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Narrative Review

Painful Rheumatoid Arthritis

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Rheumatoid arthritis is a crippling disease that is often associated with severe pain, suffering, and diminished function, thereby detracting from an optimal quality of life. Over the past decade a greater appreciation of the pathophysiology of rheumatoid arthritis has been gained. In the past "decade of pain research," biologic agents which may modify rheumatoid arthritis have emerged as potent therapeutic antirheumatic drugs. Biologic agents include 5 tumor necrosis factor alpha inhibitors (etanercept, infliximab, adalimumab, golimumab, certolizumab pegol), interleukin-1 blockers (anakinra), monoclonal antibodies against B cells (rituximab), T cell costimulation blocker (abatacept), and interleukin-6 inhibitors (tocilizumab).

Currently, utilizing therapy aimed at targeting various abnormalities of rheumatoid arthritis may be possible. It appears that the combined use of etanercept and methotrexate may improve the imbalance of Th1/Th2 and Th17/regulatory T cells (Treg) (and related cytokines) often seen in rheumatoid arthritis. Furthermore, this improvement in Tcell ratios/cytokines is also associated with improvement in clinical indicators of rheumatoid arthritis severity. Although rheumatologists are generally the specialists "called on" to manage complex patients with rheumatoid arthritis, pain specialists may be asked to join interdisciplinary teams managing patients with advanced refractory rheumatoid arthritis with severe pain since one of the most common and debilitating symptoms of rheumatoid arthritis is pain. Thus, pain specialists should have some appreciation of the current thoughts regarding rheumatoid arthritis pathophysiology and treatment.

This narrative review of rheumatoid arthritis is intended to familiarize the interventional pain specialist with current concepts surrounding rheumatoid arthritis.

Key words: Rheumatoid Arthritis, Pain, DMARDs, biological agengs, TNF inhibitors

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Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder thought to be autoimmune in nature that predominately affects synovial joints. Inflammation of the synovium (synovitis) is associated with hyperplasia of synovial cells, excess synovial fluid, and pannus formation. Pannus represents a thickened membrane-like covering of inflammatory granulation tissue over the articular cartilage. RA also may affect the lungs, pleura, pericardium, sclera and subcutaneous tissue.

RA has a prevalence of about 1% in the United States and has a comparable prevalence worldwide (1). The clinical hallmark of RA is polyarticular synovial inflammation of peripheral joints - typically in the hands (metacarpophalangeal joints and proximal interphalangeal joints), causing pain, stiffness, and often some degree of irreversible joint damage, deformity, and disability. Additionally, there is also a significant systemic inflammatory state present that may promote a number of other extra-articular effects,

including coronary artery disease, pulmonary fibrosis, osteoporosis, and vasculitis (2).

The diagnosis of RA remains a clinical diagnosis; however immunologic blood tests may be helpful in confirming that the patient has RA. Although the pathophysiology of RA remains uncertain, it appears that B cell lymphocytes and tumor necrosis factor alpha (TNFα) are important mediators. Antigens are typically presented to T cells by B cells via HLA-DR4. The presence of autoantibodies, such as rheumatoid factor (RF) and anti–citrullinated protein antibody (ACPA) (tested as anti–cyclic citrullinated peptide [anti-CCP]), can precede the clinical manifestation of RA by many years (3-8).

In the NEAR study, patients responded to questionnaires revealing that 17.5% identified RA as having a significant impact on quality of life, 15.7% felt that RA affected their ability to enjoy life, and 14.3% had difficulties in performing activities of daily living (9). Some activities were found to be more difficult for a patient with RA (on a scale of 0 to 10), such as gardening (6.36) and practicing sports (5.79). Other basic tasks were also considered difficult, including household chores (5.76), sleeping (5.08), walking (4.99), and working (4.86). Pain is almost universally present (87.9%), although a majority of patients also complain of arthritis (78%), pain when moving (65.5%), fatigue (60.1%) and joint deformities (58.3%) as very common symptoms. Diminishing pain (81.2%), a general improvement of symptoms (73.1%) in a lasting way (57.4%) and reducing arthritis (59.2%) appeared as the main concerns of patients with RA (9).

Smoking was shown in several studies to be a risk factor for the rheumatoid factor-positive or ACPA-positive subset of rheumatoid arthritis and to have no or a very minor effect on the autoantibody-negative subset (10-13). A major environmental interaction was noted between HLA-DR risk alleles and smoking in patients who were positive for rheumatoid factor or ACPA, in 3 European investigations (11-13), and to a smaller extent, in one North American study (14).

These findings suggest that patients with rheumatoid arthritis who are positive for ACPA are fundamentally different from those who are ACPA-negative with respect to genetic and environmental risk factors, with ACPA-positive patients having more joint inflammation and disease activity than ACPA-negative patients (15).

Juvenile rheumatoid arthritis (JRA) is a spectrum of conditions involving chronic inflammatory arthritis defined by objective arthritis (swelling, limitation of movement, or pain with movement of one or more joints) for at least 6 weeks, and the exclusion of other causes of arthritis in children younger than 16 years (16). Pauciarticular JRA is classified by the involvement of 4 or fewer joints during the first 6 months of the illness. The other 2 subgroups of JRA are polyarticular JRA and systemic JRA (16). JRA is also referred to as juvenile idiopathic arthritis (JIA) according to the nomenclature adopted by the International League of Associations for Rheumatology (17). The classification and diagnostic criteria of JIA have not yet been validated, unlike the criteria for the classification and diagnosis of JRA originally put forward by the American College of Rheumatology (16, 18).

JIA is a heterogenous group of arthridites thought to be largely autoimmune in nature which begins before age 16, and persists for more than 6 weeks. JIA differs markedly from adult rheumatoid arthritis (19). JIA may be associated with prominent systemic characterisitics (e.g. fever, rash, serositis). A subpopulation of patients with JIA seems to respond relatively well to treatment with interleukin-1 blockade while other subpopulations do not (19,20).

1.0 Pathophysiology

B cells which may produce antibodies in immune complex formation can function as antigen-presenting cells leading to T cell activation. Antigen-presenting cells communicate with T cells through the T-cell receptor (TCR)–MHC interaction, and T-cell activation happens only in the presence of co-stimulatory signals mediated via the CD28–B7 receptor family (CD80/86). Macrophages activated by signals from T cells and by immune complexes produce many proinflammatory cytokines, such as TNF, interleukin-1, and interleukin-6, which can increase expression of cell-adhesion molecules and cytokine production.

T-helper 17 (Th17) cells, which are dependent on interleukin-6 stimulation may produce interleukin-17 which enhances cytokine release, production of cartilage-destructive enzymes, and expression of bone destruction-related molecules, such as RANKL (21,22). TNF, interleukin-1, and probably interleukin-6, can drive RANKL expression and its release from fibroblasts, T cells, and osteoblasts (15,23). TNF-α stimulates the development of osteoclasts and also promotes recruitment of leukocytes into the joint through upregulation of adhesion molecules (such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1, and E-selectin and through endothelial layer permeability increases (24). Finally, TNF- α stimulates the acti-

vation of osteoclasts and also some metalloproteinases (MMP) which may promote bone erosion (25), and also inhibits the production of tissue inhibitors of metalloproteinases (TIMPs) by synovial fibroblasts (22). Figure 1 illustrates how various treatment strategies attempt to target specific processes involved in RA pathophysiology.

Destructive joint changes have been shown to be dependent on involvement of RANKL (receptor activator of NFκB ligand) in osteoclast activation and subsequent bone destruction (26,27). Osteoprotegerin, a soluble protein of the TNF-receptor superfamily functions as a decoy receptor for RANKL, thus being able to inhibit production of osteoclasts through interfering with the activation of RANK on the surface of osteoclast precursors by RANKL. Balance between RANKL and osteoprotegerin expression results in normal bone metabolism, with good equilibrium between bone production and destruction. Imbalance of the system, with relative predominance of RANKL (either by deficient osteoprotegerin expression or by increased RANKL expression) results in activation of osteoclasts with subsequent bone destruction (28).

The onset of arthritis is preceded by a pre-articular phase comprising evidence of a breach of self-tolerance (i.e., autoimmunity); for example, the presence of ACPA and RF (29). Clinically evident disease manifests within the joint with synovitis and attendant cartilage and bone damage (30). ACPA-positive disease may be separated from seronegative disease and should be considered a distinct clinical syndrome (15) with attendant prognostic and comorbid features.

Human RA synoviocytes invade and degrade the collagen-rich structures associated with joint tissues including tendons, ligaments, bone, and cartilage (31-33). Sabeh and colleagues (34) demonstrated that the RA synoviocyte-derived proteinase MT1-MMP alone confers RA synoviocytes with the ability to degrade or invade cross-linked collagen networks as well as initiate or promote neovascularization.

In RA, the synovium expands to create the pannus, a highly vascularized granulation tissue that is composed largely of synoviocytes, macrophages, and T cells (34,35). Activated CD4 and CD8 T cell subsets, B cells, plasmablasts and plasma cells are abundant in synovium (30). The synovial lesion in RA contains a macrophage/fibroblast-rich lining layer overlying interstitial tissues containing an abundance of activated leukocytes including macrophages (M1 phenotype), dendritic cells (DCs), B cells, CD4/CD8 T cells, mast cells, and NK and NKT cells (30).

The rheumatoid pannus actively invades and destroys the underlying cartilage as well as subchondral bone (34). Angiogenesis is recognized as a key event for the expansion of the synovial lining of joints in RA; vascular endothelial growth factor (VEGF) appears to have a central role. The serum VEGF level is important as an index of the activity of RA based on angiogenesis and a prognostic factor regarding joint destruction (36). The serum angiopoietin-1 (Ang-1) level may be useful as an index of sustained arthritis based on the maintenance of newly formed vessels. The serum angiopoietin-2 (Ang-2) level may reflect a state of marked angiogenesis (36).

Overproduction of proinflammatory cytokines is likely to be largely due to macrophage-like synoviocytes. Fibroblast-like synoviocytes also show abnormal behavior in rheumatoid arthritis. In experimental models, co-implantation of fibroblast-like synoviocytes with cartilage leads to fibroblasts invading cartilage (37), behavior that correlates with joint destruction (38). The role of osteoclast activation is a vitally important process leading to bone erosion. Specific inhibition of osteoclast activation can reduce joint destruction without affecting joint inflammation (39).

The clinical effect of the separation of the 2 pathways, cartilage versus bone destruction, has been shown in a phase II trial of a RANKL inhibitor, which was effective at preventing erosions but not inflammation or joint-space narrowing (39) (Fig. 1). Up to 70% of patients who present with early inflammatory arthritis have typical radiographic results at the initial visit, whereas ultrasonography and magnetic resonance imaging (MRI) can detect erosions in much higher numbers, and up to 2 years earlier than with plain radiographs (40,41).

2.0 Assessment and Treatment Goals

2.1 Treatment Goals

There has been a paradigm shift in the goals of treatment for rheumatoid arthritis. Decades ago, treatment was largely focused on controlling symptoms such as pain, which then moved to stepped disease-modifying antirheumatic drug (DMARD) therapy aimed at calming inflammation (i.e., reducing it by half). Current views of RA treatment focus on targeted therapy and early and aggressive so-called "tight control" therapy in an effort to eliminate synovitis and put the activity of the disease into remission. In most cases this will require biologic agents.

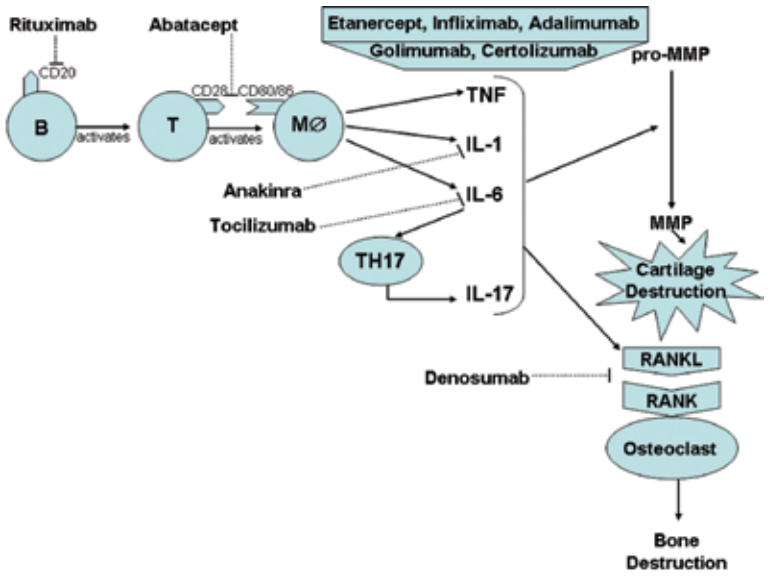


Fig. 1. *Schematic of potential RA pathophysiology (with potential therapeutic targets)*

An ACR20 response rate to RA treatment has been defined by the American College of Rheumatology (ACR) (42). The variables included in this definition are:

- tender joint count
- swollen joint count
- patient's assessment of pain (visual analog scale [VAS] or Likert scale)
- patient and physician assessment of disease activity (VAS or Likert scale)
- patient assessment of functional ability (Health Assessment Questionnaire [HAQ], Arthritis Impact Measurement Scales [AIMS], McMaster Toronto [MACTAR])
- Arthritis patient preference questionnaire
- inflammatory markers, such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).

An ACR20 response is defined as a 20% improvement in tender and swollen joint counts and the same level of improvement in 3 of the 5 following variables: patient global assessments, physician global assessments, pain scores, HAQ score, and laboratory acute phase reactants. Improvement in Disease Activity Score (DAS)/DAS28). is this a subheading? The Disease Activity Score (DAS) is a composite index that includes a combination of the values of tender and swollen joint counts, the patient's global assessment of disease activity, and the ESR value (43). A DAS28 score is used when a 28 joint count is used as the index (44). The DAS28 is a measure of an absolute level of disease activity that includes a tender joint count and blood ESR or CRP. Currently, an accepted clinical goal of RA treatment is to achieve a DAS28 < 3.2. For example, a typical patient with RA with one tender and one swollen joint and an ESR of 15 has a DAS28 of 3.1. The Tight Control of Rheumatoid Arthritis (TICORA) trial (45) showed that patients who are treated to a specific target (DAS < 2.4), rather than treated only to symptom relief, have much improved clinical courses, including fewer swollen joints, lower ESRs, and slower radiographic progression of the disease (1). Although RA research treatment goals are generally tools such as ACR20, ACR50, or DAS28, these should generally translate clinically to optimal comfort, function, and quality of life for RA patients with minimal adverse effects.

2.2 Assessment

A rapid assessment of physical function, pain, and global status scores in patients with RA is known as the Rheumatology Assessment Patient Index Data (RAPID)-3 (46) (Table 1). RAPID-3 can be expanded by adding the Rheumatoid Arthritis Disease Activity Index self-report (RAPID-4) and the physician/assessor global estimate (RAPID-5) templates that are included in the

Table 1. *Rheumatology Assessment Patient Index Data*

The abbreviated 3 part [RAPID3] assessment (46-Pincus 2007) is:
Part I- Select the one best answer [without any difficulty (0), with some difficulty (1), with much difficulty (2), unable to do (3)]
Over the past week were you able to: Dress yourself, including tying shoelaces, doing buttons? Get in and out of bed? Lift a full cup or glass to your mouth? Walk outdoors on flat ground? Wash and dry your entire body? Bend down and pick-up clothing from the floor? Turn regular faucets on and off? Get in and out of a car, bus, train, or airplane? Walk two miles? Participate in sports and games as you would like?
Part II- How much pain have you had because of your condition over the past week?
□ □ □ □ □ □□ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ No Pain←0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5,5. 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10→Pain as bad as it could be
Part III- Considering all the ways n which illness and health conditions may affect you at this time, plese indicate below how you are doing?
□ □ □ □ □ □□ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ Very Well ←0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5,5. 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10→ Very poorly

Table 2. *2010 ACR/EULAR RA Classification Criteria*

Factor		**Points**
Joint Involvement	1-large joint (shoulder, elbow, hip, knee, ankle)	0
	2-10 large joints	1
	1-3 small joints (metacarpophalangeal, proximal interpharlangeal, metacarpophangeal, carpal)	2
	4-10 small joints	3
	>10 joints (at least 1 small joint required)	5
Serologic Studies	Negative RF & anti-CCP	0
	Weakly positive RF and/or anti-CCP	2
	Strong positive RF and/or anti-CCP	3
Acute-Phase Reactants	Normal (CRP and/or ESR)	0
	Elevated (CRP and/or ESR)	1
Disease Duration	< 6 month	0
	>6 month	1
TOTAL		

RA = At least 1 swollen joint (unexplained by another disease) and a total of at least 6 points from table below {At least 1 laboratory test result needed for classification.]
Legend: CRP=C-reative protein, ESR=erythrocyte sedimentation rate, RF=rheumatoid factor, anti-CCP=anticyclic citrullinated peptide antibodies, Joint Involvement

Multi-Dimensional Health Assessment Questionnaire (MDHAQ) forms. These forms and instructions for their use can be downloaded from www.mdhaq.org (47).

It has become widely accepted that the 1987 ACR criteria for classification of rheumatoid arthritis were suboptimal, largely due to a low sensitivity in identifying early rheumatoid arthritis. The ACR and the European League Against Rheumatism (EULAR) sponsored a collaborative, multiphase project to develop updated and more sensitive criteria for the classification of rheumatoid arthritis (48, 49).

To meet the new classification criteria for rheumatoid arthritis, a patient must have at least one swollen joint not explained by another disease and 6 points summed from the following 4 factors (Table 2):

- joint involvement

- serologic studies
- acute-phase reactants
- disease duration.

Optimal outcomes for patients with rheumatoid arthritis are likely obtained with multimodal interdisciplinary treatment involving nonpharmacologic as well as pharmacologic therapeutic approaches (Fig. 2).

There exists a growing body of evidence revealing an abnormal expression of specific micro(mi)-RNAs (miRNAs) in RA tissues. The use of a blood-based miRNA signature may serve as a biomarker for early and optimal diagnosis which would allow an earlier institution of treatment strategies (50).

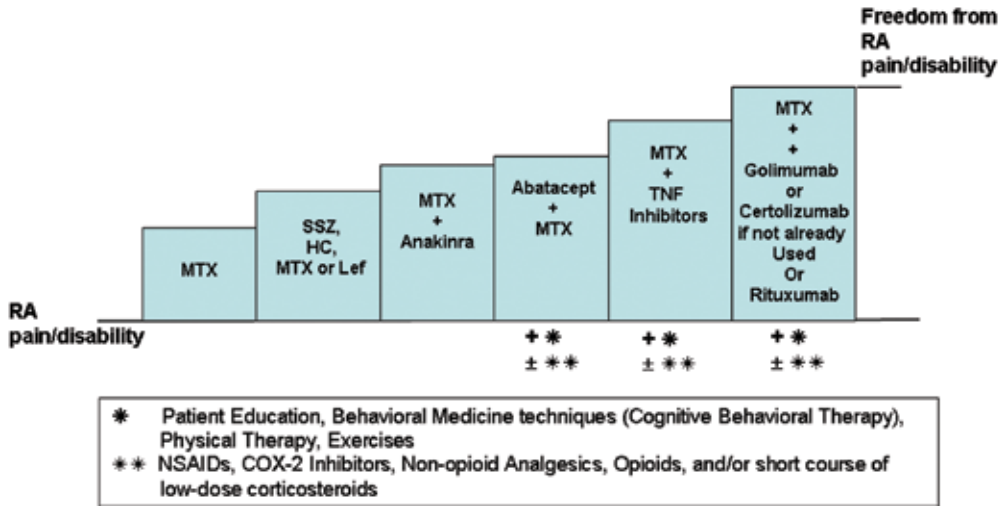
3.0 Treatment

Several national and regional guidelines for managing rheumatoid arthritis exist, including recommendations from ACR, EULAR, and the United Kingdom's National Institute for Health and Clinical Excellence (51-53).

3.1 Nonpharmacologic Therapy for RA

Forestier and colleagues (54) performed a systematic literature review and retrieved 1,819 articles, of which 817 were analyzed and 382 cited in their review. They concluded that aerobic activities, dynamic muscular reinforcement, and therapeutic patient education appear valuable in non-drug management of RA. Baillet and colleagues (55) evaluated 14 RCTs,which included 1,040 patients, in an effort to determine the efficacy of aerobic exercise in RA on quality of life, function, and clinical and radiographic outcomes by a systemic review and meta-analysis. Aerobic exercise appeared safe and improved post-intervention quality of life , HAQ scores, and pain VAS (although the benefit was relatively small).

- Other potential treatments which may possess some benefit for the treatment of RA include progressive resistance training (56), tai chi (57,58), and aquatic exercises (59).
- Behavioral medicine approaches to the treatment of RA may also provide significant therapeutic benefit to patients with RA. Astin and colleagues (60) performed a meta-analysis of 25 randomized controlled trials and concluded that psychological interventions may be important adjunctive therapies in the medical management of RA. Sharpe and colleagues (61) examined the efficacy of cognitive and behavioral therapy (CBT) for RA in a blind, randomized, controlled trial of patients with recent onset rheumatoid arthritis.. Their results suggest



Lef = Leflunomide, HC = Hydroxychloroquine, SSZ = Sulfasalazine; MTX = Methrotrexate, RA = Rheumatoid Arthritis

Fig. 2. *Schematic of potential treatment approaches for Rheumatoid Arthritis*

that cognitive-behavioral intervention offered as an adjunct to standard clinical management early in the course of RA is efficacious in producing reductions in both psychological and physical morbidity (61).

- Evers et al (62) suggested customizing behavioral treatments to patient characteristics thereby utilizing tailor-made cognitive-behavioral therapy may optimize outcomes from behavioral approaches for patients with RA (62). Sharpe and colleagues (63) evaluated the 5-year follow-up of their original randomized trial comparing cognitive-behavioral intervention for patients with recently diagnosed rheumatoid arthritis with no psychological intervention. Their results suggest that CBT administered early in the course of RA can reduce health care utilization for the first 5 years after treatment, supporting the notion that brief psychological treatments can have long-term effects (63).

Barsky and colleagues (64) evaluated the benefits of 3 psychosocial treatments for RA. RA patients were randomized to cognitive-behavior therapy (CBT), relaxation response training (RR), or arthritis education (AE). They aggregated the results for all 3 groups and found significant benefits for pain, other RA symptoms, self-care activities, and social activities and concluded that all 3 psychosocial treatments were beneficial, with small to moderate treatment effect sizes. These benefits were achieved over and above benefits resulting from medical management and were sustained at long-term follow-up. The 3 psychosocial treatments appear to constitute an effective augmentation to usual medical therapy for RA (64).

Interventional techniques may include intraarticular injections of various joints, as well as epidural injections, facet joint nerve blocks, and other interventional techniques with involvement of the spine (65-87).

3.2 Pharmacologic Therapy of RA

Over the past 60 years, there have been a number of drugs approved in the U.S. for the treatment of RA; however, in the last decade ("the decade of pain research"), there has been a significant explosion of antirheumatic drugs (Fig. 3). Caution is needed in patients of childbearing age because many pharmacologic treatments have negative effects on conception and pregnancy (88).

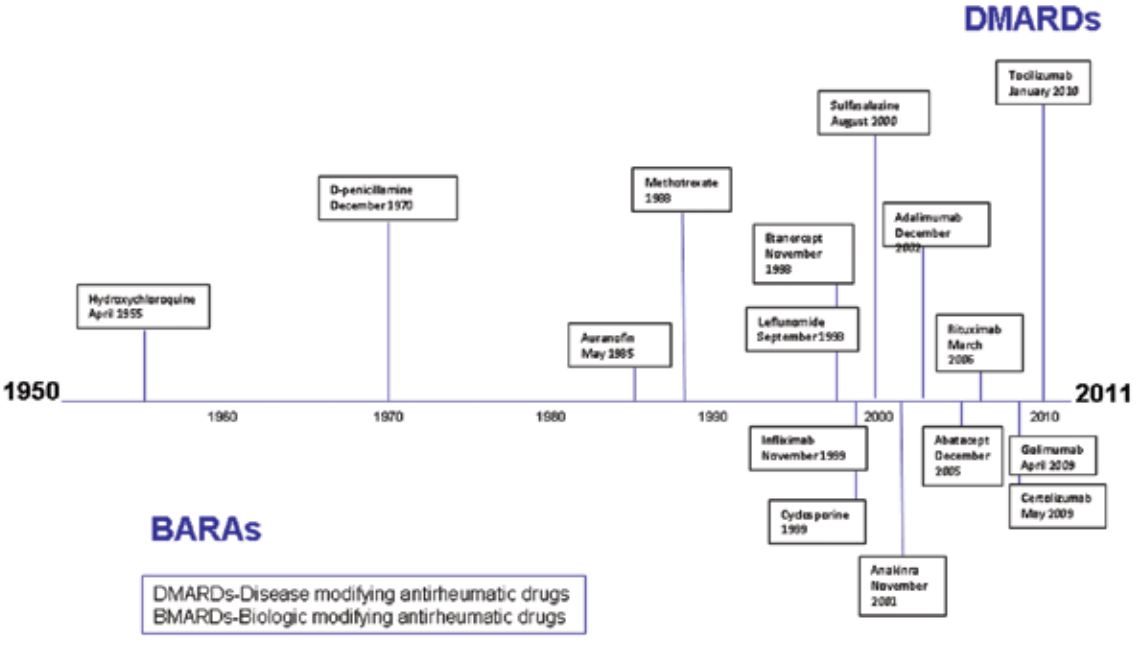


Fig. 3. *Timeline of therapeutic agents for the treatment of RA. BARAs are biological agents.*

3.2.1 Symptom-Modifying antirheumatic drugs (SMARDs)

Symptom-modifying antirheumatic drugs (SMARDs) include analgesics (opioid and nonopioid analgesics) to reduce pain, and nonsteroidal anti-inflammatory drugs (NSAIDs) (including "traditional" or nonselective NSAIDs as well as cyclooxygenase-2 [COX-2] inhibitors) to lessen pain and stiffness. Both groups of drugs are widely used to control symptoms of rheumatoid arthritis.

Although support for the use of NSAIDs for control of RA symptoms is strong (89), NSAIDs have lost their historical role as a first-line treatment because of concerns about their limited effectiveness, inability to modify the long-term course of the disease, and toxic gastrointestinal and cardiac effects (90,91).

3.2.2 Disease-modifying antirheumatic drugs

DMARDs are a heterogeneous collection of agents grouped together by use and convention. Historically, they have been the mainstay of treatment for rheumatoid arthritis (92). They reduce joint swelling and pain, decrease acute-phase markers, limit progressive joint damage, and improve function.

Analgesics do not help in the control of RA disease activity, but can be helpful adjuncts for pain control (93). There is no evidence that these treatments alter the course of RA (94,95). The fundamental goal of RA treatment is to eliminate synovitis and disease activity. With few exceptions, all patients should be treated with a DMARD and/or a biologic agent (based on comorbid conditions, age, patient preference, or the presence of very limited disease activity). DMARDs should be used at full doses unless full treatment effect is gained at a lower dosage or limiting toxicity is reached. For methotrexate (MTX), the full dose is at least 20 mg per week; for sulfasalazine (SSZ) it is 3 g per day.

Active rheumatoid arthritis needs intensive treatment. Step-up DMARDs, with extra DMARDs added to achieve disease control, is the most conservative strategy. Initial MTX–biological combinations are an alternative. Parallel treatment, with several DMARDs started concurrently, is an intermediate option. DMARD combinations or MYX–TNF inhibitor regimens have similar efficacy (96). Early addition of biological agents for patients with incomplete responses to DMARDs seems highly effective.

The treatment of patients with rheumatoid arthritis has changed dramatically in the past decade. DMARDs, such as hydroxychloroquine, SSZ, cyclosporine, azathioprine, D-penicillamine, auranofin, and intramuscular gold were the only choices for DMARD treatment for many years (97). Weekly methotrexate assumed a dominant role in the 1980s and 1990s because its efficacy and safety were demonstrated in both short-term trials (98,99) and long-term observational studies (100,101).

MTX is the dominant DMARD. SSZ and leflunomide are also widely used. Their efficacy has been established in placebo-controlled trials (92,102-104). Hydroxychloroquine and chloroquine have DMARD-like properties. Gold (rINN sodium aurothiomalate) and cyclosporin are additional DMARDs; their use is limited by toxic effects. DMARDs are sometimes combined, and several combinations of DMARDs have proven efficacy (105). An example is MTX, SSZ, and hydroxychloroquine—termed triple therapy, or SSZ, MTX and prednisolone, occasionally referred to as "COBRA therapy" (for COmbinatie therapie Bij Rheumatoide Artritis).

After 11 years, initial COBRA combination therapy resulted in numerically lower mortality and similar prevalence of comorbidity compared with initial SSZ monotherapy. In addition, lower progression of joint damage suggests long-term disease modification (106). The COBRA study was a double blind, randomized controlled trial in patients with early RA that compared the combination of 3 traditional DMARDs (SSZ, MTX and prednisolone) with monotherapy (SSZ). COBRA therapy was shown to be a rapidly effective treatment for RA (107), including a sustained decrease of radiological progression after a mean of 4.5 years follow-up (108).

At doses of 7.5 mg to 25 mg per week, MTX relieves pain, reduces the number of affected joints, and provides a functional improvement. It has the adverse effects common to all immunosuppressants, particularly those immunosuppressants utilized for gastrointestinal and hematologic disorders. Treatment withdrawals due to adverse effects are infrequent at the doses used for RA. Other synthetic antirheumatic drugs such as azathioprine, chloroquine and its derivatives, cyclosporin, cyclophosphamide, D-penicillamine, leflunomide, gold salts and SSZ are no more effective than MTX. Some are less effective, and others are more toxic.

MTX can cause serious liver and lung toxicity (109,110), but both can be prevented by careful monitoring and by avoiding MTX use in patients at particular risk for harm (111,112). In addition, other MTX-associated toxicities can be avoided with the use of supplemental folate (113,114).

Leflunomide is thought to work by reversibly inhibiting dihydroorotate dehydrogenase (the enzyme

which catalyzes the conversion of dihydrorotate to orotate) in the intramitochondrial pyrimidine biosynthetic pathway, resulting in decreased levels of pyrimidine nucleotides, such as ribonucleotide uridine monophosphate. Dividing cells need to increase the pool of pyrimidine precursors 8-fold to move from the G1 phase to the S phase of cell growth. In the presence of leflunomide, this pool can increase only 2-fold through cellular salvage pathways (115,116). These actions result in inhibition and/or reduction of activated T lymphocytes.

Leflunomide is virtually entirely protein-bound and undergoes continuous enterohepatic recirculation (117). Its half-life is nearly 15 days, which means that effective antimetabolic levels will remain for many months after discontinuation of drug use (117). Leflunomide may, however, be efficiently removed from patients with the addition of the resin cholestyramine, which will bind the drug in the gut with ultimate removal in the stool (117).

Leflunomide is actually a prodrug that undergoes rapid and complete hepatic metabolism to its active metabolite, the malononitriloamide A77 1726, two-thirds of which is excreted by the gut and one-third of which is excreted by the kidney (117). Although leflunomide is not contraindicated in patients with renal impairment, it should be used with caution in this setting. Patients with hepatic compromise, including those who are regular heavy consumers of alcohol or those with a history of hepatitis, should probably not take leflunomide (117).

3.2.3 Glucocorticoids

The use of steroids for management of RA more than 60 years ago was followed by uncertainty about their value for improving outcomes and their risk/benefit ratio. Short-term glucocorticoids (GCs) reduce synovitis; in the long term, they may decrease joint damage (118) but have significant adverse risks, such as infections and osteoporosis, and their overall risk/benefit ratio is deemed unfavorable (119).

GCs are used extensively in patients with RA. Recent data on the efficacy of these drugs in alleviating symptoms of inflammation, but also in retarding erosive damage, have been presented. In addition, a critical review of the rather limited literature on the adverse effects of chronic use of low dose GCs has been given. It becomes clear that the net effect of low-dose GCs in the treatment of RA favors the beneficial aspects of these drugs above the negative aspects. Prudent use of GCs can be recommended (120).

Gorter and colleagues (121) performed a systematic review relating to the use of GCs for RA which include 11 publications (including 3 Cochrane reviews comprising 33 trials) that met the criteria for detailed assessment (121). In practice, GCs are often used to bridge the time period between the start of a newly initiated or changed DMARD regimen and the time point at which this DMARD will become clinically effective (bridging therapy) (122). Robust evidence that GCs are effective as bridging therapy was obtained. The addition of GCs, to either standard synthetic DMARD monotherapy or combinations of synthetic DMARDs, yields clinical benefits and inhibition of radiographic progression that may extend over many years. There is some evidence that appropriate timing of GC administration may result in less morning stiffness (121).

In early RA, the addition of low-dose GCs (< 7.5 mg/d) to DMARDs leads to a reduction in radiographic progression; in longstanding RA, GCs (up to 15 mg/d) improve disease activity (121). GCs appear to be effective in relieving signs and symptoms and inhibiting radiographic progression, either as monotherapy or in combination with synthetic DMARD monotherapy or combination therapy (121).

GCs can be especially useful in 2 settings. First, short-term use during flare-ups in disease can lead to rapid improvement and allow other treatments—such as DMARDs, which have a slower onset of action—to be adjusted. Second, intra-articular GCs are a highly effective local treatment for individual active joints (123).

Owing to the systemic side-effects and also their susceptibility to the first pass metabolism, their liberal use is being discouraged. To circumvent this, triamcinolone (TA) was encapsulated in chitosan microspheres with glutaraldehyde as the cross-linking agent to achieve a prolonged drug release (124).

3.2.4 Biological Antirheumatic Agents

Biological agents (biologics) include:

- tumor necrosis factor alpha (TNF-α) blockers — etanercept (ETN) (Enbrel), infliximab (IFX) (Remicade), adalimumab (ADA) (Humira), golimumab (GLM), certolizumab (Simponi)
- interleukin 1 (IL-1) blockers — anakinra (ANA) (Kineret)
- monoclonal antibodies against B cells — rituximab (RTX) (Rituxan)
- T cell costimulation blocker — abatacept (ABT) (Orencia)
- interleukin 6 (IL-6) blockers — tocilizumab (TCZ) (an anti-IL-6 receptor antibody) (RoActemra, Actemra).

TNF inhibitors were the first licensed biological agents, followed by ABT, RTX, and TCZ, all of which are highly effective (125-131). Caution is needed when comparing treatments because populations of patients with RA in various trials are dissimilar. The efficacy of biological agents is most obvious with short-term studies in late disease, when placebo responses are low; it is generally less clearcut in early disease, when active comparators can achieve good responses. Effects of biological agents can be especially striking in the subset of inadequately treated or nonresponsive patients selected for trials. Uncertainty exists about the extent to which the strongly positive trial results for use of these agents translates into routine clinical practice, when drugs can be given to people with less active disease who will have diminished responses (132). Biological agents are combined conventionally with MTX. Initially, this combination was to reduce antibody formation (133), but it potentially increases efficacy. Leflunomide can replace methotrexate (134). Some biological agents are self-injected at twice weekly to monthly intervals; others are given by infusion. It is conceivable that TNF-α inhibitors may improve asthma symptoms in patients with RA and asthma (135).

3.2.5 TNF Inhibitors

Only 5 TNF- α blockers that have been approved by the US Food and Drug Administration (FDA) are currently available. The chronological order of approval for RA treatment is as follows: ETN, infliximab, ADA, GLM, and certolizumab pegol (CZP) (Table 3).

These agents can be divided into 2 groups. The first group is constituted from antibody to TNF- α (infliximab, ADA, GLM, and CZP). Infliximab, ADA and GLM are TNF-specific monoclonal antibodies. CZP is a TNF specific Fab fragment bound to polyethylene glycol (136). The second one is constituted from TNF- α receptors linked to fragment crystallizable (Fc) domains (ETN). ETN is a fusion protein comprising 2 TNFR2 extracellular domains fused to a single human IgG1Fc fragment containing the CH2 domain, the CH3 domain and hinge region, but not the CH1 domain (136). GLM is a fully human antibody raised against TNF- α. GLM is indicated for the treatment of active RA, ankylosing spondylitis (AS) (137), and psoriatic arthritis (PA) (138). This antibody has demonstrated, as expected, low immunogenicity because only 6.5% of patients have developed human anti-human antibodies (HAHA) and only 21% of patients developed autoantibodies such as anti-nuclear antibodies (ANA) with nonsevere adverse effects (139).

All 5 TNF blockers can bind sTNF and mTNF, but the fusion protein ETN has additional specificity for both soluble and membrane-associated LTα which is also able to engage both TNFR1 and TNFR2. All agents are capable of blocking the interaction of mTNF with receptors on other cells, however IFXis able to cross-link mTNF and in some circumstances this can have agonistic effects on the target cell. ETN, which is capable of binding a single homotrimer and therefore unable to cross-link mTNF, shares some but not all of these properties (140).

TNF blockers may be associated with multiple adverse events including local injection site reactions, however infection is the major concern. The increased risk of tuberculosis is particularly significant and appropriate screening should be performed (skin testing, chest radiography, and/or whole -blood testing for Mycobacterium tuberculosis) (141); along with screening for hepatitis B and C infection. Studies of the long-term risks of biologic agents studied by meta-analysis (142) and routine-practice registries (143) reveal that infection (which may be bacterial , viral or fungal) (144) represents the single most important side effect. There is no robust data to support any concerns regarding risks

Table 3. *TNF Inhibitors*

	Infliximab	Entanercept	Adalimumab	Certolizumab	Golimumab
Structure	Monoclonal Ab	P75 TNFR/Fa Fusion	Monoclonal Ab	Pegylated Monoclonal Ab	Monoclonal Ab
Administration Route	Intravenous (IV)	Subcutaneous (SC)	SC	SC	SC or IV
Frequency	8 weeks	Weekly	2 weeks	2 weeks	4 weeks
Half-life in Humans (days)	9.5	3	14	14	12
Loading dose required	Yes	No	No	Yes	No

of demyelinating neurologic disorders, cancer, or hematologic malignancies such as lymphoma (145).No convincing evidence has ever been shown that TNF inhibitors increase the risk of lymphoma above that of the already elevated risk of developing lymphoma from severe RA (146).Etanercept

The structure of ETN consists of 2 p75 TNF receptors attached or "fused" to an IgG1 Fc region of a human immunoglobulin molecule. This construct is administered subcutaneously twice weekly (mean half-life, approximately 3 days) and is capable of significantly lowering levels of circulating TNF (97). The most common side effects are erythema and pruritis at the injection site, and these reactions usually disappear after 3 months of regular dosing (147).

The TEMPO study demonstrated that the combination of ETN and MTX was significantly better in reduction of disease activity, improvement of functional disability, and retardation of radiographic progression compared with methotrexate or ETN alone (148).

Emery and colleagues (149) describe the COMET study of treatment of early rheumatoid arthritis with the combination of ETN and MTX, compared with MTX alone. Remission and radiographic non-progression are goals in the treatment of early rheumatoid arthritis. The aim of the combination of MTX and ETN in active early rheumatoid arthritis in the COMET trial was to compare remission and radiographic non-progression in patients treated with MTX monotherapy or with MTX plus ETN (149). They found that both clinical remission and radiographic non-progression are achievable goals in patients with early severe rheumatoid arthritis within one year of combined treatment with ETN plus MTX (149). The results of Anis and colleagues (150) analyzed from the COMET study (149) demonstrated that early treatment with ETN plus MTX led to a significant attenuation of absenteeism from work among patients with early active RA (150). These productivity gains represent benefit beyond the traditional measures of clinical and radiographic improvements and thus, increased work productivity. Emery and colleagues (149) reported that early sustained combination ETN-MTX therapy was consistently superior to MTX monotherapy in a 2-year, double-blind, randomized study. Combination therapy resulted in important clinical and radiographic benefits over 2 study years, without significant additional safety risk (151). ETN maintained therapeutic benefits beyond 10 years of therapy in both early rheumatoid arthritis (ERA) and long-standing rheumatoid arthritis (LRA) patients, suggesting that ETN is well tolerated and effective as a long-term, continuous therapy for the treatment of RA with a favorable risk-benefit ratio (152).

3.2.5.1 Infliximab

IFX is a chimeric monoclonal antibody whose target is TNF. It is administered intravenously in an outpatient setting every 4 to 8 weeks. The hypervariable region of the antibody is murine in origin, while the remainder of the immunoglobulin consists of a human IgG1 Fc heavy chain and partial k light chain. Because of the chimeric nature of the antibody, it should have less potential to generate an immune reaction than a fully murine molecule but more potential than a fully humanized construct (97).

Doyle and colleagues (153) analyzed data from patients with RA who received IFX or placebo in the multicenter, placebo-controlled, double-blind, randomized ATTRACT, ASPIRE, and START studies, which were included in a post-hoc, pooled analysis (153). Treatment with IFXplus MTX significantly improved hemoglobin level among anemic RA patients when compared with treatment with placebo plus MTX, even after adjusting for improvement in disease activity (153).

Doyle and colleagues (153) evaluated the effect of TNF-α inhibition on blood hemoglobin level in RA patients with anemia using data from 3 prospective, randomized, double-blind, placebo-controlled, multicenter clinical trials: Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) (154-156), Active-controlled Study of Patients receiving IFXfor the treatment of Rheumatoid arthritis of Early onset (ASPIRE) (157), and Safety Trial for rheumatoid Arthritis with Remicade Therapy (START) (158).

Zintzaras and colleagues (159) performed a meta-analysis of 12 randomized controlled trials that included 4,899 patients who were randomized to either IFX+ MTX (3,919 patients) or MTX alone (980 patients). They found that higher dose IFX(10 mg/kg) in combination with MTX may be more effective than the standard 3 mg/kg dose, particularly for patients with severe disease activity (159). The benefits of high-dose treatment appeared to accrue over time, and patients who received higher doses of IFXdid not experience a higher incidence of severe adverse events. The addition of oral low-dose steroids significantly enhanced IFXefficacy (159).

3.2.5.2 Adalimumab

ADA is a human monoclonal antibody that is given subcutaneously every 2 weeks. The addition of ADA at a

dosage of 20 mg, 40 mg, or 80 mg administered subcutaneously every other week to long-term MTX therapy in patients with active RA provided significant, rapid, and sustained improvement in disease activity over 24 weeks compared with MTX plus placebo (160).

Navarro-Sarabia et al (161) performed a systematic Cochrane Review with 6 studies including 2,381 patients and found that ADA in combination with MTX is efficacious and safe in the treatment of the rheumatoid arthritis. ADA 40 mg sc e.o.w. and 20 mg e.w. slows radiographic progression at 52 weeks (161). The PREMIER study found that patients with early, aggressive RA, when treated with combination therapy with ADA plus MTX results were significantly superior to either MTX alone or ADA alone in improving signs and symptoms of disease, inhibiting radiographic progression, and effecting clinical remission (162).

3.2.5.3 Golimumab

GLM (CNTO-148) is a novel anti-TNF-α human monoclonal antibody that blocks both soluble and transmembrane TNF-α. GLM is a human monoclonal antibody to TNF-α. The drug was derived from hybridomas generated from a transgenic mouse containing activated human immunoglobulin genes and inactivated mouse immunoglobulin genes for heavy chain and κ light chain (163). It is indicated in the treatment of adults with moderately to severely active rheumatoid arthritis in combination with MTX, in adults with active and progressive psoriatic arthritis, either alone or in combination with MTX, and in adult patients with active ankylosing spondylitis who have had an inadequate response to conventional therapies. GLM has generally been well tolerated in clinical trials with a safety profile comparable to other currently available TNF-α inhibitors. Its advantages are that it can be administered subcutaneously once monthly, it is labeled for patient self-administration and is suitable for both subcutaneous (SC) and intravenous administration (164).

Three phase III trials of SC administration of GLM have been conducted in 3 different subgroups of patients with RA. The GO-BEFORE trial was designed to assess the efficacy and safety of GLM administered every 4 weeks as monotherapy or in combination with MTX in patients with active RA who had not been previously treated with MTX (MTX-naïve) (165).

The GO-FORWARD trial was also designed to assess the efficacy and safety of GLM in patients with active RA despite MTX therapy (165). Results from this trial confirm the efficacy of GLM in patients with active RA despite MTX therapy that was observed in the Phase II trial (166), and demonstrate that 50 mg GLM or 100 mg GLM administered every 4 weeks in combination with MTX significantly reduces signs and symptoms and improves physical function in patients with RA (165). This study is the first double-blind, placebo-controlled prospective trial to demonstrate the efficacy of an anti-TNF-α agent in patients with active RA despite previous treatment with other TNF-α antagonist(s), and supports the use of GLM in patients who have experienced loss of efficacy, or are intolerant, to treatment with another TNF-α inhibitor (165).

Smolen and colleagues (167) showed that GLM reduced the signs and symptoms of rheumatoid arthritis in patients with active disease who had previously received one or more TNF-α inhibitors (167). The GLM in patients with active rheumatoid arthritis after treatment with tumor necrosis factor α inhibitors (GO-AFTER) study, a multicenter, randomized, double-blind, placebo-controlled, Phase III trial, found that subcutaneous injections of GLM 50 mg or 100 mg reduced the signs and symptoms of rheumatoid arthritis in patients with active disease who had previously received one or more TNF-α inhibitors (167).

Singh et al (168) performed a Cochrane Review which included 4 RCTs with 1,231 patients treated with GLM and 483 patients treated with placebo using American College of Rheumatology improvement criteria (ACR50),concluded that GLM is significantly more efficacious than placebo in treatment of patients with active RA, when used in combination with MTX. The short-term safety profile, based on short-term RCTs, is reasonable with no differences in total adverse events, serious infections, cancer, tuberculosis or deaths. Long-term surveillance studies are needed for safety assessment (168).

Although the primary end point (patients achieving a 50% ACR50 response at week 14) was not met, intravenously administered GLM plus MTX appears to have benefit in the longer-term reduction of RA signs/symptoms in MTX-resistant patients, with no unexpected safety concerns (169).

3.2.5.4 Certolizumab

CZP is a novel pegylated anti-TNF consisting of a Fab' attached to a 40-kDa PEG moiety, which is approved for the treatment of adult patients with moderately to severely active RA. Attachment of PEG to the Fab' increases the plasma half-life of CZP to approximately 2 weeks, allowing dosing every 2 or 4 weeks,

and may contribute to the preferential distribution of the drug to inflamed tissues that has been observed in animal models (170). CZP lacks an Fc region, so it does not induce complement- or antibody-dependent cell-mediated cytotoxicity, which has been observed in vitro with ADA, ETN and IFX(171).Three published clinical trials of CZP in RA in patients with active disease who have shown an inadequate response to DMARDs, including MTX, RA prevention of structural damage (RAPID 1 (172) and 2 (173), which evaluated the efficacy and safety of CZP added to MTX when dosed every 2 weeks, and efficacy and safety of CZP - 4 weekly dosage in rheumatoid arthritis (FAST4WARD) (174) which evaluated CZP monotherapy when dosed every 4 weeks (175).

The REALISTIC (RA Evaluation In Subjects Receiving TNF Inhibitor Certolizumab Pegol) multicenter Phase IIIb study included a 12-week, randomized, double-blind (DB), placebo-controlled phase followed by an open-label extension (> 16 weeks) (176). REALISTIC was designed to investigate the safety and efficacy of CZP in a broad patient population with active RA more closely resembling routine clinical practice, versus the pivotal trials, including patients with or without prior TNF-inhibitor exposure, with or without concomitant MTX or other disease-modifying antirheumaticdrugs (DMARDs), and varying lengths of disease duration. The primary endpoint of an ACR20 score at week 12 was met. At week 12, more than half (51.1%) of patients in the CZP treatment group achieved ACR20 response versus the control group (25.9%) (176).

Strand and colleagues (177) examined data from the Rheumatoid Arthritis PreventIon of structural Damage (RAPID) 2 trial to investigate the number needed to treat (NNT) based on patients reporting improvements ≥ minimal clinically important differences (MCID), correlations between individual patient reported outcomes (PROs) and other clinical parameters, and times to onset of "responses" (improvements ≥ MCID) as predictors of disease activity at week 24 (177). CZP 200 mg and 400 mg plus MTX were associated with rapid, clinically meaningful improvements in all PROs. The NNT for participants to report changes ≥ MCID in up to 5 PROs was 2 to 3, and 5 for all 6 PROs (pain, PtGA, physical function, fatigue and short-form 36-item Physical and Mental Component Summary Scores). More patients with improvements ≥ MCID in pain at week 6 than those at week 12 had lower disease activity at week 24. Week 12 pain responders had better clinical outcomes at week 24 than non-responders (177).

4.0 Non-Tnf Blocker Baras

4.1 Tocilizumab

A chimeric antibody to the IL-6 receptor that blocks both soluble and membrane-bound IL-6 activity was found to inhibit collagen-induced arthritis in cynomolgus monkeys, paving the way for human trials targeting this pathway (178,179). The first trial to evaluate inhibition of structural damage with TCZ was the SAMURAI (Study of Active Controlled Monotherapy Used for Rheumatoid Arthritis an IL-6 Inhibitor) study (180). The first results from a European study of TCZ, CHARISMA, (Chugai Humanized Anti-Human Recombinant Interleukin-6 Monoclonal Antibody) were published in 2006 (181).

A 20% response (improvement) according to the American College of Rheumatology criteria (ACR20 response) was achieved by 61% and 63% of patients receiving 4 mg/kg and 8 mg/kg of TCZ as monotherapy, respectively, and by 63% and 74% of patients receiving those doses of TCZ plus MTX, respectively, compared with 41% of patients receiving placebo plus MTX (181). Statistically significant ACR50 and ACR70 responses were observed in patients receiving combination therapy with either 4 mg/kg or 8 mg/kg of TCZ plus MTX ($P < 0.05$). A dose-related reduction in the Disease Activity Score in 28 joints was observed from week 4 onward, in all patients except those receiving monotherapy with 2 mg/kg of TCZ (181).

4.1.1 The OPTION study (Tocilizumab Pivotal Trial in Methotrexate Inadequate Responders)

This was a double-blind, randomized, placebo controlled trial of 623 participants with moderately to severely active RA, who had not adequately responded to MTX (182). Significantly more participants receiving TCZ also achieved ACR50 and ACR70 responses, compared to those in the placebo group (183).

The RADIATE (Research on Actemra Determining Efficacy after Anti-TNF Failures) trial studied a combination of TCZ with MTX in RA patients refractory to TNF antagonist therapy (184). Another randomized, double-blind, placebo-controlled Phase III trial (TOWARD, Tocilizumab in Combination with Traditional DMARD Therapy) evaluated 1,220 patients with active disease, despite stable doses of DMARDs (the most common being MTX) randomized to receive monthly TCZ or placebo infusions (185). At 24 weeks, the TCZ group had significantly improved ACR20 response rates and significantly improved DAS28 scores, as well as, signifi-

cantly, rates of remission (also by DAS28) (183).

Improvements in function (measured with the HAQ) and fatigue (measured with FACIT-F) were also significantly greater in the patients in the TCZ group (183). Finally, The AMBITION study (Actemra versus Methotrexate Double-Blind Investigative Trial in Monotherapy) assessed the efficacy of TCZ compared with MTX in an MTX-naïve population (186). At 24 weeks, patients in the TCZ-treated groups were 5-times more likely to achieve DAS28 remission and 4-times more likely to achieve at least a moderate EULAR response than in the MTX-treated group (183).

An initial dose of 4 mg/kg by IV infusion every 4 weeks is recommended (presumably because of the lower toxicity profile at this dose), with an increase to 8 mg/kg in the event of an inadequate clinical response, although there are no guidelines on the timing of this decision (183). Singh and colleagues (187) published a Cochrane Review to assess the efficacy and safety of TCZ in patients with RA using the data from published randomized or quasi-randomized controlled trials (RCTs). Eight RCTs were included in this systematic review with 3,334 participants; 2,233 treated with TCZ and 1,101 controls. Of the 2,233, 1,561 were treated with TCZ 8 mg/kg every 4 weeks, which is the approved dose. In patients taking concomitant MTX, compared to placebo, TCZ-treated patients were 4 times more likely to achieve ACR50 (absolute %, 38.8% versus 9.6%), 11 times more likely to achieve Disease Activity Score (DAS) remission (absolute %, 30.5% versus 2.7%), 1.8 times more likely to achieve a clinically meaningful decrease in Health Assessment Questionnaire (HAQ/mHAQ) scores (absolute %, 60.5% versus 34%), 1.2 times more likely to have any adverse event (absolute %, 74% versus 65%) and 0.6 times less likely to withdraw from therapy for any reason (absolute %, 8.1% versus 14.9%) (187). TCZ is beneficial in decreasing RA disease activity and improving function. TCZ treatment was associated with a significant increase in cholesterol levels and in total adverse events. Larger safety studies are needed to address these safety concerns (187). In the LITHE study Kremer and colleagues (188) reported that TCZ plus MTX results in greater inhibition of joint damage and improvement of physical function than does MTX alone, and TCZ has a well-characterized safety profile (188).

4.2 Abatacept

ABT is a soluble human fusion protein that is approved for the treatment of adults with moderately to severely active RA in a number of countries, including the United States (189), Canada (190), and the European Union (191). Structurally, ABT consists of the extracellular domain of human cytotoxic T-lymphocyte–associated antigen 4 (CTLA4) linked to the modified Fc portion of human immunoglobulin G1 (190). ABT selectively modulates the CD80/CD86:CD28 costimulatory signal required for full T-cell activation, downregulating subsequent immune-effector mechanisms (e.g., production of proinflammatory cytokines, autoantibodies, and joint-eroding enzymes) (190,192). The modified Fc portion of ABT is not active; thus, ABT is not associated with adverse events (AEs) resulting from either complement- or antibody-dependent cell-mediated cytotoxicity (192).

In 2 trials of patients whose RA had been refractory to MTX, those who received ABT had significantly less radiographic progression compared with those who received placebo ($P = 0.01210$ and $P < 0.0113$). After one year of treatment in the AIM (Abatacept in Inadequate Responders to Methotrexate) trial (193), the median changes from baseline in Genant-modified total Sharp scores were 0.25 (25th and 75th percentiles: 0.0 and 1.8, respectively) with ABT and 0.53 (25th and 75th percentiles: 0.0 and 2.5) with placebo ($P = 0.012$). Thus, statistically, ABT significantly reduced disease activity in patients with RA and an IR compared to MTX (193).

The improvements in signs and symptoms, physical function, and health related quality of life (HRQOL) observed after one year of ABT treatment were maintained through 2 years of treatment (194). This durability was accompanied by a safety profile consistent with that in the double-blind portion of the study. Radiographic progression was further inhibited in year 2 compared with year one, suggesting an increasing effect of ABT on the inhibition of structural damage in year 2 (194). ABT also has been reported to be effective in patients whose RA is refractory to TNF-α inhibition. After 6 months of treatment in ATTAIN (Abatacept Trial in Treatment of Anti-TNF Inadequate Responders) (195), ACR response rates were significantly higher with ABT compared with placebo (ACR20: 50.4% vs. 19.5%, respectively [$P < 0.001$]; ACR50: 20.3% vs. 3.8% [$P < 0.001$]; and ACR70: 10.2% vs. 1.5% [$P = 0.003$]).

Schiff et al (196) conducted ATTEST (Abatacept or Infliximab vs. Placebo, a Trial for Tolerability, Efficacy and Safety in Treating Rheumatoid Arthritis) assessing the efficacy and safety profile of ABT (approximately10 mg/kg every 28 days via IV infusion) or IFX(3 mg/kg every 56 days via IV infusion) compared with placebo in 431 biologic-naive patients with RA who had an inad-

equate response to MTX. The authors concluded that ABT has a more acceptable safety profile than IFXin the population studied (197).

As reported by Weinblatt et al (198), ASSURE (Abatacept Study of Safety in Use With Other RA Therapies) was a placebo-controlled trial of the safety profile of ABT added to background traditional nonbiologic and/or biologic DMARDs over one year. Based on the less favorable safety profile of ABT plus background biologic DMARDs relative to ABT plus nonbiologic DMARDs, as well as a lack of added benefit, the authors concluded that ABT should not be combined with biologic DMARD therapy (197).

The multicenter, open-label, 6-month, Phase IIIb ARRIVE (Abatacept Researched in RA Patients with an Inadequate Anti-TNF Response to Validate Effectiveness) trial, reported by Schiff et al (199), was the first to evaluate a direct switch from an anti-TNF agent to ABT without a washout period. Westhovens et al (200) reported one-year results from AGREE (Abatacept Study to Gauge Remission and Joint Damage Progression in Methotrexate-Naive Patients with Early Erosive RA) is this study called AGREE ? Could not find that in the article) , a 2-year study assessing the efficacy and safety profile of ABT plus MTX compared with MTX alone in MTX-naive patients with early RA who had factors associated with poor radiographic outcome (positive for rheumatoid factor and/or anti–cyclic citrullinated peptide, evidence of erosions). The combination of ABT and MTX provided significantly better clinical and radiographic efficacy compared with MTX alone and had a comparable favorable safety profile (200).

The integrated safety analysis by Sibilia and Westhovens (201) included data from the 5 core ABT trials (2 Phase IIb studies and the Phase III AIM, ATTEST, and ASSURE trials). The trials enrolled a total of 2,944 patients, 460 in the Phase IIb studies and 2,484 in the Phase III trials. Discontinuations due to serious adverse events (SAEs) occurred with a numerically higher frequency in patients receiving ABT compared with placebo (2.8% vs. 1.6%). Serious infections occurred in 3.0% and 1.6% of patients. Emery et al (202) revealed that ABT delayed progression of undifferentiated arthritis or very early RA in some patients. An impact on radiographic and MRI inhibition was seen, which was maintained for 6 months after treatment stopped. This suggests that it is possible to alter the progression of RA by modulating T-cell responses at a very early stage of the disease (202).

4.3 Rituximab

RTX, a chimeric monoclonal antibody directed against CD20 that effectively depletes B cells in peripheral blood can be used for the treatment of patients with RA who have failed to obtain benefit from conventional therapy and anti-TNF-α agents or those patients who may have lost an effective response, developed toxicity, or have contraindications to these agents (203). Several trials suggest 6-month fixed intervals (204-208) of RTX therapy may lead to optimal RA control retreatment.

The IMAGE trial was a double-blind, randomized controlled Phase III study which included 755 MTX-naïve patients with active RA who were randomly assigned to MTX alone, RTX 2×500 mg + MTX or RTX 2×1000 mg + MTX (186). The primary end point at week 52 was the change in joint damage measured using a Genant-modified Sharp score. Treatment with RTX 2×1000 mg in combination with MTX is an effective therapy for the treatment of patients with MTX-naïve RA (209).

The Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE) (210) then evaluated the efficacy and safety of different doses and retreatment of RTX: a randomized, placebo-controlled trial in patients who are biological-naïve with active rheumatoid arthritis and an inadequate response to MTX. Emery found that RTX (at 2 x 500 mg and 2 x 1000 mg) plus MTX significantly improved clinical outcomes at week 24, which were further improved by week 48. No significant differences in either clinical or safety outcomes were apparent between the RTX doses (210).

Results from the SUNRISE trial (211) demonstrated that 2 courses of RTX about 6 months apart resulted in improved and sustained efficacy at one year, compared with one course, with a similar safety profile.

The safety of RTX has been evaluated in the short-term (6 months) and in the medium-term (up to 10 years) in patients who had been previously treated with antagonists of tumor necrosis factor (a-TNF) and/or with MTX and in patients who had not. Data obtained from clinical trials demonstrated that RTX is well tolerated either after a single course or after multiple courses. The overall rate of adverse events was stable after the first 3 courses. The most frequent adverse event was infusion-related reactions (IRR) (212).

Vander Cruyssen et al described the results of the Belgian "MabThera In Rheumatoid Arthritis (MIRA)" registry which suggested that treatment of RA patients with RTX could be optimized by earlier retreatment (213).

Vital et al found that RA patients whose disease did not respond to an initial cycle of RTX have higher circulating pretreatment plasma cell numbers at baseline and incomplete depletion (214). Their findings suggested that an additional cycle of RTX administered prior to total B cell repopulation enhances B cell depletion and clinical responses (214).

In RA, B cell "depletion" occurs in all patients treated with RTX, but the clinical responses to RTX are variable. The degree of "depletion" may be complete or partial. At 12 months, 59% of complete responders had a moderate-to-good EULAR response, compared with 21% of those with partial depletion (P=0.01). Patients in whom B cells were depleted only after the second infusion did no better than those in whom depletion was never complete and had poorer clinical outcomes than those in whom depletion was initially complete (215). Dass and colleagues, using a highly sensitive analysis, demonstrated that RTX therapy is associated with variable diminution in B cell numbers. A lack of complete depletion of B cells after one infusion was associated with a poorer outcome (215).

The B-cell chemokine, CXCL13, is a proposed serum biomarker of synovitis in RA. Serum CXCL13 is predictive of the rate of B-cell repopulation following a course of RTX in RA (216). Serum CXCL13 correlates with synovial CXCL13 measured at a single joint, suggesting synovitis as an important source of circulating CXCL13. Within the synovium, CXCL13 expression is highly correlated with markers of synovitis (216).

Lee et al performed a meta-analysis of RCTs to determine the treatment efficacy and safety outcomes of RTX (one course, consisting of 2 infusions of 1,000 mg each) concomitant with MTX (217). The 3 RCTs included 938 DMARD or TNF-blocker-resistant or intolerant RA patients. Follow-up periods ranged from 24 to 48 weeks. ACR20, ACR50, and ACR70 response rates were significantly higher for the RTX plus MTX than for placebo controls (primary efficacy outcome, ACR50; risk ratio [RR] 3.648, 95% confidence interval [CI] 2.478-5.369, P < 0.001). For those treated with RTX, the incidence of adverse events of all systems were not higher than in those treated with placebo (RR 1.062, 95% CI 0.912-1.236, P = 0.438). With respect to the number of patients that experienced at least one serious adverse event, no significant difference was observed between patients treated with RTX and placebo (RR 0.855, 95% CI 0.622-1.174, P = 0.333). A single course of RTX with concomitant MTX therapy was found to be effective in DMARD or TNF-blocker-resistant or intolerant patients with active RA (217).

4.4 Anakinra

ANA (Kineret) is a recombinant form of a human interleukin-1 receptor antagonist (IL-1ra) and is the first biologic agent designed specifically to modify the biological immune response of IL-1. Mertens and Singh (218) performed a Cochrane review which included 5 trials involving 2,876 patients, 781 randomized to placebo and 2,065 to ANA (these numbers do not add up: 781 + 2,065 = 2,846 NOT 2,876) and concluded that anakinra is a relatively safe and modestly efficacious therapy for rheumatoid arthritis (218).

Thirty-two patients treated with ANA (100 mg/day subcutaneously) and MTX were categorized as responders when their 28-joint DAS (DAS-28) had decreased by ≥ 1.2 at 3 months. Pre-treatment blood samples had been drawn. For 7 responders and 7 non-responders, 52 microarray-identified mRNAs were expressed as a function of the response to treatment, and unsupervised hierarchical clustering correctly separated responders from non-responders. The levels of 7 of these 52 transcripts, as assessed by real-time, quantitative RT-PCR, were able to accurately classify 15 of 18 other patients (8 responders and 10 non-responders), with 87.5% specificity and 77.8% negative-predictive value for responders (219).

5.0 Combination Therapy for RA

At least in certain subpopulations it appears that a combination of "usual RA therapies" may be more effective than monotherapy. Some clinicians still practice by starting with MTX monotherapy because they feel it is cost-effective (220). In patients with RA, measure of C-reactive protein and swollen joint count after 12 weeks of MTX monotherapy emerged as the factors most associated with radiographic progression at Week 52 (221). If an inadequate response is encountered, or perhaps also in patients with high C-reactive protein levels or high swollen joint counts, combination therapy (the use of 2 or more pharmacologic agents) appears to be associated with favorable outcomes (222-224). In the future, it is conceivable that early combination therapy may be useful for patients with biomarkers potentially predictive of progressive radiographic destruction such as baseline ACPA isotype profile with multiple isotypes (225), high plasma levels of hepatocyte growth factors (HGF) (226), and/or high serum adiponectin levels (227). Combination therapy achieving better outcomes than

when either agent is used alone is generally due to synergism. Additionally, this may lead to lower doses of agents being used with reduced adverse effects. In fact, certain combination therapy such as ETN in combination with MTX ameliorates RA activity by normalizing the distribution of TH17 and Treg, and other related cytokines, which may partly explain the mechanism of combined therapy of ETN plus MTX in RA treatment (228).

5.1 "Tight Control" of RA

Clinical trials demonstrate that intensive treatment of early rheumatoid arthritis with a combination of DMARDs improves short-term outcomes. An extension study from a pivotal trial has now shown that such intensive early therapy can achieve a reduction in the rate of erosive progression over a period of 11 years (229).

Both intensive steering strategies and intensive medication strategies resulted in better outcomes than less intensive strategies in patients with early active RA (230). Proof in favor of any particular steering therapeutic method in efforts to achieve remission of synovitis and disease activity is lacking, and the best medication sequence is still not known (230).

The Finnish Rheumatoid Arthritis Combination Therapy trial (231), which compared DMARD combination therapy against DMARD monotherapy in patients with early RA, suggested that the use of early aggressive combination DMARD therapy could alter the course of the disease by inducing long-lasting remission (47). In the combination group, patients received SSZ, MTX, hydroxychloroquine, and prednisolone. Treatment was intensified by increasing the doses of MTX and prednisolone at 3 months if improvement in 2 of the 3 measures (swollen joint score; tender joint score; and ESR or CRP) was < 50%. In the monotherapy arm, patients initially received SSZ, the dose of which was increased if clinically indicated (47).

The multicenter randomized BeSt (Behandel-Strategieen; "treatment strategies") study assessed 4 different treatment strategies to induce remission in 508 patients with early RA (232). This study confirmed that remission is possible with early aggressive combination therapy and introduced the "treat-to-target" concept.

Remission in rheumatic diseases is usually defined as remission while receiving therapy, not drug-free remission as is sometimes presumed in other diseases (233). The definition of remission in this trial was a (DAS28 less than 1.6. All patients were treated to a target DAS28 less than 1.6 (210). If the DAS28 was maintained at less than 1.6 for more than 6 months, DMARD therapy was discontinued. When the DAS28 increased to more than 1.6, treatment with the last DMARD that the patient used was restarted. During the 5-year period, drug-free remission was achieved in 115 of 508 patients (23%); of those, it was maintained in 59 patients (51%) for a median of 23 months. A total of 53 patients (40%) (how was this percentage figured? 53 is 40% of what?) needed to restart DMARD therapy; of those, 39 (74%) achieved remission again within 3 to 6 months (232). A multivariable analysis showed that the predictors for restarting therapy were the presence of anti-CCP, the last DMARD used being sulfasalazine, low (good) baseline functional score, and a high baseline DAS28 (232).

The study also supported that initial treatment should be aggressive, with early use of biologic therapy considered, and that treatments should be altered quickly (either by dose escalation or switching to alternative effective agents) if the patient is not achieving the desired low level of disease activity (47).

The TICORA (Tight Control of Rheumatoid Arthritis) study compared an intensive management strategy with routine care in 111 patients with active RA (45). During this 18-month study, the mean decrease in DAS was significantly greater in the intensive management group than in the routine care group (–3.5 vs. –1.9, respectively; $P < 0.0001$), and more patients in the intensive management group had a good response (decrease in DAS ≥ 1.2, 82% vs. 44%; $P < 0.0001$) or were in remission (DAS < 1.6, 65% vs. 16%; $P < 0.0001$) than patients receiving routine care.

The open-label CAMERA (Computer Assisted Management in Early Rheumatoid Arthritis) trial (234) in intensive treatment with MTX was compared with conventional MTX treatment in patients with early RA. In the intensive treatment group, 50% of patients achieved at least one period of remission during the 2-year trial compared with 37% of those receiving conventional treatment ($P = 0.03$). Efficacy was significantly greater in the intensive group for almost all clinical variables, including morning stiffness ($P = 0.009$), ESR ($P = 0.007$), tender joint count ($P < 0.001$), swollen joint count ($P < 0.001$), VAS general well-being ($P < 0.001$), and VAS pain ($P = 0.001$) (47).

In a pilot study, 21 patients with early RA were treated with an intensified COBRA regimen (SSZ, MTX, and high-dose step-down prednisolone, intensified by adding hydroxychloroquine and continued low-dose prednisolone) with the option to further intensify MTX

treatment after 8 or 21 weeks and to add IFXtherapy after 21 Weeks (235). After 40 weeks of treatment, an impressive 19/21 patients (90%) had achieved remission (DAS28 < 2.6) (47).

Tanaka and coworkers (236) followed 2,775 patients in an observational cohort study for which 3 years of data were available. A significant correlation was found between tight disease control (DAS28 < 2.6) and functional disability score (using the Japanese version of the HAQ); tight control was significantly associated with improving functional capability. Sano and colleagues (237) conducted a study in patients receiving anti-TNF treatment for ≥ 1 year found that mean DAS28 among patients who did not require joint surgery (n=70) was significantly lower (P < 0.001) than among patients who required joint surgery (n=21) (237). The authors concluded that tight disease control was important in reducing the need for joint surgery among patients receiving biologic therapy (47).

6.0 RA Treatment Guidelines

EULAR recommendations for the management of RA with synthetic and biological disease-modifying antirheumatic drugs lead to a final set of 15 recommendations for the management of RA (52):

- Treatment with synthetic DMARDs should be started as soon as the diagnosis of RA is made
- Treatment should be aimed at reaching a target of remission or low disease activity as soon as possible in every patient; so long as the target has not been reached, treatment should be adjusted by frequent (every 1–3 months) and strict monitoring
- MTX should be part of the first treatment strategy in patients with active RA
- When MTX contraindications (or intolerance) are present, the following DMARDs should be considered as part of the (first) treatment strategy: leflunomide, SSZ or injectable gold
- In DMARD naïve patients, irrespective of the addition of GCs, synthetic DMARD monotherapy rather than combination therapy of synthetic DMARDs may be applied
- GCs added at low to moderately high doses to synthetic DMARD monotherapy (or combinations of synthetic DMARDs) provide benefit as initial short-term treatment, but should be tapered as rapidly as clinically feasible
- If the treatment target is not achieved with the first DMARD strategy, addition of a biological DMARD should be considered when poor prognostic factors are present; in the absence of poor prognostic factors, switching to another synthetic DMARD strategy should be considered
- In patients responding insufficiently to MTX and/or other synthetic DMARDs with or without GCs, biological DMARDs should be added (Current practice would be to start a TNF inhibitor [ADA, certolizumab, ETN, GLM, infliximab])
- Patients with RA for whom a first TNF inhibitor has failed, should receive another TNF inhibitor, ABT, RTX or TCZ
- In cases of refractory severe RA or contraindications to biological agents or the previously mentioned synthetic DMARDs, the following synthetic DMARDs might also be considered, as monotherapy or in combination with some of the above: azathioprine, cyclosporin A (or exceptionally, cyclophosphamide)
- Intensive medication strategies should be considered in every patient, although patients with poor prognostic factors have more to gain
- If a patient is in persistent remission, after having tapered GCs, one can consider tapering biological DMARDs, especially if this treatment is combined with a synthetic DMARD
- In cases of sustained long-term remission, cautious titration of synthetic DMARD dose could be considered, as a shared decision between patient and doctor
- DMARD naïve patients with poor prognostic markers might be considered for combination therapy of MTX plus a biological agent

When adjusting treatment, factors apart from disease activity, such as progression of structural damage, comorbidities and safety concerns should be taken into account (52).

When patients have active RA disease despite an adequate trial of MTX for 3 months, another agent(s) should be added. Trial data exist to support the use of many commercially available medications added to MTX including leflunomide (238), ETN (239), SSZ (240), hydroxychloroquine (240), SSZ+hydroxyl chloroquine (240), IFX(241), ANA (242), ADA (243), gold (244) RTX (245), ABT (193), GLM (246), certolizumab (247) and TCZ (182).

Several approaches have been studied in patients who have failed the combination of MTX and at least one TNF inhibitor: switching to another TNF inhibitor 167,248-250), adding rituximab (251) to existing MTX,

adding ABT to existing MTX (252) or adding TCZ to MTX (184).

Nam and colleagues (253) performed a systematic review in effort to review the evidence for the efficacy and safety of 9 biological agents in patients with RA to provide data to develop treatment recommendations by the EULAR Task Force, including: IFX, ETN, ADA, CZP, GLM, ANA, ABT, RTX and TCZ (253).

Eighty-seven articles and 40 abstracts were identified. In MTX-naïve patients, biological therapy with IFX, ETN, ADA, GLM or ABT has been shown to improve clinical outcomes (level of evidence 1B). In MTX/other synthetic DMARD failures, all 9 biological agents confer benefit (1B), with lower efficacy noted for ANA. RTX, ABT, TCZ and GLM demonstrate efficacy in tumor necrosis factor inhibitor (TNFi) failures (1B) (253).

Biological and MTX combination therapy is more efficacious than a biological agent alone (1B), particularly within the first 6 months of treatment initiation; increased tuberculosis (TB) rates with TNF inhibitors are highest with the monoclonal antibodies (3B) (253). There is good evidence for the efficacy of biological agents in patients with RA. Safety data confirm an increased risk of bacterial infection and TB with TNF inhibitors compared with conventional DMARDs (253).

Salliot and colleagues (254) performed a meta-analysis of randomized clinical trials of patients with inadequate response (IR)-MTX; anti-TNFs demonstrated a higher probability of achieving an ACR50 response than abatacept. In IR-anti-TNF, no difference was found among RTX, ABT, and GLM (254).

7.0 Future Potential Treatment Directions

New biological agents in development include drugs that target proximal effects of the immune response and growth factors for T-cell subsets (such as interleukin 17) (232). New conventional drugs with DMARD-like properties might also have important future roles. Clinical trials of inhibitors of the kinases tyrosine Janus kinases (JAK) and spleen tyrosine kinase (Syk) have provided promising data, and other targets are under investigation (256,257).

7.1 JAK Signaling

JAK can be activated by interferon-γ and other cytokines playing a significant role in the pathogenesis of RA (258). Pfizer developed a JAK3 inhibitor, tofacitinib (CP-690,550), which has already been in a Phase II clinical trial in participants with moderately- to severely-active RA who had an inadequate response to MTX alone (259). In Japanese patients with active RA and an inadequate response to MTX alone, tofacitinib in combination with MTX over 12 weeks was efficacious and had a manageable safety profile (259). The most commonly reported AEs were nasopharyngitis (n=13), and increased alanine aminotransferase (n=12) and aspartate aminotransferase (n=9). AEs were mild or moderate in severity (259).

A proof-of-concept 6-week trial in which CP-690,550 was given as monotherapy was associated with highly efficacious responses at the mid and higher twice-daily dose ranges employed (260). A subsequent 24 week dose-ranging trial in which CP-690,550 was administered in combination with MTX showed ACR20 responses, which were also statistically significant versus placebo interventions. CP-690,550 treatment was associated with side effects, which included headache and nausea. Infections were more common versus placebo as were elevations in transaminase enzymes when administered in combination with MTX, and increases in low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol (260). There are currently 5 ongoing Phase III trials of the CP-690,550 janus kinase (JAK) inhibitor (260).

UR-67767 is a balanced JAK selective inhibitor, and is a potential drug used for the treatment of RA. It exhibits balanced equipotency for all JAK isoenzymes, and nanomolar activity in human cells.

7.2 Syk Signaling

Syk is a key molecule in the intracellular signaling pathway in several cells involved in immune response. It regulates the production and activities of multiple cytokines and matrix metalloproteinases. Also, its activation plays a key role in the TNFα induced expression of proinflammatory cytokines and proteolytic enzymes by synovial fibroblasts (261). Syk inhibitors are small molecules and therefore potential oral biologic agents. Inhibition of Syk in murine models of inflammatory arthritis has successfully decreased synovial inflammation (262). R788 (fostamtinib disodium) is an oral prodrug that is rapidly converted to a potent and relatively selective inhibitor of Syk (R406) (240). Use of an Syk kinase inhibitor (Fostamatinib disodium) has produced very good results with regard to attenuation of clinical activity of RA (257,264,265).

Weinblatt and colleagues (265) conducted a multicenter, randomized, double-blind, placebo-controlled trial of the Syk inhibitor R788 (265). A total of 457 pa-

tients with active RA despite MTX treatment were randomly assigned to receive 2 doses of R788 or placebo. The primary outcome was 20% improvement in the ACR 20 at 6 months (265).

In the R788 groups, ACR 20 responses were observed in the first week of treatment in many patients. These responses occurred in 67%, 57%, and 35% of patients receiving 100 mg of R788 twice daily, 150 mg of R788 daily, and placebo, respectively ($P < 0.001$). Both R788 groups had higher ACR 50 and ACR 70 responses (that is, 50% and 70% improvement in ACR criteria) as well as improvement in the DAS28 compared with the placebo group (265).

Diarrhea was a common adverse effect, occurring in 19% of patients receiving 100 mg of R788 twice daily, 12% of those receiving 150 mg of R788 daily, and 3% of those receiving placebo. Other adverse effects more frequently seen in the R788 groups were upper respiratory tract infections and neutropenia (265).

PRT062607, a novel, oral Syk-specific kinase inhibitor treats chronic inflammatory diseases, including RA and certain cancers. PRT062070, a dual Syk-JAK inhibitor, has been shown to be a highly potent inhibitor of Syk and the JAK family kinases in a broad panel of in vitro kinase and cellular assays.

7.3 Cathepsin Inhibitors

Cathepsin K (EC 3.4.22.38) is expressed by osteoclasts and synovial fibroblasts and its proteolytic activity is hypothesized to play a role in the pathology of RA. Svelander and colleagues (266) explored the effects of the cathepsin K inhibitor N-(1-{[(Cyanomethyl)amino] carbonyl}cyclohexyl)-4-[2-(4-methylpiperazin-1-yl)-1,3-thiazol-4-yl]benzamide (L-006235) in murine collagen-induced arthritis (266).

After prophylactic or therapeutic administration, L-006235 significantly reduced biomarkers reflecting bone and cartilage degradation. Pathological changes at the histological level were significantly reduced after prophylactic treatment ($P<0.01$), but not after therapeutic treatment. Prophylactic treatment with L-006235 delayed disease onset ($P<0.01$) and reduced the disease severity score ($P<0.05$) (266).

7.4 NF-kB Inhibitors

Activation of the nuclear factor-κB (NF-κB) family of transcription factors results in the expression of numerous genes involved in the regulation of the innate and adaptive immune responses, and has been implicated as a key mechanism in chronic inflammatory diseases including RA. The IκB kinases (IKKs) are key components in the signaling pathway by which proinflammatory stimuli, such as lipopolysaccharide and tumor necrosis factor-α lead to the activation of NF-κB. The most widely studied of the IKKs is IKKβ. Inhibitors of the kinase activity of IKKβ offer opportunities for intervention in RA, as well as other inflammatory disorders. Some examples for which the most extensive data are available will here be reviewed (267).

Konda et al (268) suggest that in a mouse model of RA, the multikinase inhibitor META060 , which inhibits NF-kappaB activation and expression of markers of inflammation ; reduces swelling in a model of acute inflammation and inhibits bone and cartilage destruction in a model of chronic inflammation. Its efficacy is associated with the inhibition of multiple protein kinases, including Syk, Btk, PI 3-kinase, and GSK3. These results warrant further clinical testing of META060 for its therapeutic potential in the treatment of inflammatory diseases (268). Osteoclast activity depends on RANKL, which is inhibited by denosumab, an investigational fully human monoclonal IgG2 antibody against RANKL. Sharp and colleagues (269) conducted a randomized placebo controlled study which included 227 patients with active erosive RA and found that twice-yearly injections of denosumab with ongoing MTX treatment significantly reduced cortical bone loss in RA patients for up to 12 months.

7.5 Cytokine Inhibitors

7.5.1 Newer IL-1 Inhibitors

In efforts to develop a "new generation" of IL-1 inhibitors, attempts at increasing the affinity to IL-1, improving efficacy, decreasing the risks of local adverse effects, and signaling the dosing led to the development of canakinumab (ACZ885), a humanized monoclonal antibody targeting IL-1. Its mode of action is based on the neutralization of IL-1β signaling, resulting in suppression of inflammation in patients with disorders of autoimmune origin (270). In June 2009 the drug was approved by the US Food and Drug Administration for the treatment of familial cold auto-inflammatory syndrome and Muckle-Wells syndrome, which are inflammatory diseases related to cryopyrin-associated periodic syndromes. The drug is currently being evaluated for its potential in the treatment of RA (270).

7.5.2 IL-17 Inhibitor

Th17 cells, a subset of memory T-cells that play a key role in an autoimmune inflammation, are a major source of IL-17. IL-17 increases production of several proinflammatory cytokines such as IL-1, IL-6, or TNFα and regulates osteoclastogenesis. Inhibition of IL-17 generated successful results in the treatment of an experimental arthritis model (271). Hueber and colleagues (272) investigated the efficacy and safety of AIN457, a human antibody to IL-17A, in patients with psoriasis, rheumatoid arthritis, and chronic noninfectious uveitis. Patients with chronic plaque-type psoriasis (n=36), RA (n=52), or chronic noninfectious uveitis (n=16) were enrolled in clinical trials to evaluate the effects of neutralizing IL-17A by AIN457 at doses of 3 to 10 mg/kg, given intravenously. AIN457 treatment induced clinically relevant beneficial responses of variable magnitude in patients suffering from each of these diverse immune-mediated diseases. The rates of adverse events, including infections, were similar in the AIN457 and placebo groups. These results support further study to determine if there is a role for IL-17A in the pathophysiology of diverse inflammatory diseases including psoriasis, RA, and noninfectious uveitis (272).

7.5.3 IL-23 Inhibitor

A positive effect of an IL-23 blocking antibody was described in collagen induced arthritis (273) and one proof-of-concept study has shown that besides associated psoriatic skin lesions, ustekinumab treatment can also reduce the signs and symptoms of arthritis in patients with psoriatic arthritis (274). Clinical trials of ustekinumab in the treatment of RA are in progress.

7.5.4 Interference with RANK Signaling

Osteoblasts/stromal cells produce osteoprotegerin (OPG), a decoy receptor which binds RANKL, thus preventing binding to RANK and also preventing the resultant osteoclast activation and bone destruction from RANK agonism. Similar to TNF, RANKL is abundantly produced by infiltrating T cells and synoviocytes in RA (275-278).

Amgen created a recombinant Fc-OPG (AMGN-0007) to treat multiple myeloma and bone metastatic breast cancer. Results from the Phase I trial were encouraging, in that Fc-OPG was well tolerated and its inhibitory effects on bone resorption were similar to the bisphosphonate, pamidronate (279). However, due to the superior efficacy of their newer agent, denosumab (AMG-162) – a fully human monoclonal antibody that specifically neutralizes RANKL – at inhibiting bone resorption, and concerns regarding deleterious OPG-mediated protection from TRAIL mediated apoptosis in cancer cells, Amgen ceased further clinical development of AMGN-0007 (280).

The US Food and Drug Administration approved denosumab (Xgeva) on November 19, 2010 to help prevent skeletal-related events (SREs) in patients with cancer that has spread (metastasized) and damaged the bone (SREs include bone fractures from cancer and bone pain requiring radiation). Denosumab is not approved for patients with multiple myeloma or other cancers of the blood, and is certainly not FDA-approved for the treatment of RA. However, intuitively, by examining its mechanism of action, it seems that denosumab should be able to inhibit some of the bone destruction associated with RA.

Deodhar and colleagues (281) found that in patients with RA, denosumab provided protection against erosion, and not only prevented bone loss but increased hand bone mineral density as measured by dual x-ray absorptiometry.

8.0 Conclusion

RA is a chronic inflammatory disease affecting millions of persons worldwide, largely affecting synovial joints and thought to have an autoimmune basis. It may progress to an advanced illness with severe joint damage and deformity associated with substantial morbidity. RA affects each individual differently and there is a wide spectrum of varying degrees of pain, stiffness, function, joint deformity, disability, and extra-articular effects. RA is a potentially crippling condition that is usually associated with moderate to severe pain as well as patients possibly experiencing suffering, reduced quality of life, isolation/loneliness, and diminished physical functioning. Knowledge surrounding the pathophysiology of RA is rapidly changing. As clinicians understand and appreciate this pathophysiology, therapy may be better able to target specific abnormalities thought to contribute to poor clinical outcomes. It is hoped that a greater understanding of RA pathophysiology and potential treatment options may translate into improved patient outcomes with reduced pain and better quality of life. Future research will hopefully entail the development of new therapeutic agents to modify the disease of RA as well as its symptoms (e.g.; novel analgesics for refractory pain). However, perhaps equally important may be biomarkers and other testing to help clinicians in early diagnosis and in selecting the optimal combination of agents to target a specific patient's pathophysiology.

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