ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune disorder of unknown aetiology characterized by joint erosion and destruction. It is the most common inflammatory arthritis and is a major cause of disability. Recent advances in understanding the cytokine networks that are responsible for the ongoing inflammatory response, targeted therapy in RA has been attempted. The treatment of RA has been revolutionized by advances in the understanding of disease at cellular as well as molecular level accompanied by the technology to target specific mediators of disease. Targeting pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α) or interleukin-1 (IL-1) is well established in clinical care of RA patients. However, lack or loss of clinical response occurs in up to 25% of the patients in the long run. New strategies beyond these targets, namely blocking T-cells by abatacept or B-cells by rituximab, have been introduced recently. Current knowledge of different pathogenetic mechanisms of RA has been translated into clinical practice by the scientists. Newer targets are oriented against other interleukins, agents for T-cell or B-cell inhibitions, and ‘small molecule inhibitors’ with possible peroral administration. This monogram will review the outline of targets of treatment in RA i.e., different cytokine inhibitors and modulators of immune response currently on use or under ongoing clinical trials.

INTRODUCTION

Rheumatoid arthritis is a chronic, systemic, autoimmune, inflammatory disease which primarily targets the synovial tissue. The disease follows a chronic course with substantial disability and morbidity, which results in a shortened life span. RA affects nearly 0.8% of adult population worldwide, and is more common in women (M:F=3:1). As on today, although the precise pathogenesis of RA remains unclear, it has been postulated that multiple exogenous or endogenous antigenic triggers, or both, act in the presence of a background genetic predisposition to initiate a self-perpetuating series of autoimmune responses in the synovial compartment. Many cell populations, including monocytes, macrophages, B-cells, T-cells, endothelial cells, and fibroblasts, participate in the ongoing inflammatory process.1-3

Cytokines are the key mediators of immune functions. Though RA is a T helper 1 (Th1) predominant state, B-cells have been shown to participate in chronic rheumatoid synovitis; they undergo antigen-dependent clonal expansion, affinity maturation, and differentiation into plasma cells, and produce rheumatoid factor (RF), a well-recognized prognostic factor for aggressive RA.4 Hence, the key biologic targets of the currently recommended treatment for RA includes aggressive combination therapy, and use of agents that targets cytokines (TNF-α and IL-1), and B-cells. A fraction of RA patients still remain non-responders to such treatments, however, due to still-undefined mechanisms of resistance. Because of the high prevalence of RA, the clinical impact of this subgroup is important.

EARLY DIAGNOSIS

The diagnosis of RA cannot be established by a single laboratory test or procedure but is aided by American College of Rheumatology (ACR) criteria, meticulous physical examination and physician's insight. Joint damage occurs early in the disease process as proved by 30% radiographic bone erosions at the time of diagnosis which increases to 60% by two years, and unfortunately bony erosions and deformities are largely irreversible. Initiation of treatment with disease-modifying anti-rheumatic drugs (DMARDs) within three months after the diagnosis of RA is crucial, and thus early diagnosis, although challenging, is critical. ATTRACT (Anti-TNF Therapy in RA with Concomitant Therapy) study encourages use of biologics in early RA.

OUTLINE OF CURRENT MANAGEMENT OF RHEUMATOID ARTHRITIS

Medications that are used to treat RA are divided into three main classes:

1. NSAIDs (non-steroidal anti-inflammatory drugs),
2. Corticosteroids
3. DMARDs
   - Synthetic (the classical DMARDs)
   - Biologic (biologic response modifiers)

NSAIDs and corticosteroids are not within the purview of discussion in this monogram under targeted treatment of RA. Synthetic DMARDs have the potential to reduce or prevent joint damage.
Therefore, early and universal use of DMARDs is fundamental to all current treatment strategies for RA. Commonly used DMARDs are methotrexate, hydroxychloroquine, sulphasalazine and leflunomide while infrequently used agents are gold, cyclosporine-A, azathioprine, cyclophosphamide, chlorambucil, D-penicillamine and minocycline. Synthetic DMARDs are cost-effective and widely used.

The following 7 biologic response modifiers (Table 1) are now recommended to treat RA.

**Infliximab (anti-TNF therapy)**
- a chimeric (25% mouse and 75% human) monoclonal antibody
- dose is 3 mg/kg, I.V infusion at 0, 2 and 6 weeks followed by maintenance dose every 8 weeks thereafter. It should always be used in conjunction with methotrexate (10-25 mg/once a wk) to block the deleterious effects of HACA (human antichimeric antibody; developed after use of infliximab)
- contraindications: hypersensitivity, active infections

**Etanercept (anti-TNF therapy)**
- a fusion protein of p75 soluble TNF receptor with Fc fragment of human immunoglobulin G1 (IgG1); manufactured from mammalian cells. Etanercept mops out the circulating cytokine
- dose is 25 mg, S.C. twice a week, or 50 mg, S.C once a week. May or may not be co-prescribed with methotrexate
- contraindications: same as infliximab

**Adalimumab (anti-TNF therapy)**
- recombinant human IgG1 monoclonal antibody that specifically blocks TNF activity; binds with circulating and cell surface TNF-α
- dose is 40 mg, S.C, 2 weekly. As it is fully humanized, HACA is not generated. In RA, used as monotherapy or with methotrexate
- contraindications: hypersensitivity, active infections

**Anakinra (anti-IL-1 therapy)**
- recombinant native human IL-1Ra (receptor antagonist); IL-1Ra + IL-1 receptor → blocks signaling; acts by competitive inhibition of cellular receptors.
- dose is 100 mg, S.C, daily; used as monotherapy or with methotrexate
- contraindications: hypersensitivity, active infections

**Tocilizumab (anti-IL-6 therapy)**
- first IL-6 receptor-inhibiting monoclonal antibody developed for the treatment of RA
- dose is 8 mg/kg, I.V, every 4 weeks given as an I.V infusion over 1 h. Used in combination with methotrexate; indicated for the treatment of adult patients with moderate to severe RA
- contraindications: infusion reactions, active infections

**Rituximab [B-cells (anti-CD20 therapy)]**
- Genetically engineered human-mouse chimeric monoclonal antibody. A CD20 antagonist and B-cell action depletor
- dose is 1000 mg per infusion on days 1 and 15 (slow infusion for several hours) with 100 mg I.V methylprednisolone
- contraindications: hypersensitivity, active infections, severe heart failure

**Abatacept [T-cells (CTLA-4 Ig)]**
- only co-stimulatory blocking agent (CD80/86) approved by USA. It modulates the immune response by binding to CD80/CD86 on an antigen presenting cell (e.g. dendritic cell), and thereby preventing co-stimulatory binding of CD28 on naive T-cells and attenuating T-cell activation
- dose is 10 mg/kg, I.V every 2 weekly for 3 doses, followed by every 4 weekly
- contraindications: hypersensitivity, active infections, chronic obstructive pulmonary diseases

**Adverse reactions of biologic response modifiers:**
1. Injection site reactions and infusion reactions.
2. Infections (especially, risk of activation of latent tuberculosis or developing new tuberculosis).
5. Congestive cardiac failure.
6. Malignancy (as TNF provides immune surveillance for malignancy).
7. Antinuclear antibody (ANA) positivity.
8. Demyelinating neurological diseases.

**TARGETS OF TREATMENT IN RHEUMATOID ARTHRITIS**

Over the past decade, biologicals have been a welcome addition to our armamentarium, biological therapy has become a cornerstone in the treatment of RA with inadequate response to standard DMARDs. As on today, seven approved biological agents are available to the rheumatologists (Table 1). Though biological therapy targeting molecules and cells specific for processes associated with the pathogenesis of RA is very efficient, yet unable to induce remission or even ‘cure’ in most patients. Every time a novel biological agent emerges in the market, it comes with its own benefits and risks; clinical studies prove their realistic worth in patients with RA and this should be the area of focus. Expanding spectrum of potential therapies is currently being tested in various stages of clinical trials throughout the globe.

Guidelines for the use of biologics:
- must have failed to response with at least 2 DMARDs including methotrexate (20-25 mg/wk)
- must have active disease
- have no major infections in preceding 6 months
- have no malignancies
- non-pregnant, non-breast feeding women

Biological agents are divided into two classes:

- monoclonal antibodies
- small molecules

**MONOCLONAL ANTIBODIES**

To start with, these treatments consisted of chimeric antibodies with human constant regions of light and heavy chain, and the variable murine binding site for the target molecule. In recent years, improved technology has led to a reduction of immunogenicity, and humanized and eventually fully human antibodies were manufactured. These monoclonal antibodies function by neutralizing a target cytokine or its receptor, blocking co-stimulation molecules, and inducing cytolysis, depletion of target cell molecules or apoptosis.

- TNF-α inhibitors – infliximab, etanercept and adalimumab are being used for last few years with some success. Two additional TNF-α blocking agents are likely to be approved in 2009 for the treatment of RA are subcutaneously administered golimumab (CNTO148) and certolizumab pegol. Both are humanized monoclonal anti-TNF-α antibody.

- IL-1 inhibitors – Anakinra was in the basket, and to simplify the dosing and decrease the risks of local adverse events, a humanized monoclonal antibody targeting IL-1, canakinumab (ACZ885), has been recently developed with promising preliminary results on clinical trials.

- IL-6 inhibitors – A humanized monoclonal antibody, tocilizumab, works against IL-6 receptor. There is a favorable benefit-to-risk balance for tocilizumab in combination with methotrexate, and is now approved in the treatment of moderate to severe active RA in adult patients who have either responded inadequately or were intolerant to one or more DMARDs or TNF-α inhibitors.

- IL-15 inhibitor – An open, placebo-controlled, double blind study proved the humanized monoclonal antibody against IL-15 (HuMaxIL-15) to be efficient in reduction of bone and cartilage destruction in patients with RA.

- IL-17 inhibitor – Production of several pro-inflammatory cytokines e.g., IL-1, IL-6, or TNF-α are increased by IL-17, which also regulates osteoclastogenesis. Th17 cells are the major source of IL-17. Clinical trial of a monoclonal antibody against IL-17 (AIN457) in RA is currently in progress.

- IL-12/IL-23 inhibitor – Ongoing clinical trials in RA patients blocking pro-inflammatory cytokines IL-12 (a key inducer of Th1 polarization) and IL-23 (responsible for the proliferation of a Th17 subset of memory T-cells) by a specific monoclonal antibody ustekinumab has generated promising results. Ustekinumab works against the p40 subunit of cytokines IL-12 and IL-23.

- Inhibitors of osteoclastogenesis – Denosumab, a monoclonal antibody against receptor activator for nuclear factor-kappa B ligand (RANKL), is in phase III clinical trial and is showing promising results in active RA patients by inhibiting osteoclastogenesis when administered subcutaneously at 6 months’ interval.

- Inhibitors of the TNF superfamily members – Clinical trial are on the way with baminercept (BG9924), an inhibitor of LT β (lymphotoxin-β), and belimumab, a fully human monoclonal anti-BAFF (B-cell activating factor) antibody. Encouraging results are coming out with atacicept (a recombinant fusion protein of BAFF), which shows a depletion of peripheral B-cells as well as decrease in RF and anti-cyclic citrullinated peptide antibodies (ACPA) in active RA patients.

- Inhibitors of chemokines and angiogenesis – It is well-known that angiogenesis occurs in early part of RA and results in migration of inflammatory cells into the synovium. Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), is under trial.

- Apoptosis regulators – The Fas receptor (FasR) is the most intensely studied death receptor. Cells from synovial tissue of RA patients are resistant to apoptosis, and thus ac-
activated synovial fibroblasts may escape the effects of biologics. The first monoclonal anti-FAS IgM antibody (ARG098) is under clinical trial (intra-articular injection) in patients with RA. Researchers opine that effects of methotrexate, sulphasalazine and infliximab in RA patients might be mediated by apoptosis.

b. Inhibitors of MAP (mitogen activated protein) kinase p38

k. T-cell inhibitors – A fusion protein CTLA-4 Ig (cytotoxic T-lymphocyte-associated antigen-4 with immunoglobulin 1), abatacept, is the first in a new class of drugs known as co-stimulation blockers, is safe and efficacious and received approval for treating patients with RA. Currently clinical trials targeting T-cells are ongoing with alematuzumab (anti-CD52), keliximab (chimeric monoclonal anti-CD4 antibody) or clenoliximab (the IgG4 version of the previous antibody), which showed severe lymphocytopenia and skin rash leading to discontinuation of the trials.

d. Inhibitor of Syk kinase
   d. Inhibitor of Syk kinase[17] – Intracellular Spleen tyrosine kinase (Syk) has significant immunomodulatory activity. Use of Fostamatinib disodium (a Syk kinase inhibitor) has produced promising results by reducing disease activity in RA patients with 12 weeks of peroral administration of 150 mg of the drug twice a day.

e. Inhibitors of transcription factors – Antagonists of transcription factor NF-κB (nuclear factor κB) activation are under study.

e. Inhibitors of transcription factors

f. Inhibitor of cytokines and chemokines – Small molecule IL-12/IL-23 inhibitor (Apilimod mesylate) is under trial and decreases several pro-inflammatory cytokines and progression of RA.

CONCLUSION[18]

An upcoming knowledge of the pathogenesis of autoimmune inflammatory disorders has expanded the spectrum of new molecules and therapeutic targets of RA. The promising therapeutic strategies of recent years are small molecules which are mostly inhibitors of intracellular signaling pathways with an advantage of peroral administration. Other targets in future for treatment of RA are regulatory T cells (Treg cells), innate immune system, Toll like receptors, RNA interference or epigenetic alterations, complement pathway mediated by CsA or adipokines (visfatin/ PBEF). Anti-IL-12 antibodies, protein-A immunoabsorption column and Alpha V Beta 3 Integrin are some other modalities under trial. Gene therapy in RA at present remains experimental. With the help of these newer drugs, the future may well see rheumatologists talking not about symptomatic relief but potential ‘cure’ for RA.

REFERENCES


