

Recent Advances in Management of Rheumatoid Arthritis

Sandeep Kharkar¹

ABSTRACT

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune condition that, if inadequately treated, leads to joint destruction, disability and increased mortality. Despite the cure remaining elusive, rheumatologists now have a wide range of effective drugs that will control disease, result in less (or even prevent) joint damage, reduce co-morbidities and increase quality of life to a level that could not have been envisaged before.

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune condition that, if inadequately treated, leads to joint destruction, disability and increased mortality. It affects nearly 1% of the adult population and is associated with significant co-morbidities, including an increased risk of developing cardiovascular disease, neoplasia and infection. In the past, treatment for RA was poor few drugs were there to suppress the underlying inflammatory process, and even those were withheld until joint damage had become established and disability developed. This should not be surprising, since the pathological processes underlying the disease were largely unknown.

Today, the outcome may not be more different. A combination of both scientific and clinical advances, discussed briefly in this short article, have led to a reasonable expectation that a person newly diagnosed with RA today can expect at least a major suppression of their disease indeed, full remission in many cases and live a normal life.

Early Detection and Dynamic Therapy :

Rheumatologists consider there to be a 'window of opportunity' of two to three months from the onset of symptoms to the initiation of DMARD therapy during which irreversible damage to joints can be prevented. This has led to many rheumatology units setting up specialist 'early arthritis clinics', where patients with suspected RA can be fast tracked for

diagnosis and treatment. Once diagnosed, therapy is now dynamic, with drugs and dose escalated according to objective measures of disease activity, typically the Disease Activity Score of 28 joints (DAS 28), until remission is achieved, or at least low disease activity.

The introduction of a 'treat-to-target' approach for RA has allowed therapy to catch up with similar such approaches for other chronic diseases such as hypertension and has provided excellent outcomes for patients.

Treatment Approaches And Strategies :

The goal of treatment for all patients with RA is remission or at least low disease activity; other than toxicity concerns and, obviously, issues relating to expense. There is no magic or correct DMARD or combination of DMARDs that is right for all patients. Each patient presents a unique challenge and comes with unique expectations, biases, disease activity level, damage burden, co-morbidities. Some investigators have suggested that treatment should be different for patients with RA who have good prognosis versus poor prognosis. This concept is problematic, because separating patients into those who have a good versus a poor prognosis is difficult. Regardless of the prognostic factors, the goal for each individual patient is to achieve at least a low level of disease activity. Until or unless parameters are identified, rheumatologists will of necessity continue to use their clinical judgment at the individual patient level.

Without parameters that predict in a differential manner the response to medications in terms of efficacy or toxicity, one approach to treatment

¹Consultant Rheumatologist & Physician

Address for Correspondence -

Dr. Sandeep Kharkar

E-mail : drsandeep2k@yahoo.com

Received on 18th December 2018

Accepted on 23rd December 2018

decisions is illustrated in (Figure 71-3). Note that several “spins” of the wheel may be required. makes the point that we do not have these much-needed parameters. The figure also emphasizes that if we hope to treat RA in a rational, scientific way, it is critical that we find these parameters, and it highlights and reinforces the need to include biobanks with all of our clinical trials. .

Treatment for Rheumatoid Arthritis :

DMARDS : Early DMARD initiation has been shown to result in both lower disease activity and less radiographic progression, and methotrexate has become the anchor therapy in treatment of RA. Other DMARDs commonly used by rheumatologists include hydroxychloroquine, sulfasalazine and leflunomide. Studies have shown that combination therapy of two or more DMARDs plus corticosteroid in early disease offers optimal

reduction in joint damage and earlier remission. Other DMARDs such as azathioprine, gold, ciclosporin and penicillamine are now only rarely used due their unfavourable risk / benefit ratio.

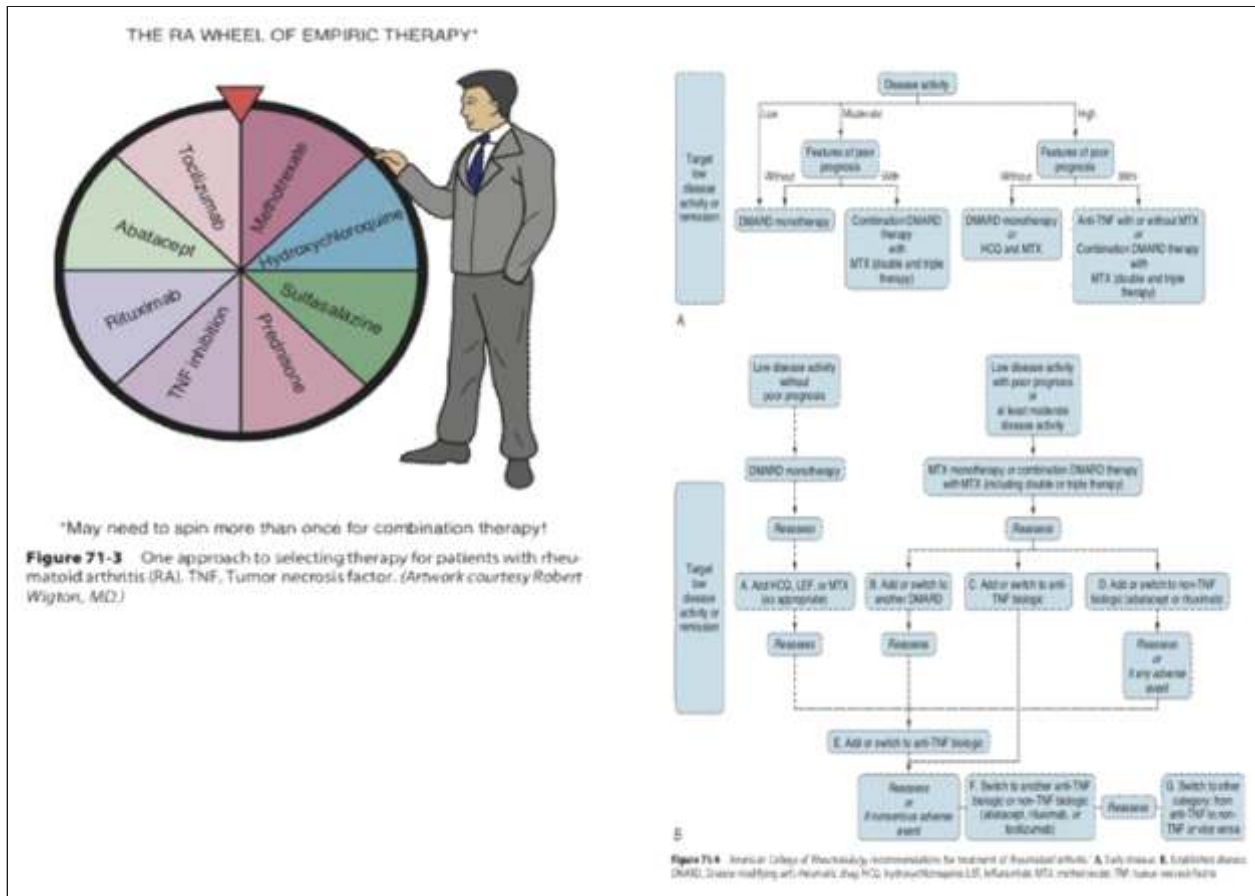
GLUCOCORTICOIDS : Low doses for short durations are preferred to minimise the risk of steroid-related side-effects.

Biologics :

The last 10 years have been an exciting time in the treatment of RA. Better understanding of the pathophysiology has informed the development of many biological therapies designed to specifically target key components of inflammation that can effectively prevent disease progression and improve patient outcomes.

As proteins, these drugs are administered by sc injection or iv infusion

Figure 71.3



ANTI-CYTOKINE THERAPIES

Tumor Necrosis Factor Inhibitors :

Infliximab : Infliximab is a chimeric mouse-human monoclonal anti- body composed of constant regions of human immuno-globulin (Ig)G1 coupled to the variable regions of a high-affinity neutralizing murine antihuman TNF anti- body. The typical initial dose of infliximab in RA is 3 mg/kg given as an intravenous (IV) infusion in combination with MTX, followed by doses 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

Etanercept : Etanercept is formed by the linkage of two soluble p75 TNF-R extra-cellular domains to the Fc portion of human IgG1 (see Figure 63-1). The TNF-R domains in etanercept bind to two of the three receptor binding sites on the TNF trimer, thus blocking the ability of TNF. Etanercept is administered by subcutaneous injection in doses of 25 mg twice weekly or 50 mg once weekly in RA, psoriatic arthritis (PsA), and ankylosing spondylitis (AS).

Adalimumab : is a human anti-TNF IgG1 monoclonal anti-body generated through repertoirecloning. It neutralizes the biologic activity of TNF by binding with high affinity to the soluble and transmembrane forms of TNF and inhibiting the binding of TNF with its receptors. The recommended dosing for adalimumab in RA, PsA, and ankylosing spondylitis is 40 mg subcutaneously every other week.

Golimumab : is a human IgG1 monoclonal antibody specific for human TNF. Golimumab was created by using genetically engineered mice

immunized with human TNF, resulting in an antibody with human-derived antibody variable and constant regions. It is administered by subcutaneous injection, 50 mg once a month, in patients with RA, PsA, and AS.

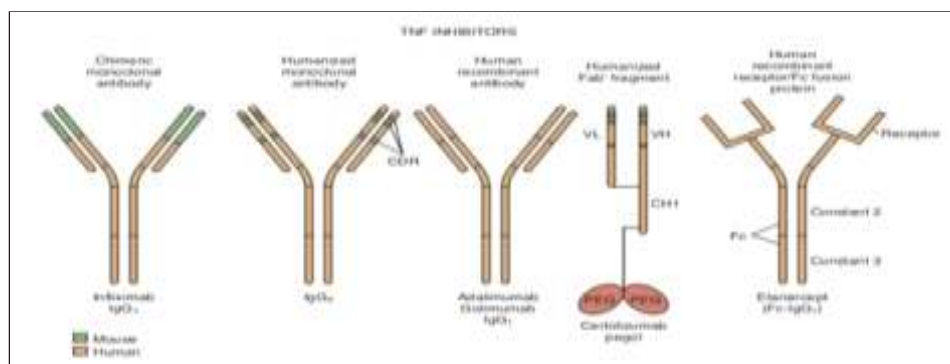
Certolizumab Pegol : is a Fab fragment of a recombinant, humanized anti-TNF monoclonal antibody that has been fused to a 40 kDa PEG moiety. The recommended dose of is 400 mg initially and at weeks 2 and 4, followed by 200 mg every other week AND maintenance dosing 400 mg every 4 weeks can be considered.

INTERLEUKIN-1 (IL-1) :

Anakinra : is a recombinant, nonglycosylated homolog of IL-1R that differs from native human IL-1R by the addition of a single methionine residue at its amino terminus. Anakinra blocks the activity of IL-1 by competitively inhibiting IL-1 binding to the IL-1RI receptor. The recommended dose of anakinra for the treatment of patients with moderately to severely active RA is 100 mg / day administered by subcutaneous injection.

Rilonacept : previously known as IL-1 Trap, is a fusion protein consisting of the human IL-1 receptor extra-cellular domains and the Fc portion of human IgG1. It is administered subcutaneously with a loading dose of 320, followed by 160 mg once weekly.

Canakinumab : Canakinumab is a human monoclonal antibody that selectively targets IL-1 . It is given subcutaneously 150 mg every 8 weeks to patients weighing greater than 40 kg. For patients whose body weight is between 15 and 40 kg, the recommended dose is 2 mg/kg.



INTERLEUKIN-6 (IL-6) :

Tocilizumab : Tocilizumab is a recombinant humanized anti-human IL-6 receptor monoclonal antibody of the immunoglobulin IgG1 (gamma 1, kappa) subclass with a typical H2L2 polypeptide structure. Each light chain and heavy chain consists of 214 and 448 amino acids, respectively. The recommended starting dose is 4 mg/kg, followed by an increase to 8 mg/kg based on clinical response.

Sarilumab : is human monoclonal antibody directed against the IL-6 receptor. It showed efficacy in two different doses (150 mg and 200 mg) given subcutaneously every 2 weeks in the MOBILITY studies.

Sirukumab : A human monoclonal antiIL-6 monoclonal antibody, sirukumab has also shown improvements in signs / symptoms of RA when given 100 mg subcutaneously every 2 weeks.

Cell - Targeted Biologics and Emerging Targets :

Rituximab : is a chimeric mouse-human monoclonal anti-body directed against the extracellular domain of the CD20 antigen. It initiates complement-mediated B cell lysis and may permit antibody-dependent, cell-mediated cytotoxicity when the Fc portion of the antibody is recognized by core sponding receptors on cytotoxic cells. Clinical trials in patients with active, established RA confirm that a single cycle of rituximab given as two infusions of 1 g each, together with once-weekly oral methotrexate, produces an enduring clinical response. A treatment cycle of two infusions of 500 mg is also efficacious .

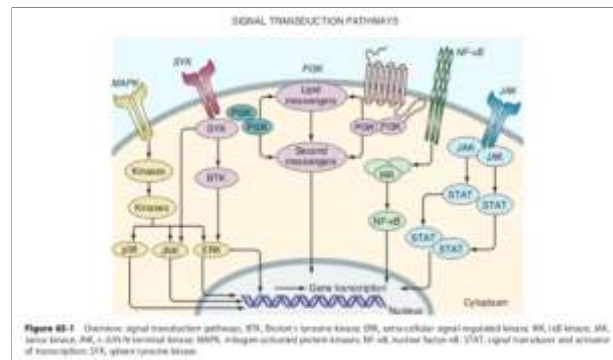
Abatacept : is a novel, fully human fusion protein consisting of the extra-cellular portion of CTLA-4 and the Fc fragment of human IgG-1 (CTLA-4Ig). Abatacept binds to CD80 and CD86 on antigen presenting cells, thus preventing these molecules from binding their ligand, CD28, on T cells, with the consequent inhibition of optimal T cell activation.

Novel Intra-cellular Targeting Agents in Rheumatic Disease :

Mek Inhibitors : MEK is a MAPKK involved in growth factor signal transduction and cytokine production. Inhibitors of MEK demonstrated

efficacy in pre-clinical models of RA. Based on the pre-clinical observations, ARRY-438162, an oral inhibitor of MEK1 /MEK2.

Spleen Tyrosine Kinase Inhibitors : SYK inhibitors have been evaluated as a potential treatment for RA. SYK is a nonreceptor protein tyrosine kinase that is a modulator of immune signaling in cells bearing Fc -activating receptors, including B cells, mast cells, macrophages, neutrophils, eosinophils, basophils, and synoviocytes. SYK binds to the cytoplasmic region of these receptors that contain the immune-receptor tyrosine-based activation motif (ITAM). Receptor binding results in ITAM phosphorylation activating SYK.



P38 Map Kinase Inhibitors : The MAP kinases were identified in the 1990s as involved in the production of pro-inflammatory cytokines after cell stimulation by various stressors. There are three major families of MAP kinase: extra-cellular signal-regulated kinase (ERK), c-JUN N-terminal kinase (JNK), and p38 .

Janus Kinase Inhibitors :

JAKs are protein tyrosine kinases that bind the cytoplasmic region of transmembrane cytokine receptors and mediate signaling through type 1 and type 2 cytokine receptors. After receptor-ligand interaction, various JAKs are activated, resulting in tyrosine phosphorylation of the receptor and subsequent activation of STATs (signal transducer and activators of transcription), which act as transcription factors. JAK/STAT signaling mediates cellular responses to multiple cytokines and growth factors. These responses include proliferation, differentiation, migration, apoptosis, and cell

survival, depending on the signal and cellular context. Activated STATs enter the nucleus and bind to specific enhancer sequences in target genes, impacting their transcription. JAKs consist of four types: JAK1, JAK2, JAK3, and TYK. The JAKs signal as pairs JAK3 is primarily expressed in hematopoietic cells and is critical for signal transduction from the common α -chain of the receptors for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 on the plasma membrane to the nuclei of immune cells.

Tofacitinib : is a JAK inhibitor that has been approved by the U.S. Food and Drug Administration (FDA) for patients with RA with active disease, despite MTX treatment at a dose of 5 mg, twice daily, in combination with nonbiologic DMARDs or as monotherapy .

Baricitinib : has a selectivity for JAK2/JAK1 and less potency for JAK3, or TYK2.⁷⁷ In addition to RA baricitinib is under development to treat psoriasis and diabetic neuropathy. Baricitinib is rapidly absorbed and has a T_{1/2} of 6 to 8 hours and is dosed once daily.

Fibotinib (GLPG0634) : is an orally available, selective inhibitor of JAK1 under development for the treatment of RA and Crohn's disease. The molecule displays a JAK1 / JAK2 inhibitor profile in biochemical assays .

Decernotinib (VX-509) : is a JAK inhibitor previously in development with selectivity for JAK3 over JAK1/2 and TYK2. Two highest doses (100 mg and 150 mg) demonstrated statistically significant ACR20, ACR50, ACR70, and DAS-28 responses of 66%, 49%, 22% and -3.06%, respectively.

Peficitinib (ASP015K) : is an once daily oral JAK inhibitor that is in development for RA. ASP015K has shown selectivity of JAK1 / JAK3 versus JAK2 in cell-based assays. Concomitant DMARD therapy were randomly assigned equally to once-daily dose of ASP015K 25 mg, 50 mg, 100 mg, 150 mg.

BTK Inhibitors :

Oral Btk inhibitors (ibrutinib) have been approved for treatment of patients with mantle cell lymphoma and chronic lymphocytic leukemia and now in early

development as a potential treatment for RA. Btk plays a prominent role in BCR signal transduction and also has a role in Toll - like receptor and FcR signaling in myeloid cells.

PI3K Inhibitors :

PI3Ks are lipid kinases that play central role in regulation of cell cycle, apoptosis, DNA repair, senescence, angiogenesis, cellular metabolism, and motility. PI3Ks transmit signals from the cell surface to the cytoplasm by generating second messengers phosphorylated phosphatidylinositol which in turn activate multiple effector kinase pathways, including Btk, AKT, PKC, NF- κ B, and JNK/SAPK pathways, and ultimately result in survival and growth of normal cells.

Sphingosine 1 phosphate modulators :

Sphingosine-1-phosphate (S1P) is an abundant, biologically active lysophospholipid. In the immune system, changes in local S1P concentrations and gradients can modify lymphocyte migration patterns, alter inflammatory cell responses, and affect the barrier function of endothelial cells. Fingolimod, a sphingosine-1-phosphate receptor modulator was approved in 2013 for relapsing-remitting multiple sclerosis.

Conclusion :

This short review has only been able to touch on some of the many significant developments in the treatment of RA. Despite the cure remaining elusive, rheumatologists now have a wide range of effective drugs that will control disease, result in less (or even prevent) joint damage, reduce co-morbidities and increase quality of life to a level that could not have been envisaged before.

References :

1. Cush JJ. J Rheumatol Suppl 2007;80:1-7.
2. Nell VP, et al. Rheumatology 2004;43:906-14.
3. Lard LR, et al. Am J Med 2001;111:446-51.
4. Weinblatt ME, et al. N Engl J Med 1985;312:818-22.
5. Landewé RB, et al. Arthritis Rheum 2002;46(2):347-56.
6. van der Heijde D, et al. Arthritis Rheum 2006;54(4):1063-74.
7. Galloway JB, et al. Rheumatology 2011;50:124-31.
8. Lopez-Olivo MA, et al. JAMA 2012;308(9):898-90.
9. NICE. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. TA130. October 2007.10. Kelley and Firestein's Textbook of Rheumatology