INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic systemic immunoinflammatory disease of unknown cause that primarily targets synovial tissues. It is relatively common with a prevalence of approximately 0.8% in adults all over the world. The prevalence in India is consistent with the world prevalence data at about 0.75%. RA shortens survival and significantly affects quality of life in most patients. The primary target of RA is the synovium where in synovial tissue proliferate in an uncontrolled fashion, resulting in excess fluid production, destruction of cartilage, erosion of marginal bone, and damage to tendons and ligaments. In the last decade, the landscape of therapy of RA has changed dramatically.

The notable changes in the management of RA are based on appreciation of following mandate.

1. The natural history of RA is punctuated by time-dependent early persistent inflammatory disease (3 months to 3 years from onset) and established disease (beyond 3 years) with relapse and remission
2. Remission is the ultimate and perhaps achievable goal of therapy in absence of cure
3. The measurement and monitoring of disease activity and therapeutic outcome are re-defined
4. The disease biology and targeted therapy have been well appreciated to achieve tight control of disease
5. The meaningful use of biologic DMARDs (disease modifying anti-rheumatoid drugs) in addition to conventional DMARDs treatment modalities has improved in the management of RA, with better clinical response rates and improved control of radiographic progression both in early and established disease

CURRENT STATUS OF CONVENTIONAL DMARDs

The conventional DMARDs are increasingly used in RA patients with persistent inflammation beyond 3 months to control synovitis. Early treatment is desirable in order to have greatest impact in preventing damage and disability; yet treatment initiated or ramped up at any phase of the disease will still be capable of decreasing inflammation and preventing additional damage.

There are four general strategies of DMARDs treatment in RA
1. Sequential monotherapy
2. Step-up therapy
3. Induction therapy
4. Individualized targeted ‘tight’ control

All four approaches can be applied early or late in disease, although most commonly these strategies are addressed to be reasonably successful in early (DMARD naïve) disease. The combination of DMARD therapy to increase efficacy of treatment has been supported by clinical trials which include TICORA, COBRA and FINRACO.

However, drawbacks of efficacy and safety have also been reported in various studies. Remission rates with conventional DMARDs have been in the range of 18-35%. With the advent of biological therapies and their combination with conventional DMARD in early disease, remission in the tune of 50% has been achieved.

Corticosteroids and non-steroidal anti-inflammatory drugs exert anti-inflammatory and analgesic effects, but they do not prevent the progressive damage to cartilage and adjacent soft tissues of the joints with only minor benefit for bone erosion and have great potential for gastrointestinal and cardiovascular side effects.

CYTOKINE NETWORK AND BIOLOGICAL DMARDs

The last decade has witnessed phenomenal advances in understanding of molecular pathogenesis of RA followed by usage of modern biotechnical approach in its therapy. This led to the evolution of new classes of therapeutic agents; most recent and notable have been biological response modifiers (BRM) or biological therapies. The traditional disease-modifying nonspecific immune-modulators have been noted to have substantial drawbacks in terms of efficacy and safety. The new biologic agents namely monoclonal antibodies, soluble receptors and molecular mimetics offer the potential to enhance or replace the traditional
Advances in the Management of Rheumatoid Arthritis

Cytokines are essential small protein molecules that act as messengers between the cells of immune system with important roles in defense against infection and tumors. These are abundant at the sites of active inflammation as in rheumatoid arthritis, spondyloarthopathies, psoriatic arthritis. Some cytokines such as interleukin 1 (IL-1) and tumor-necrosis factor alfa (TNF-α) are pro-inflammatory while others like tissue growth factor beta and interleukin-10 (IL-10) are anti-inflammatory. In 1980 Maini and Feldman first identified TNF-alfa as a versatile culprit cytokine that alters tissue remodeling, epithelial-cell barrier permeability, activation of macrophages and recruitment of inflammatory infiltrates and upregulation of adhesion molecules. It also plays a fundamental role in the development, homeostasis and adaptive responses of the immune system. The blocking of pro-inflammatory cytokines or increasing the anti-inflammatory cytokines by genetic engineering forms the possible foundation of treatment strategy.

The production of pro-inflammatory cytokines such as TNF-α, IL-1 is overwhelming in several immuno-inflammatory arthritis such as rheumatoid arthritis (RA). In inflammatory states macrophages predominantly secrete TNF-α as observed in the pathogenesis of RA. The cytokine binds to its receptor on a target cell and it sets a signal cascade and alteration of gene transcription producing various inflammatory mediators. The IL-1 is also abundant in inflammation. Although IL-1 and TNF-α share many biologic actions, research in animal models suggest that IL-1 is the main cartilage destroying cytokine. The receptors for cytokines are present as surface receptors and soluble receptors. The anti-inflammatory substances produced in RA include soluble TNF receptors, IL-1 receptor antagonists (IL1 –Ra) and IL-10.

**CYTOKINE MODULATION**

Broadly there are four mechanisms to block or upregulate cytokine network to restore balance in inflammation. These are –

1. Anticytokine antibodies against TNF-α e.g. Infliximab, Adalimumab
2. Soluble cytokine receptors e.g. Etanercept
3. IL-1 receptor antagonists e.g. Anakinra
4. Antagonistic cytokines e.g. IL-10
5. Antagonistic to IL6 – Tocilizumab

**GENERAL CHARACTERISTICS OF BIOLOGICALS**

The general characteristics of the biologicals vary according to its inherent qualities in terms of composition, structure and mode of action as tabulated below.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Composition</th>
<th>Structure</th>
<th>Mode of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>66% human only and chimeric with mouse</td>
<td>Anti TNFAb + IgGI</td>
<td>Binds to trimeric TNF</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Human</td>
<td>IgGI Specific TNF</td>
<td>Binds to cell surface TNF</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Human</td>
<td>TNF soluble receptor + FcIgGI</td>
<td>Binds to two TNF molecules</td>
</tr>
<tr>
<td>Anakinra</td>
<td>Human</td>
<td>IL-1 Ra</td>
<td>Binds to IL-1 Ra</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Chimeric</td>
<td>Monoclonal Anti CD20Ab</td>
<td>Anti CD20 Ab</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>Human</td>
<td>Monoclonal Anti-IL6</td>
<td>Inhibition of IL6</td>
</tr>
<tr>
<td>Abatacept</td>
<td>Human</td>
<td>T-lymphocyte antigen 4</td>
<td>Co-stimulatory blockade</td>
</tr>
<tr>
<td>CTLA4Ig</td>
<td>Human</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Golimumab</td>
<td>Human</td>
<td>Monoclonal Anti- TNF</td>
<td>Blocks TNF</td>
</tr>
</tbody>
</table>

Currently the following agents have been approved to be used in RA

1. Infliximab (Remicade)
2. Etanercept (Enbrel)
3. Adalimumab (Humira)
4. Anakinra (Kineret)
5. Rituximab (Mabthera)
6. Tocilizumab (Actemra)
7. Abatacept (Orencia)
8. Golimumab (Symponi)

**DOSE SCHEDULE AND ADVERSE REACTIONS**

The dose schedule of commonly used biologicals and their adverse reactions are tabulated below.

**GENERAL GUIDELINES FOR THE USE OF BIOLOGICALS**

- Must have failed at least two DMARDs including Metho-
Table II: Dose schedule and adverse reactions of commonly used biologicals

<table>
<thead>
<tr>
<th>Agent</th>
<th>Usual dose &amp; Route</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>3mg/Kg IV infusion at weeks 0, 2 and 6 wks followed by maintenance dosing every 8 weeks in combination with MTX</td>
<td>Local reactions, Infections, Antibody formation, Demyelination Lymphomas</td>
</tr>
<tr>
<td>Etanercept</td>
<td>25mg SC twice a week or 50mg once a week with or without MTX</td>
<td>Local reaction, ANF positivity, Infections, Demyelination</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>40mg SC every 2 weeks with or without MTX</td>
<td>Uri, Local reactions, Infections, Demyelination</td>
</tr>
<tr>
<td>Anakinra</td>
<td>100mg SC once daily with or without MTX</td>
<td>Local reactions, Infections, Neutropenia</td>
</tr>
<tr>
<td>Rituximab</td>
<td>500-1000mg IV infusion at weeks 0 and 2</td>
<td>Local reaction, Infections</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>8mg/Kg every 4 weeks by IV infusion</td>
<td>Local reaction, Infections</td>
</tr>
<tr>
<td>Golimumab</td>
<td>50-100mg every 4 weeks by sc or IV infusion</td>
<td>Local reaction, Serious Infections</td>
</tr>
</tbody>
</table>

Trexate (20-25mg/week), DAS28>5.1
- Early Rheumatoid Arthritis
- Must have active disease
- Have no major infections in preceding six months
- Non-pregnant, non-breast feeding women

CLINICAL IMPLICATIONS

The early and effective therapy within 3 years of onset of RA is rewarding in terms of prompt clinical improvement and retardation of radiographic joint damage and consequent deformities. It is agreed that in the pathogenesis of RA antigenic peptides stimulate the CD4 cells, which in turn activate macrophages, B cell and synovial fibroblasts. The TNF-alfa-primarily produced by activated monocytes and macrophages – mediates both inflammatory synovitis and articular matrix degradation. The targeted therapies have been directed at the molecules shown to cause tissue injury.

The TNF-alfa blockade in patients with active rheumatoid arthritis results in rapid and sustained improvement in symptoms and signs of disease, improvement in the quality of life and protection of joints from structural damage. Radiological progression over one or two year period was more effectively abolished. Blocking of TNF-alfa in RA results in down regulation of IL-1β mRNA at the systemic level and other cytokines like IL6 within days. Cytokine antagonists, traditionally, are indicated in resistant RA with active disease (DAS-28 Score > 5.1). Resistant RA are those who failed to respond to conventional DMARDs including at least MTX for at least 6 months.

The efficacy and safety of various biologicals have been documented by number of studies. Treatment with infliximab not only attenuates progression of joint damage but it may lead to protect the joint with healing of bone erosion and even reduction in IgM rheumatoid factor titres by approximately 37% within 6 months. The clinical improvement is dose dependent and the higher trough levels may be beneficial for treatment of certain cases of RA. Early trials with infliximab given with or without low-dose methotrexate (MTX) in patients with active RA despite methotrexate therapy demonstrated effectiveness of the compound. The safety profile seemed acceptable relative to the benefit provided. The combination therapy of infliximab and MTX provides greater clinical, radiographic and functional benefits than treatment with MTX alone as studied in ASPIRE 3-arm trial in 1049 patients.

In another study (ATTRACT) throughout 102 weeks therapy infliximab plus MTX provided significant, clinically relevant improvement in physical function and quality of life, accompanied by inhibition of progressive joint damage and sustained improvement in the signs and symptoms of RA among patients who previously had an incomplete response to MTX alone. In patients with early RA, initial combination therapy either prednisone or infliximab resulted in earlier functional improvement and less radiographic damage after 1 year than did sequential monotherapy or step-up combination therapy. Effective TNF-alfa neutralization by infliximab improves anemia of chronic disease (ACD) in RA by reducing erythroid apoptosis. Early trials with etanercept alone or with methotrexate in patients with persistently active RA has been proved to be safe, well-tolerated and clinically beneficial on long term follow up.

The combination therapy of Etanercept and MTX in active RA achieved clinical remission with functional improvement and retardation of joint damage. Efficacy of Etanercept in RA has been successfully documented in ERA (Early RA) and the TEMPO trials with improvement in ACR response and decrease in disease activity and laboratory parameters. The dose is 25mg twice a week or 50mg SC once a week. The COMET trial also shows the benefit in early RA with combination of Etanercept and Methotrexate.

Adalimumab given as monotherapy in long standing active RA is safe, well-tolerated and associated with a clinically significant improvement in the signs and symptoms of the disease. It is shown in ARMADA trial in variable dose of Adalimumab 20, 40 or 80 mg subcutaneously every other week with concomitant MTX therapy in active RA is beneficial. Anakinra has been extensively studied as monotherapy for RA and has been demonstrated to be clinically effective.

The combination of Abatacept (CTLA 41g) and MTX improved the clinical features, physical function and quality of life in active RA despite only MTX therapy only. It requires further investigations.

The eligibility criteria for anticytokine therapy are more stringent as shown in those RA patients with unacceptable disease activity despite MTX therapy in presence of five swollen joints and elevated ESR more than 28 mm/hour or C-reactive protein > 20...
mg/L and DAS-28 score more than 3.2 (44). According to WHO collaborating center there is good evidence that anti-TNF therapy is effective in early disease.\footnote{30}

Rituximab is evaluated in a small subsets of patients with active, evolving erosive RA and the results are encouraging. It is also shown to be effective to sub group of RA patient who has shown resistance to other anti-TNF alpha therapy. However the differences in B cell commitment in RA pathobiology might account for the different responses among the patients.\footnote{31} In REFLEX Study rituximab in combination with MTX in AntiTNF-alfa in RA patients with inadequate response has produced significant clinical improvement at 24 weeks.\footnote{32} In DANCER study Rituximab has been tried with 500mg or 1000mg infusion given 2 weeks apart and it is found highly effective in 24 weeks.\footnote{33} Remission in disease activity has been found as long as eighteen months with a very few patients requiring additional therapy. There are mild local reaction on Rituximab infusion.

Tocilizumab (IL-6 receptor antagonist) represents a promising new approach to the treatment of RA since IL-6 plays a pivotal role in mediating both local and systemic manifestation of RA. Tocilizumab infusion therapy (8mg/kg every 4 weeks) has been found to prevent joint destruction in RA patients as observed in SAMURAI Study.\footnote{34} Rapid reduction of disease activity with Tocilizumab has been observed in early or established RA patients in OPTION Study\footnote{35} and AMBITION Study.\footnote{36} Moreover, significant and rapid reduction in disease activity with Tocilizumab in combination with six different DMARDs in RA patients having inadequate response to DMARDs in TOWARD trial.\footnote{37}

Golimumab – a new biological against TNF alfa- is found effective in patients of active RA given by monthly subcutaneous injections despite methotrexate therapy.\footnote{38}

Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis.\footnote{39}

SAFETY AND TOLERABILITY OF BIOLOGICAL AGENTS

The efficacy of the biological agents have been shown to be impressive in different studies. However cytokine blockade at the initial phase is associated with injection site reactions and development of upper respiratory infections, cellulitis, pneumonia. TNF-alfa has a central role both in the host immune response to Myco, tuberculosis infection and the immunopathology of the disease. Anti TNF-alfa agents have caused reactivation of TB from latent infection. Most of the patients develop extrapulmonary or disseminated TB following marked immune suppression usually 12 weeks after infliximab therapy. The prevalence of TB following etanercept is rather uncommon in early clinical trials but seem to appear about 11.5 months after the initial injection.\footnote{40,41}

Before starting biological, patients must be screened for latent TB infection. A careful clinical examination, chest radiograph and Mantoux test are mandatory. These drugs are contraindicated in patients with active infections. There are no TB cases associated with use of Anakinra. The infliximab therapy has been associated rarely with histoplasmosis, aspergillosis, pneumocystis jirovacci and listeria monocytogenes infection. The use of biologics is sometimes associated with the development of antibodies e.g. antinuclear antibodies (ANF) and Anti ds-DNA. Mild lupus-like syndrome have been reported in some patients but it is reversible when drug is discontinued.\footnote{42} Etanercept and infliximab have been reported to cause cutaneous vasculitis. Demyelinating syndromes have also been reported occasionally.\footnote{43} TNF blockers are contraindicated in presence of early or advanced heart failure. Until 2002, 26 cases of malignancy (mostly lymphoma) after anti TNF therapy had been reported to the FDA of which 18 after etanercept therapy (19 per 1 lac population treated) and 8 after infliximab therapy (6.6 per 1 lac population treated). However long term observation is warranted to decide the issue.\footnote{44}

Adalimumab is well tolerated but with mild local reaction. Rituximab has not been associated with significant infusion related adverse events except some minor infection. Abatacept has been well tolerated during the clinical trials. The most common side effects are headache upper respiratory infections, nausea, vomiting, musculoskeletal pain.\footnote{45}

ACR recommendation for TB screening before use of biologicals is addressed as below.\footnote{46}

The use of biologicals in groups of patients of RA is recommended as per ACR guidelines with algorithmic approach as below

1. Entry Group
2. Failed MTX mono-therapy group
3. Failed MTX Combination therapy

CONCLUSION

The advances in the management of RA is a field of exciting

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig2.png}
\caption{ACR recommendation for screening for TB among RA patients being considered for biologicals}
\end{figure}

\footnote{Risk factors for developing TB as per CDC criteria}
Fig. 3: Algorithmic approach for use of Biologicals in RA groups of patient – ACR Recommendation for three groups of patients

- **Pts with RA < 6 mts**
  - Low/Moderate < 6 mts
  - High for < 3 mts
  - Features of Poor prognosis
  - With Conventional DMARDs
  - Without Conventional DMARDs
  - With Anti-TNF & MTX
  - Without Cost/Ins coverage

Fig. 4: Algorithmic approach for use of Biologicals in RA groups of patients – ACR Recommendation for three groups of patients

- **Pts with RA ≥ 6 mts who failed prior MTX mono therapy**
  - Low
  - Disease Activity
  - High
  - Moderate
  - Features of poor prognosis
  - With Conventional DMARDs
  - Without Conventional DMARDs
  - With Anti-TNF

Fig. 5: Algorithmic approach for use of Biologicals in RA groups of patients – ACR Recommendation for three groups of patients

- **Pts with RA ≥ 6 mts who failed prior MTX combo therapy or after sequential admin of other non-biologics**
  - Low
  - Disease Activity
  - Moderate/High
  - Features of poor prognosis
  - With Conventional DMARDs
  - Without Abatacept or Anti-TNF or Rituximab

**REFERENCES**