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New understanding and approaches to treatment in rheumatoid arthritis

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Rheumatoid arthritis (RA) is the most common autoimmune inflammatory polyarthritis. Significant advances in the understanding of its pathogenesis have led in the past two decades to major advancement in its therapy. We used data from articles in Cochrane Database of Systematic Reviews on 'rheumatoid arthritis', meta-analyses and randomized controlled trials on adult RA (age >19 years) published in English within the past 5 years and identified in PubMed, and other key papers on management of RA. Appropriate, early and aggressive therapy is required for confirmed active cases of RA. The choice of disease-modifying drugs and different combinations, especially the newer biologic agents in regards of their early and long-term usage remains debated because of high costs and long-term safety concerns. Development of newer biologic agents working on different pathways of inflammation is underway in different stages. It remains to be determined how and when each of these agents will fit in the overall management of RA. Furthermore, post-marketing surveillance of the safety and response sustainability of these drugs is warranted.

Keywords: rheumatoid arthritis/disease-modifying drugs/biologic agents

Background

Rheumatoid arthritis (RA) is the most common chronic inflammatory polyarthritis and it afflicts people of all ages and races. Its prevalence among adults is approximately 1% with women being at least twice more likely to develop the disease than men.[1] RA is an autoimmune disease involving numerous cells of the immune system with overexpression of inflammatory cytokines like tumor necrosis factor alpha (TNF-α), certain interleukins (IL), proteinases and multiple other chemokines. The amplification of inflammatory pathways and their interaction with host cells such as fibroblasts, chondrocytes and osteoclasts promotes the formation of an invasive pannus tissue (inflamed synovium) resulting in bone and cartilage destruction of synovial joints, a hallmark of RA.[2,3] The diagnosis of RA is primarily clinical, but also

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Table 1 Summary of 1987 ACR classification criteria for RA.[4]

1. Morning stiffness at least 1 hour
2. Arthritis of three or more joints
3. Arthritis of hand joints
4. Symmetric arthritis
5. Rheumatoid nodules
6. Abnormal serum RF
7. Typical radiographic changes

Patient must have at least four of these seven criteria.
Criteria 1 through 4 must be present at least 6 weeks.

relies on laboratory tests and typical radiographic changes. The 1987 American College of Rheumatology (ACR) criteria for classification of RA[4] (Table 1), though mostly used as entry criteria for clinical trials, can guide the clinician with his/her assessment. The severity of the disease varies among patients but typically, RA causes chronic and progressive disease requiring therapeutic interventions.[5] Predominant findings include symmetrical pain, tenderness and swelling with morning stiffness in the small peripheral joints alongside with non-specific constitutional symptoms such as low-grade fever and fatigue. Involvement of larger joints is also common, in particular the shoulders, knees and less frequently the hips, and can be a major cause of morbidity or disability. A minority of RA patients develop extra-articular features such as rheumatoid nodules, lung disease, vasculitis and Sjögren's syndrome, usually later in the disease course. Laboratory findings include elevations in the inflammatory biomarkers in addition to the detection of autoantibodies such as rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (anti-CCP) in 70–75% of the cases.[1] Anti-CCP antibodies tend to be more specific but equally sensitive as RF and are of value in the diagnosis of early RA and in predicting joint damage; they are currently used in combination with RF for a better yield of accurate diagnosis.[6–8] Although several genetic and environmental factors have been linked to RA, the etiology remains unknown.[1] The interaction of different environmental factors in genetically predisposed individuals is likely what triggers the disease. Smoking for example is a risk factor for the development of RA[9,10] and possibly greater disease severity.[11] Other agents like bacterial or viral infections are still suspected factors and continue to be actively investigated. Many advances in the understanding of RA pathogenesis have been in the identification of genetic risk factors, mostly the strong association found with HLA-DRB1 alleles that encode a common sequence of amino acids known as the 'shared epitope', with some variance among ethnicities.[12] More recently, other susceptibility genes outside the HLA region have been identified.[13] RA patients have a higher risk for infections,

cardiovascular disease, and certain malignancies such as lymphoma,[14] and increased mortality rates compared with the general population, largely due to their increased cardiovascular morbidity[15].

Management of the disease

Joint destruction in patients with RA begins early in the course of the disease and prompt appropriate treatment can slow its progression.[16] Treatment objectives are to control symptoms of joint pain and stiffness, improve function and quality of life and minimize the risk of structural damage by reducing inflammation. Partial symptomatic control can usually be achieved with non-steroidal anti-inflammatory drugs (NSAIDs) or low-dose glucocorticoids.[17] However, disease-modifying antirheumatic drugs (DMARDs) are needed for most patients in order to alter the disease progression. While conventional DMARDs, such as methotrexate (MTX), remain the basis of therapy, a paradigm shift in the management of the disease has occurred during the past two decades. Early aggressive therapy is the cornerstone of this shift, followed by the introduction of biologic therapies that have led to better disease control.[18] These new agents work by selective blockade of certain cytokines or receptors, resulting in a significant reduction of inflammation, slowing the progression of bony erosions. Currently available biologics include the TNF-α inhibitors (infliximab, etanercept, adalimumab, golimumab, and certolizumab), IL-1 receptor antagonist (anakinra), cytotoxic T lymphocyte associated antigen 4 immunoglobulin (abatacept), anti-CD20 antibodies (rituximab), and an IL-6 inhibitor (tocilizumab). There are variances in the usage of biologic agents among countries based on licensing, local guidelines and policies. Other newer agents are at different stages of development.

Symptomatic and supportive treatment

Improving quality of life for RA patients by reducing pain and stiffness is in part achieved with analgesics, mostly NSAIDs. These agents have to be used with prudence because of potential adverse effects such as renal damage and gastrointestinal toxicity, and controversies on possible increase in cardiovascular morbidities, more significant with COX-2 selective blockers.[19] Low-dose glucocorticoids ($\leq$10 mg of prednisone or equivalent) are also employed in the management of RA due to their potent anti-inflammatory and immunomodulatory effects.[17,20] Controversy remains about their long-term usefulness, considering their serious side effects such as cushingoid manifestations,

cataracts, blood glucose abnormalities, osteoporosis and increased risk for cardiovascular disease. Nonetheless, there is evidence that low-dose glucocorticoids can significantly reduce the rate of erosions in early RA, so their addition to standard therapy can be beneficial in the short term[21–23]. Long-term continuous use beyond 4 years is not indicated because firm evidence of benefit is lacking.[23] Higher dosages, given orally or as intramuscular injections, can be used as bridge therapy for a short period of time while waiting for the onset of action of a DMARD.

Regular exercises, physical therapy and occupational therapy can help in symptomatic and functional improvement. Reconstructive surgery is reserved for cases with significant functional impairment or unacceptable level of pain.[17]

Traditional DMARDs

Essentially, all RA patients should be considered for DMARD therapy in an effort to halt joint damage and disease progression. The initiation of such therapy should be within the first 3 months (or as soon as possible) for patients with confirmed diagnosis and active disease.[17] Most commonly used non-biologic DMARDs include MTX, sulfasalazine, hydroxychloroquine and leflunomide (Table 2).

MTX has been well studied in several trials showing substantial clinical benefit. It is commonly used as the initial DMARD.[24] Its efficacy, along with its low cost, and rather favorable toxicity profile, have made MTX the standard by which new DMARDs are evaluated.[17] Most adverse events observed with its usual dose ($\leq$25 mg/week) are mild but may lead to discontinuation of the drug, and include hepatotoxicity, myelosuppresion and gastrointestinal toxicities. Pulmonary or renal toxicity, can occur, but usually at higher dosages. Periodic monitoring of liver function, kidney function and peripheral blood cell count (every 4–8 weeks) is warranted with MTX usage.

Sulfasalazine and hydroxychloroquine have also been shown to be effective in the management of RA and are also often selected as initial therapy, usually for patients with mild disease activity.[25,26] Adverse events are generally mild. Sulfasalazine can result in gastrointestinal, skin and hematological toxicities limiting its usage in some cases.[25] Hydroxychloroquine adverse events are uncommon and rarely cause drug withdrawal.[26] These include myopathy, skin reactions, headache, dizziness or other central nervous system manifestations and gastrointestinal reactions. Ocular toxicity, including retinopathy, is very rare, but can lead to blindness, and therefore, baseline and routine surveillance with a complete ophthalmologic examination is recommended.[27]

Table 2 Commonly used traditional DMARDs.

Drug	Usual dosing	Relevant toxicities	Contraindications*
MTX	7.5–25 mg weekly oral or in subcutaneous injections	Myelosuppression; hepatic and pulmonary toxicities	Acute infections; tuberculosis†; WBC $<3000/mm^3$; platelet count $<50\,000$; treated lymphoproliferative disease of ≤ 5 years; elevated liver transaminase; hepatitis B or C; pregnancy and breast feeding; pneumonitis, pulmonary fibrosis; creatinine clearance <30 ml/min.
Sulfasalazine	1–3 g daily oral in divided dosages	Myelosuppression; photosensitivity; gastrointestinal toxicity	Platelet count $<50\,000$; elevated liver transaminase; hepatitis B or C.
Hydroxychloroquine	200–400 mg daily oral	Macular damage; myopathy; alopecia; central nervous system toxicity	Severe chronic hepatitis B or C not receiving therapy.
Leflunomide	10–20 mg daily oral	Diarrhea; alopecia; headache; hepatic toxicity	Acute infections; tuberculosis†; WBC $<3000/mm^3$; platelet count $<50\,000$; treated lymphoproliferative disease of ≤ 5 years; elevated liver transaminase; hepatitis B or C; pregnancy and breastfeeding.

*From the 2008 American College of Rheumatology recommendations. †Latent tuberculosis prior to initiation of treatment, or active tuberculosis prior to completing therapy.

Leflunomide, an immunoregulator of T lymphocyte proliferation, has efficacy comparable to MTX, but higher rates of drug discontinuation due to adverse events.[28] Most common adverse events include alopecia, elevated liver function tests and gastrointestinal symptoms.

Overall, there is no clear evidence to support one DMARD as being better than others when used as monotherapy, although through indirect comparisons hydroxychloroquine may have a reduced efficacy when compared with other agents. Combination therapy in a step-up or parallel regime is more effective than monotherapy for those who fail initial treatment, but there is no strong evidence of which combination works best.[29–31] However, what is clearly established is that early institution of DMARD therapy at disease onset leads to better clinical and radiological outcomes.[32,33]

Other drugs such as azathioprine, cyclosporine and cyclophosphamide are also effective for the treatment of RA, but their significant serious toxicity profiles limit their use to severe refractory cases.[34–36] Usage of intramuscular gold, although beneficial has significantly declined since the introduction of other agents, mainly due to potential toxicity requiring close monitoring.

Biologics

Patients often fail or are unable to tolerate traditional DMARDs. Biologic agents are therapies used for different diseases, which have been introduced for the treatment of RA over the past decade, and have quickly gained ground in the management of mainly refractory cases (Table 3). Furthermore, they have also been shown to be effective in early RA, but their substantial economic impact and long-term safety concerns have precluded their routine use at the onset of disease,

Table 3 Biologic agents approved for RA treatment.

Generic name	Molecule	Mechanism of action	Dosing	Contraindications
Anakinra*	Synthetic form of the human IL-1 receptor antagonist	IL-1 receptor antagonist	Subcutaneous injection, 100 mg/day	Acute infections
Etanercept	P75 receptor-Fc fusion protein	TNF-α inhibitor	Subcutaneous injection, 50 mg/ week	Acute infections; tuberculosis†; treated lymphoproliferative disease of ≤5 years; moderate to severe heart failure; acute or severe chronic hepatitis B or C; multiple sclerosis/other demyelinating disorder.
Adalimumab	Human monoclonal antibody	TNF-α inhibitor	Subcutaneous injection, 40 mg/2 weeks	
Infliximab	Chimeric monoclonal antibody	TNF-α inhibitor	Intravenous infusion, 3 mg/kg at 0, 2 and 6 weeks followed by maintenance every 4–8 weeks	
Golimumab	Human monoclonal antibody	TNF-α inhibitor	Subcutaneous injection, 50 mg/ month	
Certolizumab	Human, pegylated monoclonal antibody	TNF-α inhibitor	Subcutaneous injection, 200–400 mg/2–4 weeks	
Rituximab	Monoclonal antibody	Anti-CD-20 (anti-B-cell)	Intravenous infusion, 1000 mg at 0 and 2 weeks	Acute infections; tuberculosis†; acute or severe chronic hepatitis B or C.
Abatacept*	CTLA4-Ig	Selective co-stimulation modulator	Intravenous infusion, 500–1000 mg at 0, 2 and 4 weeks followed by maintenance every 4 weeks	Acute infections; tuberculosis†; acute or severe chronic hepatitis B or C.
Tocilizumab	Human monoclonal antibody	IL-6 receptor antagonist	Intravenous infusion, 4–8 mg/kg every 4 weeks	Acute infections

*Not recommended by NICE for the treatment of RA. †Latent tuberculosis prior to initiation of treatment, or active tuberculosis prior to completing therapy.

before traditional DMARDs are prescribed.[37,38] The current typical usage of biologics is mostly in conjunction with MTX for resistant or aggressive RA without adequate response to traditional therapy.[27] Choosing between different biologic agents is usually based on their safety profile, routes of administration, costs, insurance coverage and patient preferences.

An IL-1 receptor antagonist (anakinra) was the first biologic agent approved for RA, given as subcutaneous injections at 100 mg daily. When compared with TNF-α inhibitors, anakinra has shown less benefit in clinical outcomes and frequent injection site reactions.[39,40] It is seldom used now, because of the availability of better therapies. The National Institute for Health and Clinical Excellence (NICE) does not recommend its use for the treatment of RA.[41]

Inhibitors of TNF-α are the most commonly used biologic agents. There are five currently available inhibitors. Four are antibodies against both soluble and membrane-bound TNF-α (infliximab, adalimumab, golimumab and certolizumab). Etanercept is a recombinant human TNF-α receptor that binds to soluble TNF-α. Infliximab is given by intravenous infusions whereas all other TNF-α inhibitors are given subcutaneously at different intervals. Golimumab is the first monthly, subcutaneous anti-TNF-α agent. Certolizumab is a humanized, pegylated TNF-α antibody fragment with a long half-life and low manufacturing costs, thus acquiring a potential advantage over the other TNF-α inhibitors. Golimumab and certolizumab are currently going through NICE appraisal. Several studies have shown that TNF-α inhibitors are highly effective in reducing the risk of joint damage with a rapid onset of action, especially when combined with MTX[14,37,42,43] in patients with RA who have not responded well to conventional DMARDs. They also improve physical function[44] and quality of life.[45] There are no randomized controlled trials (RCTs) comparing the various TNF-α inhibitors but indirect comparison in systematic reviews do not show substantial differences in efficacy among them, although there are some variances in their toxicity profiles.[14,30,40] One prospective cohort study done to evaluate effectiveness and safety of TNF-α inhibitors favored the use of etanercept over infliximab, mostly in terms of maintenance of efficacy.[46] Most common adverse events are injection site reactions (etanercept and adalimumab), hypersensitivity reactions (infliximab) and mild respiratory infections. Concerns regarding safety of TNF-α inhibitors are mostly due to the increased risk of infections and higher incidence of tuberculosis (TB),[40] with evidence that TB risk tend be lower with etanercept due to its different structure and mechanism of action.[47,48] Routine screening for latent TB is warranted for all patients considered for TNF-α inhibitors therapy with continuous vigilance for active TB throughout treatment course; positive cases should be on

preventive TB therapy at least a month prior starting a TNF-α inhibitor. In addition, there is an increased risk for worsening congestive heart failure. While there is some evidence of increased risk for skin cancer,[49] a possible increased risk of lymphoproliferative malignancies is still under debate. Additional rare but serious adverse events have also been reported, i.e. demyelinating disease, autoimmunity and hepatotoxicity.[40]

Abatacept, a cytotoxic T lymphocyte-associated antigen 4 immunoglobulin (CTLA4-Ig) that blocks the interaction between T lymphocytes and antigen-presenting cells (selective co-stimulation modulator), is the first biologic modulating T-cell activation. It is administered in intravenous infusions, and has encouraging therapeutic results with respect to clinical efficacy, tolerability and safety profile.[50] Abatacept is not recommended by NICE for the treatment of RA.[41]

Rituximab, an anti-CD20 antibody (selective B-cell depleting agent) that has long being used for certain lymphoproliferative diseases, was introduced in recent years for the management of patients with RA after gaining better understanding of the role of B-cells in the pathogenesis of RA.[51] It is mostly reserved for patients who have failed therapy to other biologics. RCTs show significant improvement in these patients when compared with MTX alone.[52,53] Rituximab is given intravenously for only 2 doses 2 weeks apart with likely need of repeated therapy every 6–12 months. Infusions have to be premedicated with intravenous glucocorticoids to reduce the rate of infusion reactions.[40] Based on a prolonged experience from hematology and oncology clinical practice, rituximab does not appear to increase the risk of TB or malignancies. However, the likely need of recurring treatment for RA patients has raised concerns regarding potential hypogammaglobulinemia.[54] Progressive multifocal leukoencephalopathy due to JC virus infection has been reported mostly in patients with concurrent or prior usage of other immunosuppressive therapy, mandating a comprehensive neurological evaluation for any new neurological manifestation in patients treated with rituximab.

The latest biologic drug approved by the FDA and awaiting NICE appraisal is the anti IL-6 receptor monoclonal antibody, tocilizumab. Studies have showed that monthly infusion of tocilizumab is as effective as other biologic agents in patients with RA, with similar safety and tolerability profile.[55,56]

Overall, no review has proven superiority of one biologic therapy compared with others. The only RCT evaluating a head-to-head comparison between two biologics, abatacept and infliximab, showed slightly better safety and tolerability profile for abatacept when used for patients with an inadequate response to MTX).[57]

In the pipeline

Newer biologic agents are currently in various stages of development. A recent clinical trial evaluated safety and efficacy of a human monoclonal antibody (denosumab) to a key mediator of osteoclast function, the receptor activator of nuclear factor kβ ligand, showing improvement in erosions scores but not in clinical activity measures.[58] Under development are also agents targeting alternative pathways of inflammation/T-cells activation, newer humanized anti-CD-20 B-cell blockers (i.e. ofatumumab, ocrelizumab), and agents blocking other B-cell targets (i.e. B lymphocyte stimulator, toll-like receptors and different surface receptors and markers), and small molecules targeting specific inflammatory pathways (i.e. Janus kinase inhibitors).

Clinical practice guidelines

With the recent advances in understanding the pathogenesis and clinical course of RA and the advent of multiple effective novel drugs, there has been a shift from the previous conservative step-up approach in treating RA to the current standard of care with early aggressive therapy.

Several clinical practice guidelines have been developed in the past few years including recommendations by NICE, British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR), the European League Against Rheumatism (EULAR) and the ACR. Although there is some variation in guidance, for the most part, guidelines agree on their key messages that include: (i) early referral to specialist, (ii) rapid control of symptoms with lowest effective dose of NSAIDs or short-term low-dose glucocorticoids, (iii) treatment with DMARDs for active disease as soon as possible, and (iv) use of biologics if no response to traditional DMARDs.

NICE guidelines[41,59] were based on best available evidence and cost-effectiveness analysis. Specific messages include a combination of DMARDs that involves MTX for confirmed active RA cases when appropriate as soon as possible, or monotherapy with fast escalation to effective dose; this along with short-term glucocorticoids as part of the regimen or as symptomatic control measure. After the disease have achieved sustained and satisfactory levels of control, it was recommended to cautiously reduce doses of DMARDs but with continuous monitoring of activity and re-escalating dosage at the first sign of a flare-up. Other key messages were a multidisciplinary care and the routine monitoring of the disease, its comorbid conditions, and

complications (e.g. cardiovascular disease, osteoporosis, extra-articular disease). While NICE mostly focused on the early aggressive treatment rather than the choice of DMARD, it has previously issued recommendations for the usage of TNF-α inhibitors, restricting them to patients who failed two traditional DMARDs with persistent high disease activity. In consideration for its cost-effectiveness standards, NICE has recommended against switching TNF-α inhibitors (a common practice in the US) except for toxicity issues, and did not approve anakinra or abatacept for the management of RA. The newer biologics currently available (golimumab, certolizumab and tocilizumab) are currently under review.

The BSR and BHPR guidelines divided the management of RA into early disease (first 2 years)[60] and established disease (after the first 2 years),[61] providing a framework for overall health-care delivery for patients with RA. In the first 2 years, emphasis is on early diagnosis and establishment of aggressive DMARD therapy and symptomatic pain control, also stressing a multidisciplinary approach to engage patients in exercise regimens, and prevent cardiovascular disease. Beyond the first 2 years, the aim is to continue the control of synovitis and symptoms by constant reassessment and individualized management, and to improve physical and psychosocial functioning while monitoring for drug toxicities and promoting self-management techniques.

The 2006 EULAR recommendations[62] were meant for the management of early arthritis, focusing on early diagnosis and determination of patient at risk for erosive disease requiring initiation of DMARDs. They considered MTX as the anchor first-line drug, followed by regular assessment of disease activity to guide future changes in treatment to achieve remission. This continuous adjustment of therapy towards achieving and maintaining remission would include the variety of available therapy options and combinations with or without biologic agents, stressing on individualized approach rather than following protocols.

More specifically, the ACR recommendations[27] were based on three important clinical features for guiding therapeutic decisions: (i) disease duration (short <6 months, intermediate 6–24 months or long >24 months), (ii) disease activity based on various indices (low, moderate, or high), and (iii) presence of predefined relevant poor prognostic factors (functional limitation, extra-articular disease, presence of RF or anti-CCP antibodies, bony erosions on radiography). Their general recommendations for the use of traditional DMARDs are summarized in Table 4. The use of TNF-α inhibitors with MTX is recommended in early RA in patients with high disease activity and poor prognostic features. Otherwise, TNF-α inhibitors are generally reserved for later in

Table 4 General 2008 ACR recommendations for the use of common traditional DMARDs.[27]

	Presence of poor prognostic features	Absence of poor prognostic features
Moderate/high disease activity	MTX, leflunomide, or combination of DMARDs including MTX	MTX, leflunomide, sulfasalazine, or combination of DMARDs
Low disease activity	MTX, leflunomide	Hydroxychloroquine, MTX, leflunomide, sulfasalazine

the disease course for patients who have failed traditional DMARDs, reserving abatacept and rituximab for worst cases who did not respond to traditional or other biologic DMARDs. The combination among biologic agents was not recommended due to a possible increase in the adverse events rate and no evidence of additive efficacy.

Summary

The goal of therapy in any RA patient is to achieve remission by controlling synovitis and halting joint erosions. This had become more attainable in recent years since the paradigm shift towards early and aggressive therapy for confirmed active disease and the introduction of the biologic agents. Continuous vigilance for adverse events and long-term morbidities with the usage of novel agents is warranted. Although not all patients respond to traditional or biologic DMARDs, hope is that with the rapid expansion in the identification of potential pathogenesis pathways and the development of novel drugs the course or RA will continue to improve towards the ultimate goal of finding a cure in the future.

Conflict of interest: Dr Suarez-Almazor is a member of the speakers bureau for Bristol-Myers Squibb and F. Hoffman-LaRoche and is a consultant for Amgen.

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