of RA.

Conclusion

Over the last decade, several pieces of evidence have accumulated. These insights constitute the basis of recommendations for the management of RA, which are captured in a general way in Figure 4.[87] (i) Early diagnosis and initiation of DMARD therapy are pivotal to prevent damage from occurring or becoming significant.[170] (ii) The better the disease activity state reached at 6 months or one year, the lower is the progression of joint damage and the better the functional outcome; reaching stringent remission within 3- 6 months halts damage progression independent of the type of therapy, MTX or biological.[84;91] (iii) Setting a treatment target of low disease activity or remission, following patients regularly using composite disease activity measures which comprise joint counts to determine the disease activity status and adapting DMARD therapy rapidly if the targeted state has not been achieved within a period of few months leads to better outcomes than routine care.[136;171;172] (iv) Treating patients at high risk of developing joint damage and thus irreversible disability with biologics reduces the risk of bad outcome, while such treatment is not necessarily important in patients with low risk.[173] (v) Adding low dose glucocorticoids to csDMARDs maximises clinical, functional and structural benefit.[118;120] (vi) Using MTX as a first DMARD and adding a biological agent in those who do not attain low disease activity within 6 months and have high progression risk optimises the benefit.[174] (vii) If a state of low disease activity or an 80% reduction of disease activity is achieved within 3 months from start of treatment, attainment of the target of low-disease activity or remission at 6 months is highly likely. Application of this approach will maximise treatment success in RA. Hopefully, by the end of the present decade most of our patients will experience cessation of disease progression and disability with retention of high levels of quality of life.

Figure legends

Figure 1. A selection of critical loci associated with risk and progression of RA are depicted on a notional map of the key immune cells implicated in the pathogenesis of RA.

Figure 2. Etiology of and pathways to RA. In a genetically predisposed host with susceptibility genes, some of which are depicted here and in more detail in Fig 1, environmental insults, epigenetic modifications and posttranslational modifications can lead to loss of tolerance with subsequent asymptomatic synovitis, ultimately leading to clinically overt arthritis. Modified after[63;64]

Figure 3. Pathogenetic pathways in RA ca. 2016 showing pathobiologic, cell biologic and molecular biologic aspects. Adapted from[63] and Mavers M, et al. *Curr Rheum Rep*. 2009;11:378-385 and Rommel C, et al. *Nat Rev Immunol.* 2007;7:191-201. Yellow ovals: molecules or cells which are successfully targeted by respective therapies; red ovals: molecules or cells targeting which was not effective.

Figure 4. Therapeutic approach to rheumatoid arthritis. A. General strategy; B. Early treatment phase; C. Treatment approach when MTX (plus glucocorticoid) failed to allow reaching the treatment target; D. Treatment approach when a first biological failed. After[87;89]

Figure 5. Response rates to different DMARD therapies. As a surrogate of profound treatment responses the ACR70 improvement rates are shown. A. Abatacept (inhibition of T-cell costimulation); B. Golimumab (TNF-inhibitor); C. Tocilizumab (anti-IL-6 receptor antibody); D. Rituximab (anti-CD20 mediated B-cell depletion); E. Tofacitinib (pan-Jak inhibitor); F. Baricitinib (Jak1/2 inhibitor). These agents were selected because they are the only ones with published clinical trials covering the whole range of RA patient population, from early MTX-naïve to TNF-inhibitor insufficient responders. Baricitinib is not yet approved by regulatory authorities but has completed the pertinent phase 3 trials.

Table 1. Composite measures of disease activity comprising joint counts and ACR-EULAR remission criteria.

Index/ Criterion	Formula	Cutpoints REM/LDA/MDA
DAS28	0.56 x √(TJC28) + 0.28 x √(SJC28) + 0.70 x lognat(ESR) + 0.014 x GH[76]	2.6/3.2/5.1
SDAI	SJC28+TJC28+PGA+EGA+CRP[77;175]	3.3/11/26
CDAI	SJC28+TJC28+PGA+EGA[77;78;175]	2.8/10/22
ACR-EULAR remission[90]	Boolean: SJC, TJC, PGA, CRP Index-based: SDAI Index-based: CDAI	All ≤1 ≤3.3 ≤2.8

REM, remission; LDA, low disease activity; MDA, moderate disease activity; high disease activity above the highest of these cutpoints; DAS28, disease activity score using 28 joint counts; SDAI, simplified disease activity index; CDAI, clinical disease activity index;TJC, tender joint count; SJC, swollen joint count; lognat, natural logarithm; ESR, erythrocyte sedimentation rate; PGA, patient global assessment; EGA, evaluator (physician) global assessment; CRP, C-reactive protein.

Table 2. Achievement of low disease activity using MTX monotherapy in combination with glucocorticoids compared with combinations of either csDMARDs plus glucocorticoids, or biological agents plus MTX

	MTX + glucocorticoid	MTX+other csDMARD(s)+GC, or MTX+bDMARD
CareRA[117] – 4 months	87%[1]	85%[2]
tREACH[176] – 6 months	68%[3]	71%[4]
IDEA[112] – 6 months	67%[5]	65%[6]
BeSt[111] – 6 months	67%[7]	64%[8]

[1]15mg MTX + 30mg prednisone (tapered); [2]15mg MTX + 2g SSZ + 60mg prednisone (tapered); [3]25mg MTX + 15mg prednisone; [4]25mg MTX + 2g SSZ + 400mg hydoxychloroquine + 15mg prednisone; [5]20mg MTX + single iv of 250mg methylprednisolone; [6]20mg MTX + infliximab; [7]7.5mg MTX (increased to 30mg if needed) + 2g SSZ + 60mg prednisone; [8]25mg MTX + infliximab

Table 3. Currently applied DMARDs and their doses

DMARD		Name	Usual Dose	Loading dose	Comments*
csDMARDs		Methotrexate	25mg once weekly	No	Starting dose 10mg – escalation to 25mg within 4-8 weeks, folate use important (suggest 10mg/week)
		Sulphasalazine	3g/day	No	Starting dose 1g, escalation to 3g/day within 4-8 weeks
		Leflunomide	20mg/day	Optional	Loading dose associated with more GI side effects
		Hydroxychloroquine	400mg/day	No	For mild arthritis or as combination therapy
bDMARDs	TNF-inhibitors	Adalimumab	40mg every 2 weeks sc	No	Biosimilar application
		Certolizumab pegol	200mg every 2 weeks sc	Yes	
		Etanercept	50mg/week sc	No	Biosimilar approved
		Golimumab	50mg/month sc	No	
		Infliximab	3-10mg/kg iv every 4-8 weeks	Yes	Biosimilar approved
	Anti-B-cell	Rituximab	1000mg iv every 6 mo.	No	Biosimilar application
	Anti-T-cell costimulation	Abatacept	125mg/week sc	No	iv available
	Anti-IL-6R	Tocilizumab	162.6mg/week sc		iv available; Sarilumab (anti-IL-6R) and anti-IL-6 cytokine antibodies (sirukumab, clazakizumab) in development
tsDMARDs	Janus-kinase inhibitors	Tofacitinib	5mg twice daily	No	Jak 1,2,3 inhibitor; once daily medication in development; baricitinib, a Jak 1,2 inhibitor, completed phase 3 trials

*Dose reductions needed with renal or hepatic impairment; for adverse events see package inserts

Table 4. Potential future therapeutics for RA

Biologic agents
Cytokine inhibitors (human, or humanized) targeting e.g. IL-6, IL-17, IL-21, Interferons, GM-CSF, GM-CSFR
Cytokine /Ig fusion proteins e.g. IL-4:IgG
Cell targeting agents e.g. B cell depletion, co-stimulatory blockade
Intracellular signal inhibitors
Janus Kinase inhibitors e.g. baricitinib, filgotinib
Bruton's tyrosine kinase (BTK) inhibitors
PI3 Kinase inhibitors
Cellular therapies
Tolerogenic dendritic cell transfer
Stem cell transfer
T regulatory cell activation
Miscellaneous approaches
Toll-like receptor inhibitors
PADI4 inhibitors
Epigenetic modifiers e.g. histone deacetylase inhibitors
GnRH antagonists
Vagus nerve stimulation

Conflicts of interest statement:

JSS: Research support (for the institution) from from Abbvie, Lilly, MSD, Pfizer, Roche. Honoraria for consultancies or speaking engagements from Abbvie, Amgen, Astra-Zeneca, BMS, Celgene, Glaxo, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, Samsung, UCB.

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Fast Facts

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Figure 1:

A selection of critical loci associated with risk and progression of RA are depicted on a notional map of the key immune cells implicated in the pathogenesis of RA.

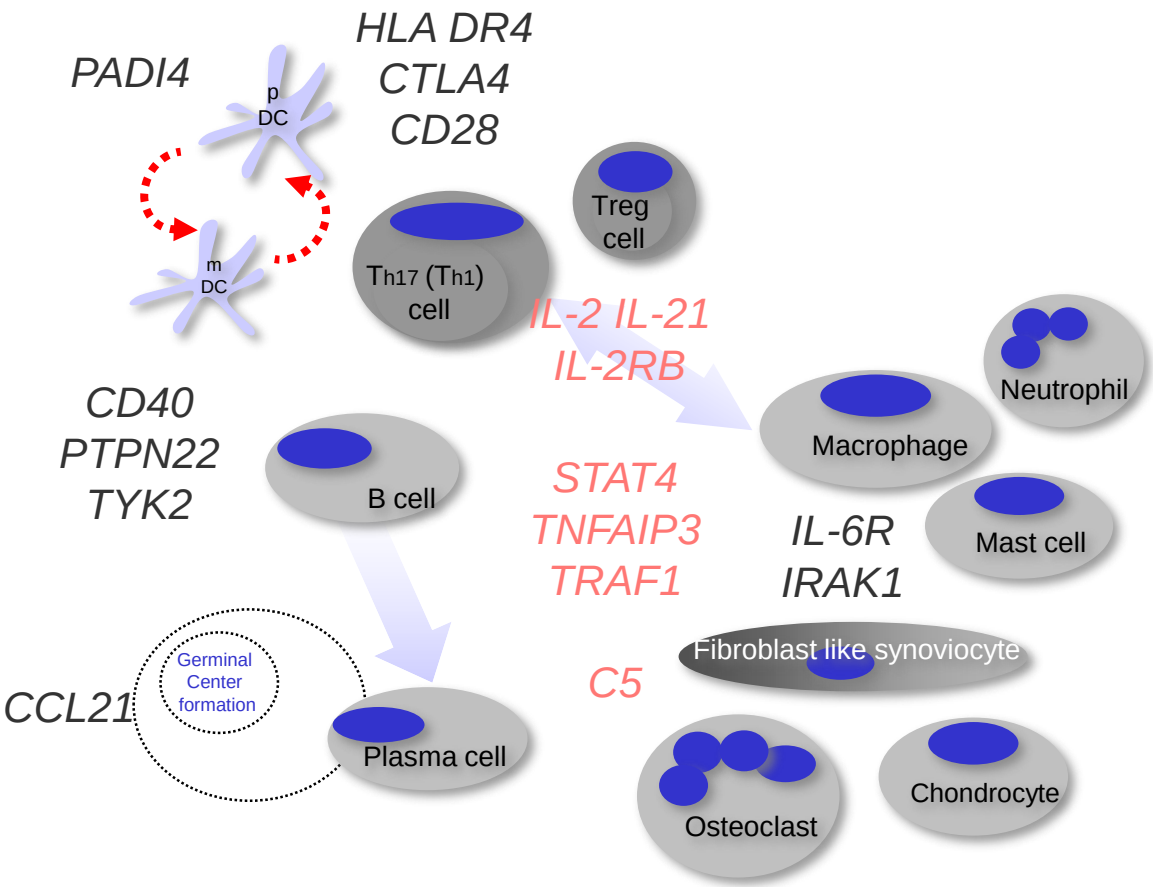
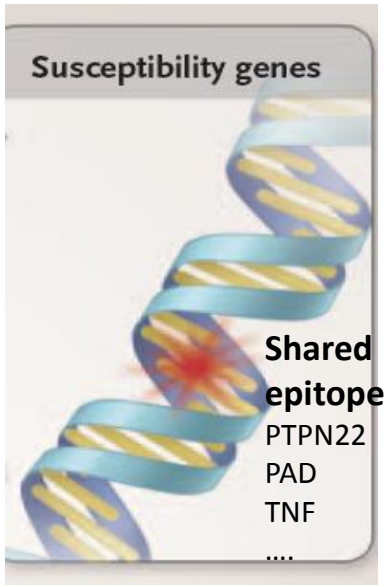


Figure 2

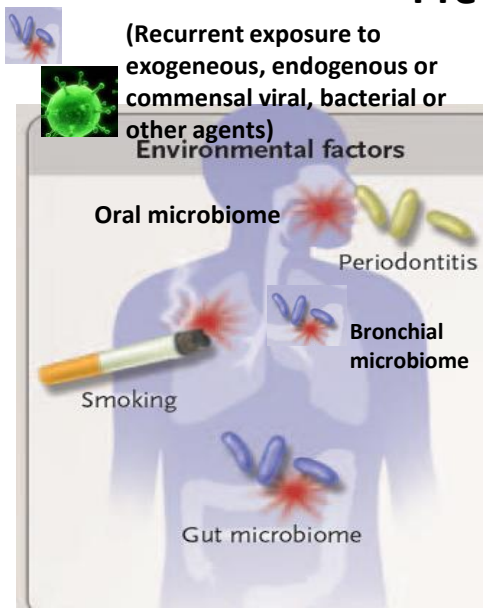
Figure 2. Etiology and pathway to arthritis

Pre-Arthritis



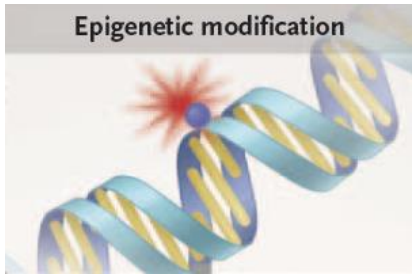
Shared epitope (Chr. 6)
PTPN22
PAD
TNF
....

+



(Recurrent exposure to exogeneous, endogenous or commensal viral, bacterial or other agents)

+



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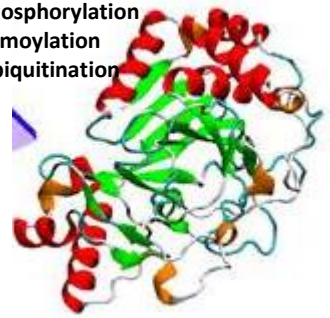
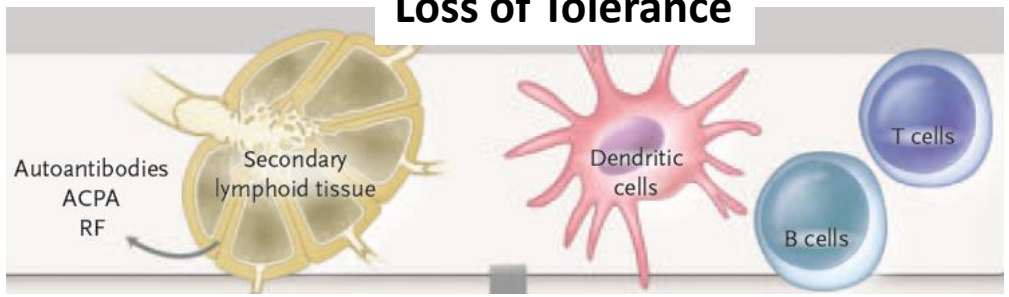
Posttranslational modifitations
- **Acetylation**
- **Carbamylation**
- **Citrullination**
- **Methylation**
- **Phosphorylation**
- **Sumoylation**
- **Ubiquitination**



=

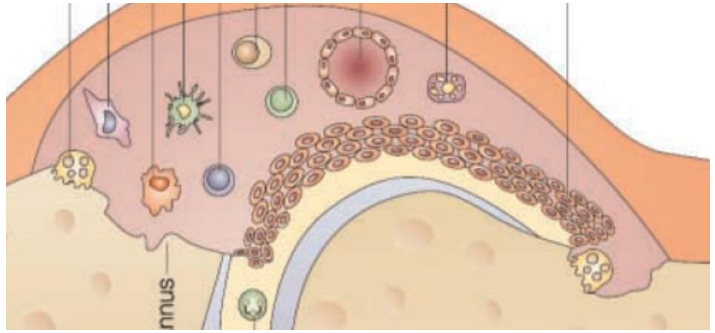
Loss of Tolerance

=



→

Asymptomatic arthritis (Cellular infiltrate)



Transition to manifest arthritis

Symptomatic arthritis (Swelling, pain, stiffness, damage)

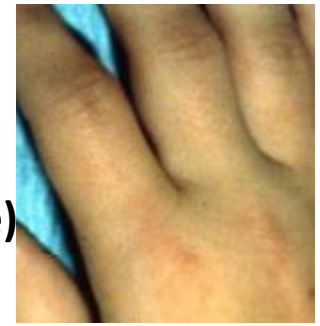


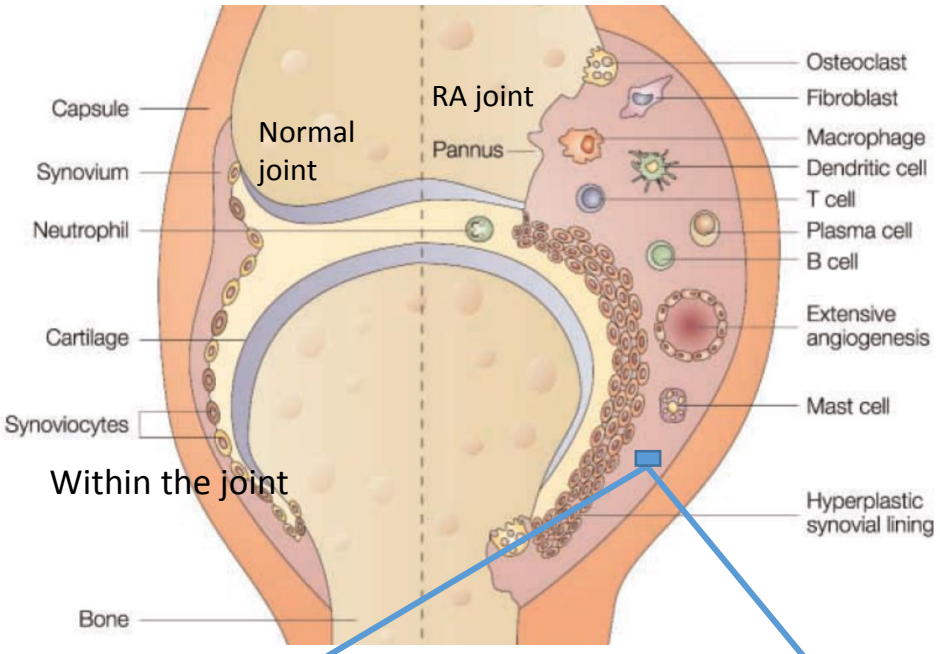
Figure 3

Figure 3
Pathogenesis

Pathobiology

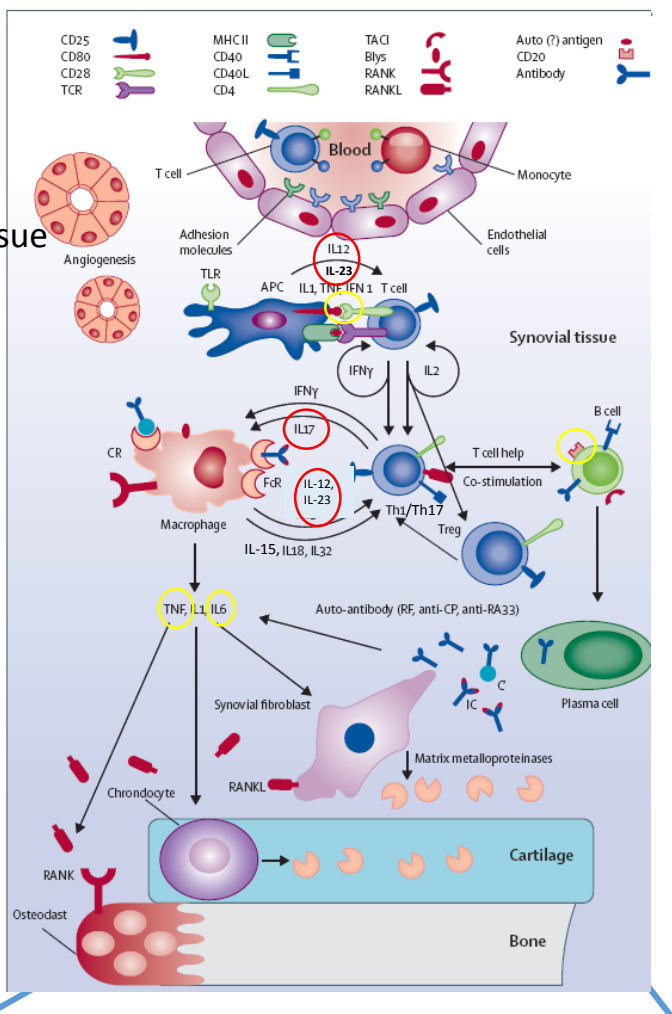
Cell biology

Molecular biology



Within the joint

Within the synovial tissue



Within a cell

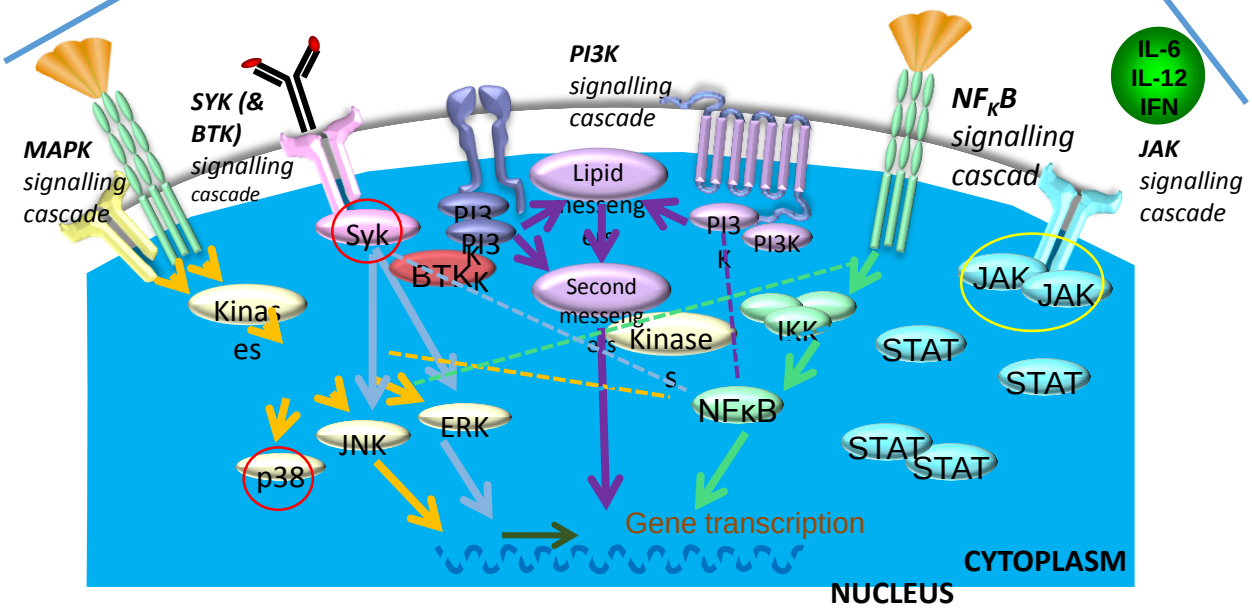
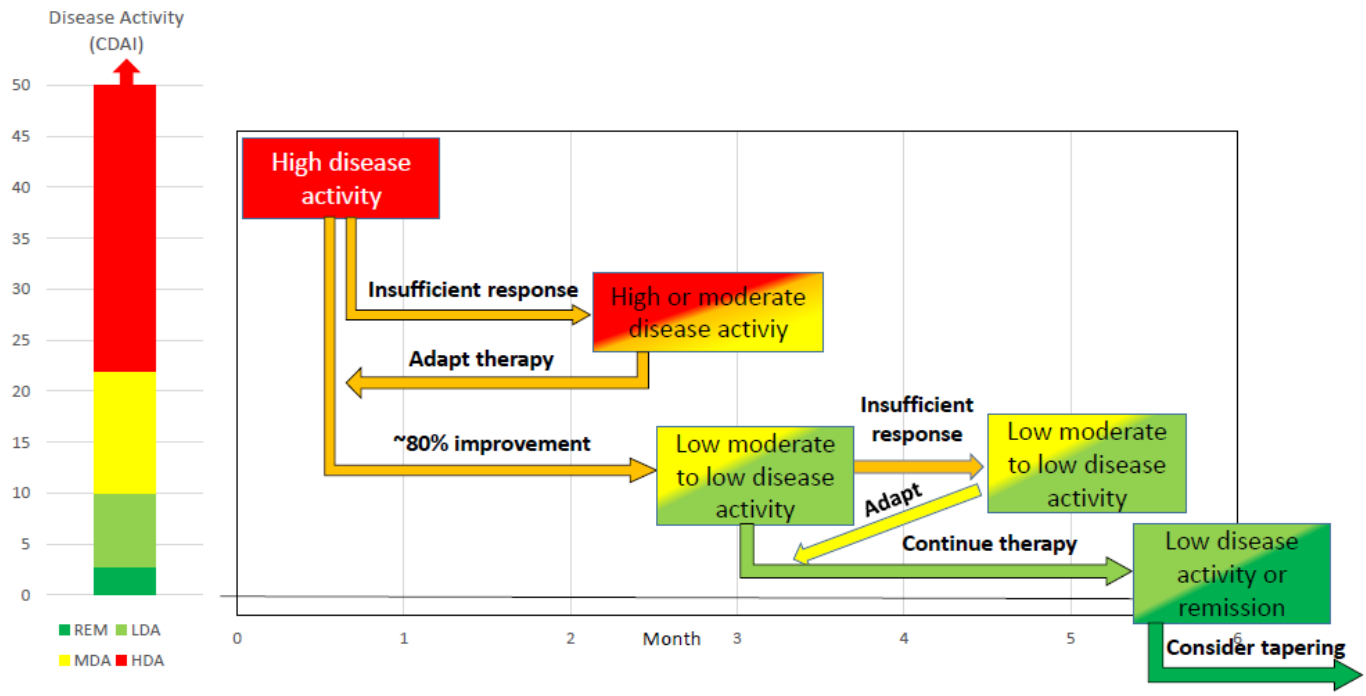


Figure 4

Figure 4. Therapeutic approach to rheumatoid arthritis. A. General strategy; B. Early treatment phase; C. Treatment approach when MTX (plus glucocorticoid) failed to allow reaching the treatment target; D. Treatment approach when a first biological failed.

A.



B.

Early diagnosis

Immediate treatment initiation

MTX+low dose glucocorticoid

C.

Upon failure: Stratify

With risk factors present **add** any biological agent

With risk factors absent **switch to** (or add) another cs DMARD

D.

Upon failure: **Switch** to any other biologic agent (even within same class) plus MTX or to a tsDMARD (+/- MTX)

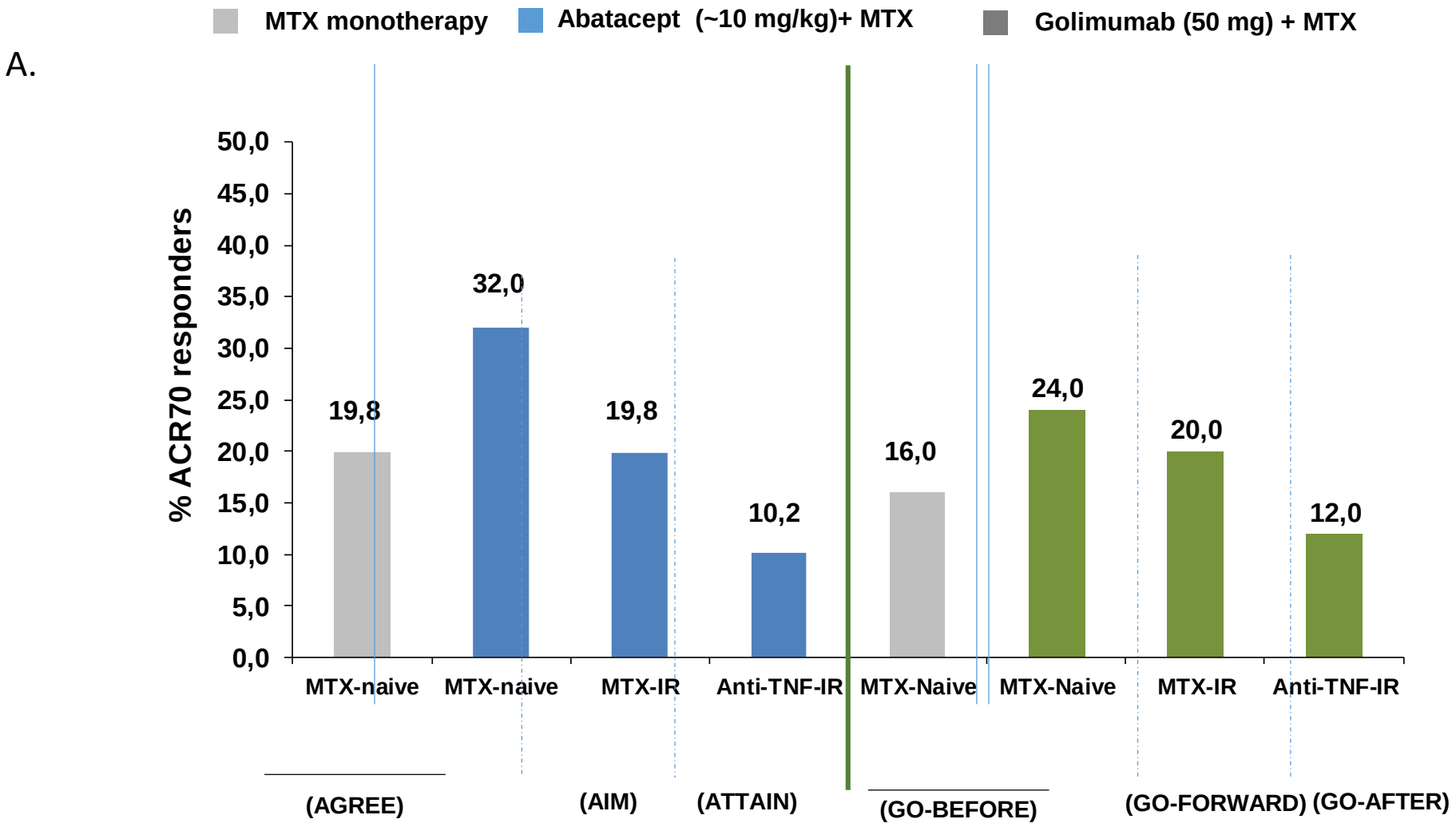
Follow patients using a composite measure of disease activity that comprises joint counts. Aim at clinical remission (ACR-EULAR criteria) or at least low disease activity within 6 months (this requires about 80% improvement of disease activity within 3 months of starting treatment)

Once any of the treatment regimens has led to the treatment target and its maintenance, consider reducing dose or increasing interval

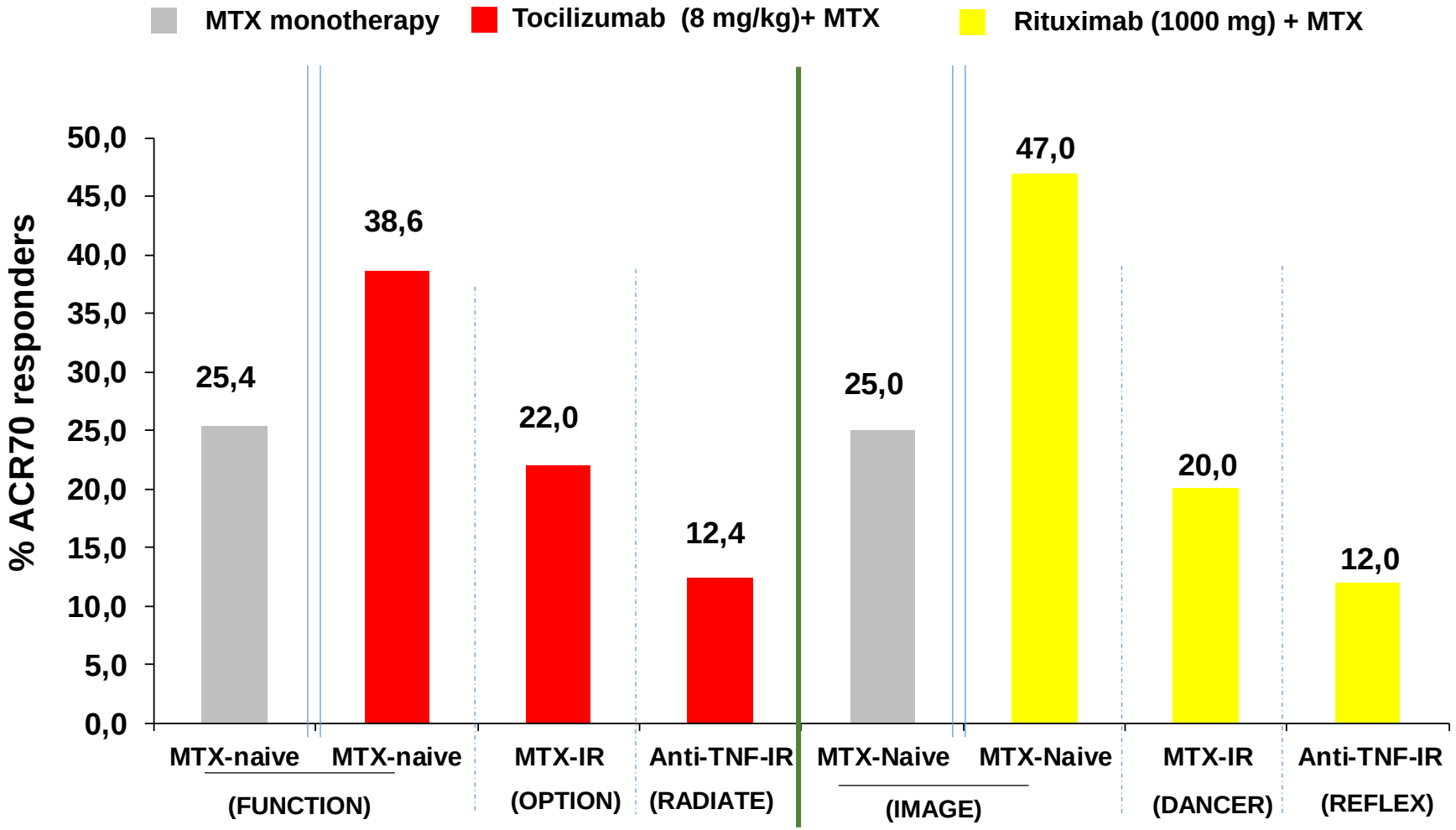
(suggested sequence: glucocorticoids, bDMARDs, csDMARDs)

Figure 5

Figure 5. ACR70 response rates with different bDMARDs and tsDMARDs

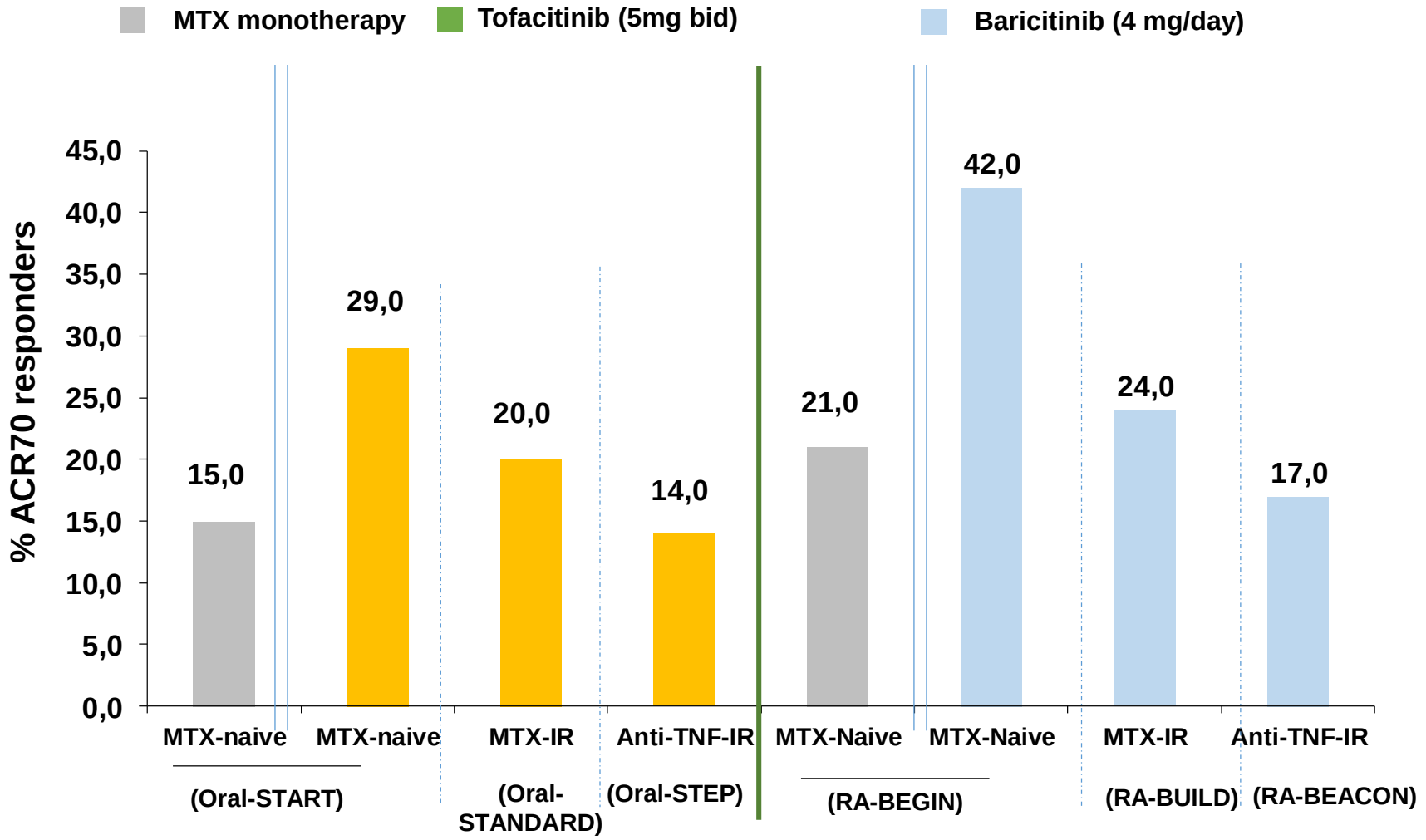


C.


MTX monotherapy
Tocilizumab (8 mg/kg)+ MTX
Rituximab (1000 mg) + MTX
% ACR70 responders
50,0
45,0
40,0
35,0
30,0
25,0
20,0
15,0
10,0
5,0
0,0
25,4
38,6
22,0
12,4
25,0
47,0
20,0
12,0
MTX-naive
MTX-naive
MTX-IR
Anti-TNF-IR
MTX-Naive
MTX-Naive
MTX-IR
Anti-TNF-IR
(FUNCTION)
(OPTION)
(RADIATE)
(IMAGE)
(DANCER)
(REFLEX)

D.

E.


MTX monotherapy
Tofacitinib (5mg bid)
Baricitinib (4 mg/day)
% ACR70 responders
45,0
40,0
35,0
30,0
25,0
20,0
15,0
10,0
5,0
0,0
15,0
29,0
20,0
14,0
21,0
42,0
24,0
17,0
MTX-naive
MTX-naive
MTX-IR
Anti-TNF-IR
MTX-Naive
MTX-Naive
MTX-IR
Anti-TNF-IR
(Oral-START)
(Oral-STANDARD)
(Oral-STEP)
(RA-BEGIN)
(RA-BUILD)
(RA-BEACON)

F.