Use of Biologics for Management of Rheumatoid Arthritis

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1 Introduction

Rheumatoid arthritis (RA) is a chronic, frequently progressive, and destructive autoimmune disease. As the disease progresses, irreversible joint damage may lead to loss of function and physical disability (World Health Organization, 2004). Patients with RA have reduced quality of life compared with healthy people. RA is associated with serious co-morbidities such as heart disease, infection, and malignancies (Boonen & Severens, 2011). This can result in a 5–10 year reduction in life expectancy (Kvien, 2004), reduced quality of life compared with other serious conditions (Lundkvist et al., 2008) and a considerable economic burden (Lundkvist et al., 2008). RA is a disabling disease, and the disability is usually measured by using a questionnaire called the Health Assessment Questionnaire (HAQ). Assessment of tenderness and swelling in the joints is done by the DAS (Disease Activity Score) for 28 joints. The counting of number of swollen and tender joints in the following 28-joints is done: 10 proximal interphalangeal joints (PIP), 10 metacarpo-phalangeal joints (MCP), 2 wrists, 2 elbows, 2 shoulders and 2 knees (Misra et al., 2008).

Since this disease cannot be cured, management of this disease becomes an important endeavor with the aim of inducing and maintaining remission, and altering the course of disease. Disease Modifying AntiRheumatic Drugs (DMARDs, methotrexate followed by leflunomide, sulfasalazine and hydroxychloroquine) are the recommended first line treatment for RA. However they are slow acting and toxicity monitoring is essential in patients on DMARDs (“Indian Guidelines”, 2002; Misra et al., 2008) Cortico-
steroids are affordable and do have a disease modifying effect, but are beneficial when used over a short period of time, beyond this side effects outweigh any benefit. Routine use of steroids is therefore not recommended (Misra et al., 2008). Other drugs like Non-steroidal anti-inflammatory drugs (NSAIDs), gold salts, hydroxychloroquine, d-penicillamine are also used in the treatment but have varied effects (Misra et al., 2008).

The approach to treatment of RA has seen significant advances in the last two decades. There has been a paradigm shift in the management of RA which now aims at induction of remission and maintenance of tight control (treat to target) through use of conventional DMARDs and biologics therapy. Biological agents that target inflammatory cytokines and cells within the synovium and immune system are now widely available. Biologics approved for RA include abatacept, adalimumab, anakinra, etanercept, infliximab, golimumab, rituximab and tocilizumab. These agents not only reduce the signs and symptoms but also slow down the progression of the disease. Despite their clinical superiority, biologics can cause side effects (pain at injection site, infusion reaction, chances of super infection and reactivation of tubercular bacteria in some cases) and do not work in some patients.

The use of biologics has consolidated the management of RA. Debate still exists as to when one should start biologics, how long they should be used, how they should be tapered off, whether one biologic can be switched with another. This review focuses on available biologics, their differences, clinical considerations for biological therapy in RA, the advent of biosimilars/intended copies in the space of RA, data from biologic registries and the future perspectives in RA treatment.

1.1 Historical Background

These agents are called biologics because they mimic the action of proteins involved in the immune system, these agents did bring about a greater relief to patients than any other treatment known and hence the real excitement in rheumatology happened after the introduction of these biological agents in 1998. They are made by genetic engineering in tissue cultures of various kinds. The work in the arena of biologics in RA started way back in the late 1980s when tumor necrosis factor-alpha (TNF-α) was identified in the synovium of RA patients (Buchan et al., 1988). Specific antibody to block this TNF-α (CA2) was simultaneously produced. This CA2 was a chimeric-mouse human antibody (later named infliximab). Initially CA2 was used as a tool for the further determination of importance of TNF-α in the pathogenesis of RA. Experiments showed that synovial membrane cells produced a number of inflammatory molecules including the cytokines TNF-α and interleukin-1 (IL-1) (Breenan et al., 1989; Feldmann et al., 1990). When TNF –α was blocked using antibodies like CA2 it appeared that it had a unique position in the hierarchy of inflammatory cytokines. Blocking TNF-α also blocked the production of other cytokines, including IL-1 (Feldmann et al., 1990). Follow up experiments demonstrated the efficacy of TNF-α blockade in animal models of RA (Williams et al., 1992). A very successful pilot study in the early 1990s showed that TNF-α blocking antibodies administered intravenously to human subjects with RA showed dramatic results (Elliot et al., 1993). In an effort to reduce the risk of immuno-
genicity as much as possible, further development has led the production of fully human antibodies that contain 100% human protein. Adalimumab was the first fully human recombinant anti-TNF-α monoclonal antibody (mAb) approved for the treatment of patients with RA (Bain & Brazil, 2003). Other biologics (etanercept, rituximab, abatacept, anakinra, golimumab and abatacept) also made their way in the RA management armamentarium.

2 Biological Agents in RA

The introduction of “biological agents” has revolutionized the treatment of RA. These therapies target pro-inflammatory cytokines (e.g. TNF-α, IL-1 or IL-6) or cellular membrane receptors (e.g. CD20 and CD4) in the sufferers (Fan & Leong, 2007). All these agents have been evaluated against the ACR 20, ACR50 and ACR70 outcomes, European League Against Rheumatism (EULAR) response criteria based on the Disease Activity Score (DAS) on 28- or 44-joint count were also adopted and the Health Assessment allowed for the accurate assessment of functional status.

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Approved Year</th>
<th>Class</th>
<th>Type</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>1998</td>
<td>Chimeric mAb</td>
<td>IgG1</td>
<td>TNF-α</td>
</tr>
<tr>
<td>Etanercept</td>
<td>1998</td>
<td>Human dimeric fusion protein</td>
<td>Fusion protein</td>
<td>TNF-α; TNF-B (lymphotoxin α)</td>
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<td>Anakinra</td>
<td>2001</td>
<td>Human interleukin-1 receptor antagonist</td>
<td>Receptor antagonist</td>
<td>IL-1</td>
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<td>Fusion protein</td>
<td>CD-28</td>
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<td>IgG1</td>
<td>CD-20</td>
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<td>2008</td>
<td>Humanized mAb</td>
<td>Fab</td>
<td>TNF-α</td>
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<td>2009</td>
<td>Human mAb</td>
<td>IgG1</td>
<td>TNF-α</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>2009</td>
<td>Humanized mAb</td>
<td>IgG1</td>
<td>IL-6R</td>
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Table 1: Lists the biologics approved in RA worldwide.

2.1 Monoclonal Antibodies in RA

2.1.1 Infliximab

• **Indications** In combination with methotrexate (MTX) for the treatment of RA in pa-
tients who have had an inadequate response to MTX alone. It is also indicated for
the treatment of active, severe RA patients' naïve for MTX or other disease modify-
ing antirheumatic drugs (DMARDs), Crohn’s disease, ankylosing spondylitis, psori-
atic arthritis, ulcerative colitis and plaque psoriasis.

- **Structure** Chimeric IgG1 mAb, with murine variable (Fv) domain of mouse anti-
human TNF-α antibody and constant (Fc) sequences of human IgG1, produced by
recombinant cell culture technique.

- **Mechanism of action** Specifically recognizes and binds with both soluble
and membrane-bound TNF-α. This binding neutralizes the biological activity of
TNF-α by inhibiting its binding to receptor (Scallon *et al*., 1995). By blocking TNF-α,
infliximab reduces the release of pro-inflammatory cytokines (IL-1 and IL-6) and
acute phase reactants, the activation of eosinophils and neutrophils, and the leuco-
cyte migration (Janssen Biotech Inc, 2013a). Infliximab does not neutralize TNF-B
(lymphotoxin a).

- **Dosage** Infliximab is usually given as a 3 mg/kg dose by intravenous (IV) infusion
to RA patients followed by similar doses at 2 and 6 weeks after the first infusion,
then every 8 weeks, although the dose can be increased up to 7.5 mg/kg. It should
be administered in combination with methotrexate (MTX).

- **Adverse events** Severe side effects are rare; however, the chances of tubercul-
osiis (TB) are highly increased in patients receiving infliximab (Gardam *et al*., 2003) and
therefore treatment of latent TB infection is recommended, prior to initiating the
therapy (Janssen Biotech Inc, 2013a). The most common adverse events are head-
ache, vertigo, viral infection, flushing, upper and lower respiratory tract infection,
(Janssen Biotech Inc, 2013a).

- **Clinical efficacy** In RA patients whose disease remains active despite MTX, inflixi-
mab, in combination with MTX, has been shown to reduce signs and symptoms, to
inhibit radiographic progression of structural damage and to improve physical
function in RA patients not responding to MTX. The three multicentre phase III cli-
nical trials termed ATTRACT (Anti- TNF Trial in Rheumatoid Arthritis with Con-
comitant Therapy) (Gardam *et al*., 2003), ASPIRE (Active-controlled Study of Pa-

tients receiving Infliximab for treatment of Rheumatoid arthritis of Early onset)
(Lipsky *et al*., 2000) and START (Safety Trial for Rheumatoid Arthritis with Remi-
cade [infliximab] Therapy) (St. Clair *et al*., 2004; Westhovens *et al*., 2006) done in
around 2500 RA patients does justify this. Herein ACR20 was reached by a 1.5- to 3-
fold higher patient rate with infliximab than placebo. Radiographic progression was
reduced not only in patients in the ATTRACT study who had a clinical response to
infliximab plus MTX, but also in those who did not have a clinical response (Smolen
*et al*., 2005).

2.1.2  **Adalimumab**

- **Indications** For RA in combination with MTX, in patients who have had an inade-
quate response to MTX alone. For the treatment of active, severe RA patients naïve for MTX or other DMARDs, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis, juvenile idiopathic arthritis, Crohn’s disease, ulcerative colitis and non-radiographic axial spondyloarthritis.

- **Structure** Adalimumab is a recombinant fully human monoclonal IgG1 antibody, composed of two kappa light chains (24 kDa each) and two IgG1 heavy chains (49 kDa each), expressed in Chinese hamster ovary (CHO) cells. Because of human origin it is less immunogenic than infliximab (Paul & Anderson, 2005).

- **Mechanism of action** Adalimumab recognizes both soluble and membrane-bound TNF-α and inhibits its biologic activity by blocking interaction with p55 and p75 cell surface TNFR1 and TNFR2 receptors (Rau, 2002). Furthermore, adalimumab treatment exerts the down regulation of expression of other pro-inflammatory cytokines, such as IL-6, IL-8 and GM-CSF (granulocyte macrophage colony-stimulating factor) (AbbVie Inc, 2014).

- **Dosage** For adult RA patients, the recommended dose is 40 mg on every other week, as a subcutaneous injection. It can be administered in combination with MTX or as monotherapy.

- **Adverse events** Because adalimumab is a fully human antibody, some potential adverse reactions and antigenicity of chimeric and humanized mAbs should be minimized. However, like infliximab, the chances of TB infection reactivation are highly increased in patients receiving adalimumab; therefore, treatment of latent TB infection is mandatory, prior to initiating the therapy (AbbVie Inc, 2014). Most common side effects are injection site reaction, upper respiratory infection, sinusitis, leucopenia, anaemia, hyperlipidaemia, and so on. The production of anti-adalimumab antibodies (AAA) has also been seen in clinical trials in patients with RA (AbbVie Inc, 2014).

- **Clinical efficacy** In patients with active RA the addition of adalimumab to long-term MTX therapy provided significant, rapid and sustained improvement in disease activity over 24 weeks compared with MTX plus placebo, as shown by the ARMADA (Anti-TNF Research study program of the Monoclonal Antibody D2E7 in patients with Rheumatoid Arthritis) trial (Weinblatt et al., 2003). The long-term, open label extension of this clinical trial demonstrated that adalimumab plus MTX was associated with sustained clinical response and remission in patients with RA over a 4-year period (Weinblatt, 2006). The PREMIER study, conducted at 133 investigational sites across the world showed that in patients with early, aggressive RA, combination therapy with adalimumab plus MTX was significantly superior to either MTX or adalimumab monotherapy in improving signs and symptoms of disease, inhibiting radiographic progression and reaching clinical remission (Breedveld et al, 2006). Moreover the ReAct (Research in Active Rheumatoid Arthritis trial) recently demonstrated that adalimumab induced a good clinical response after 12 weeks of treatment in 69 % of patients who failed with other biologic or non-biologic DMARDs (Burmester et al., 2007).
2.1.3 Rituximab

- **Indications** For the treatment of patients with moderately to severely active RA who did not adequately respond to one or more TNF antagonist therapies.

- **Structure** Rituximab is a genetically engineered chimeric murine/human monoclonal antibody to CD20 antigen found on the surface of normal and malignant B lymphocytes. It is produced by a cell suspension culture technique in a CHO cell mammalian expression system. The rituximab antibody consists of IgG1 kappa Ig containing variable region sequences of murine light chains (213 amino acids) and heavy chains (451 amino acids) and human constant region sequences (Biogen Idec Inc, 2014).

- **Mechanism of action** CD20 is a B cell-specific antigen expressed on the surface of B lymphocytes. Rituximab is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes. Upon binding to CD20, rituximab mediates B-cell lysis. Possible mechanisms of cell lysis include complement dependent cytotoxicity (CDC) and antibody dependent cell mediated cytotoxicity (ADCC). The antibody induced apoptosis in the DHL 4 human B cell lymphoma cell line. B cells are believed to play a role in the pathogenesis of RA and associated chronic synovitis. In this setting, B cells may be acting at multiple sites in the autoimmune/inflammatory process, including through production of rheumatoid factor (RF) and other autoantibodies, antigen presentation, T-cell activation, and/or proinflammatory cytokine production (Stern & Hermann et al., 2005).

- **Dosage** In RA rituximab is given as two 1,000 mg i.v. infusions separated by 2 weeks.

- **Adverse events** Common adverse events reported are infections which include upper respiratory tract infections, bronchitis, nasopharyngitis, sinusitis and urinary tract infections. The incidence of serious infections in the rituximab-treated patients was 2 versus 1 % in the placebo treated patients (Biogen Idec Inc, 2014).

- **Clinical efficacy** In patients with active RA despite MTX treatment, a single course of two infusions of rituximab (1,000 mg on days 1 and 15), alone or in combination with either cyclophosphamide or MTX, provided significant improvement in disease symptoms at both weeks 24 and 48 (Olszewski & Grossbard, 2004). A phase III study on 520 RA patients demonstrated that a single course of two 1,000 mg infusions of rituximab administered 2 weeks apart, in combination with glucocorticoids and MTX, produced significant clinical and functional benefits at 24 weeks in patients with longstanding and active RA who had an inadequate response to one or more anti-TNF-a therapies (Edwards et al., 2004).

2.1.4 Tocilizumab

- **Indications** For the treatment of patients with moderate to severe active RA who do not respond to one or more DMARDs or TNF antagonist therapies.
Structure Tocilizumab is a humanized anti-human IL-6R antibody engineered by grafting the complementarity determining regions (CDRs) of a mouse anti-human IL-6R antibody into human IgG1 to create a humanized mAb with a human IL-6R specificity (Sato et al., 1993).

Mechanism of action IL-6 is a pro-inflammatory cytokine that binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and Tocilizumab inhibits sIL-6R and mIL-6R-mediated signaling. Thus it entirely neutralizes IL-6 actions (Sato et al., 1993).

Dosage Dosage is 8 mg per kg of body weight, once every 4 weeks intravenously; however, depending on the patient’s response, the physician may decrease the dose when appropriate. There is no reported experience with the use of tocilizumab with TNF antagonists and/or other biologic treatments for RA; therefore, at the moment it is not recommended for use with other biological therapies. Tocilizumab can be used subcutaneously also.

Adverse events Upper respiratory tract infections are very common adverse events of tocilizumab; Common adverse reactions may include lung infection (pneumonia), abnormal liver function tests, conjunctivitis, headache, hypertension and serious hypersensitivity reactions.

Clinical efficacy Three multicentre, double-blind, placebo-controlled phase III trials evaluated the efficacy and safety of tocilizumab. In the OPTION (tOcilizumab Pivotal Trial in methotrexate Inadequate respONders) trial, 59 and 48% of 623 patients who received tocilizumab 8 and 4 mg/kg plus MTX, respectively, achieved ACR20 at week 24, compared with 27% of patients who received placebo plus MTX (Smolen et al., 2008). The TOWARD (Tocilizumab in cOmbination With traditional DMARD therapy) trial found that 61% of 805 patients who received tocilizumab 8 mg/kg plus DMARD(s) achieved ACR20 at week 24, compared with 25% of 415 patients treated with DMARDs plus placebo (Genovese et al., 2008). LITHE trial (tociL-Izumab safety and THE prevention of structural joint damage) showed in 1,196 patients followed for 2 years an improvement in disease activity or disease remission (DAS28- Disease activity score of 28 joints- 2.6) in 30 and 47% of patients treated with tocilizumab 4 and 8 mg/kg, respectively, compared with 8% of patients treated with placebo plus MTX. Additionally, the 1-year LITHE study results showed that patients treated with tocilizumab (4 or 8 mg/kg) plus MTX experienced a significant inhibition in the progression of structural joint damage, as measured by the change in the mean Genant-modified Sharp score, compared with patients treated with MTX plus placebo (Kremer et al, 2009).

2.1.5 Golimumab

Indications For the treatment of moderate to severe active RA, in combination with MTX, in patients who have had an inadequate response to MTX alone. It is also indicated for the treatment of active, severe RA patients naive for MTX or other
DMARDs, active and progressive psoriatic arthritis and severe, active ankylosing spondylitis.

- **Structure** Golimumab is a fully human IgG1 monoclonal antibody against TNF-α that targets and neutralizes both the soluble and the membrane-bound form of TNF-α (Hirohata et al., 2007).

- **Mechanism of action** Golimumab binds with high affinity to both the soluble and transmembrane forms of TNF-α. It forms large complexes when bound to TNF-α trimers, usually three golimumab molecules bind to one or two TNF-α trimers. The binding of golimumab with human TNF-α inhibits the binding of TNF-α to p55 and p75 TNF-α receptor fusion protein, and neutralizes TNF-α-induced cell-surface expression of the adhesion molecule E-selectin, vascular cell adhesion molecule (VCAM-1) and intercellular adhesion molecule (ICAM-1) by human endothelial cells. Golimumab does not bind with human lymphotoxin (Hirohata et al., 2007; Janssen Biotech Inc, 2013b).

- **Dosage** Golimumab is administered subcutaneously every 4 weeks. It is given in a single 50-mg dose, via a prefilled autoinjector or prefilled syringe; however, this dose could be doubled if the patient has a body weight of more than 100 kg and has no response after 3–4 doses (Janssen Biotech Inc, 2013b).

- **Adverse events** Mild to severe bacterial, viral and other infections along with anemia, headache, allergic reactions (bronchospasm, hypersensitivity, urticaria), increase in liver enzymes, constipation, abdominal pain, dyspepsia, hypertension, and so on have been reported (Janssen Biotech Inc, 2013b).

- **Clinical efficacy** Golimumab has been studied for the treatment of moderate to severe active RA in multicentre, randomized, double-blind controlled trials that enrolled over 1,500 patients. These trials were called GO-FORWARD, in which enrolled RA patients naïve for biologic TNF-α blocker (N = 444) had active RA despite a stable dosage of at least 15 mg/week of MTX (Keystone et al., 2008a); GO-AFTER, in which enrolled RA patients were previously treated with one or more anti-TNF-α agents (N = 461) (Smolen et al., 2009a); and GO-BEFORE, which enrolled patients with active RA who were MTX-naïve (N = 637) (Emery et al., 2009). In these studies golimumab was shown to improve signs and symptoms in moderate to severe active RA patients. It has been shown to be effective in RA patients who are incomplete responders or naïve to MTX, as well as in those patients previously treated with at least one anti-TNF-α therapy.

### 2.1.6 Certolizumab Pegol

- **Indications** For the treatment of adults with moderate to severe active RA in combination with MTX, in patients who have had an inadequate response to MTX alone.

- **Structure** Certolizumab pegol is a recombinant, humanized anti-TNF-α Fab conjugated to approximately 40,000 Da polyethylene glycol (PEG2-MAL40K) (Winter et
The Fab is manufactured in Escherichia coli and is subsequently purified and conjugated to PEG2MAL40K, to produce certolizumab pegol.

- **Mechanism of action** Certolizumab pegol binds to human TNF-a with high affinity and neutralizes both membrane-bound and soluble forms. It does not neutralize lymphotoxin a (TNF-B) (Nesbitt & Henry, 2004).

- **Dosage** The recommended dosage of certolizumab pegol for adult RA patients is 400 mg (given as two subcutaneous injections of 200 mg) initially and at weeks 2 and 4, followed by 200 mg every other week. However, for maintenance dosing 400 mg every 4 weeks can be considered.

- **Adverse events** Viral and bacterial infections have been commonly reported. Other common adverse events are headache, allergic reactions (bronchospasm, hypersensitivity and urticaria), increase in liver enzymes, rash, pyrexia, leucopenia, pain, and so on.

- **Clinical efficacy** Phase III FAST4WARD (eFficAcy and Safety of cerTolizumab pegol – 4 Weekly dosAge in RheumatoiD arthritis) study demonstrated that treatment with certolizumab pegol 400 mg monotherapy every 4 weeks effectively reduced the signs and symptoms of active RA in patients previously failing more than one DMARD compared with placebo, and demonstrated an acceptable safety profile (Fleischmann *et al.*, 2009). In the RAPID 1 and 2 (Rheumatoid Arthritis Prevention of structural Damage) studies conducted on over 1,600 active RA patients, certolizumab pegol allowed patients to reach ACR20, 50 or 70 in a 3- to 15-fold higher patient percentage than placebo (Smolen *et al.*, 2009b; Keystone *et al.*, 2008b).

### 2.2 Fusion Proteins in RA

#### 2.2.1 Abatacept

- **Indications** For the treatment of patients with moderate to severe active RA who had inadequate response to one or more DMARDs, including MTX and TNF-a antagonists (Moreland *et al.*, 2006). Also indicated in patients with moderate to severe juvenile idiopathic arthritis (JIA) who had inadequate response to other DMARDs, including at least one TNF antagonist and in adult RA naïve to TNF-a inhibitors. Abatacept may be used as a monotherapy or concomitantly with DMARDs.

- **Structure** Abatacept is a fully human soluble fusion protein comprising the extracellular domain of human cytotoxic T lymphocyte associated antigen-4 (CTLA-4) linked to the Fc (hinge, CH2 and CH3 domains) portion of human IgG1.

- **Mechanism of action** T cells require two distinct signals for full activation. The first signal is an antigen-specific interaction between the antigenic peptide presented in the context of the major histocompatibility complex (MHC) on the surface of antigen-presenting cells (APC) and the T cell receptor. The second signal comes from the binding of a ligand on the APC to the co-stimulatory receptor on the T cell; the
interaction of CD28 on T cells with CD80 or CD86 on APCs is a key example of a co-stimulatory signal (Linsley et al., 1992). CTLA-4 instead is the inhibitory CD28 counterpart. Abatacept binds with its extracellular CTLA-4 portion to CD80 and CD86 on APC with a higher affinity than CD28, thus blocking its interaction with CD28 on T cells (Linsley et al., 1992). Therefore, abatacept prevents the positive co-stimulation signal required for full T cell activation.

- **Dosage** Recommended dose is 10 mg/kg of body weight. For an adult patient with body weight below 60 kg the recommended dose is 500 mg, for 61–100 kg it is 750 mg and for over 100 kg it is 1,000 mg; following the initial administration, abatacept should be given at 2 and 4 weeks after the first infusion and every 4 weeks thereafter. Abatacept can be used subcutaneously also.

- **Adverse events** Most common side effects with abatacept are upper respiratory infections, including nasopharyngitis. Moreover, lower respiratory tract infections, urinary tract infections, leucopenia, headache, conjunctivitis, arterial hypertension, cough, abdominal pain, diarrhoea, nausea, vomiting, dyspepsia, increase of liver enzymes, rash, alopecia, itching, arthralgia and asthenia may also commonly be observed. (Bristol-Myers Squibb Company, 2013; Weinblatt et al., 2006)

- **Clinical efficacy** The AIM (Abatacept in Inadequate responders to Methotrexate) study, a 12-month, double-blind, randomized, placebo-controlled investigation on 638 RA patients, demonstrated that combination of abatacept and MTX improved the signs and symptoms of disease, physical function and quality of life in patients who had active RA despite ongoing MTX therapy. Clinical responses were dose-dependent; patients treated with 10 mg of abatacept per kg achieved the best results. Abatacept was safe and well tolerated, and the rate of discontinuation because of adverse events was no higher than that in the placebo group (Reiser & Stadecker, 1996). A further phase III trial called ATTAIN (Abatacept Trial in Treatment of Anti-TNF INadequate responders) of 6-month duration in RA patients with a current or previous inadequate response to TNF-a inhibitors therapy also demonstrated significant benefit with abatacept in this patient population (Emery et al., 2006). ASSURE (Abatacept Study of Safety in Use with other RA thErapies) studied the safety of abatacept compared to placebo when used in combination with biologic and nonbiologic DMARDs (Weinblatt et al., 2006).

### 2.2.2 Etanercept

- **Indications** In combination with MTX for moderate to severe active RA and juvenile idiopathic arthritis. It is also indicated for ankylosing spondylitis, psoriatic and chronic plaque psoriasis including pediatric psoriasis

- **Structure** Etanercept is a fully human dimeric fusion protein, produced by recombinant DNA technology in a CHO mammalian cell expression system. It consists of two molecules, the extracellular portion of soluble TNFR2 (p75) receptor and the constant (Fc) portion of an IgG1 heavy chain (Feldman & Maini, 2001). The Fc com-
ponent contains the CH2 domain, the CH3 domain and hinge region, but not the CH1 domain of IgG1 (Immunex Corporation, 2013).

- **Mechanism of action** Etanercept is a competitive inhibitor of the binding of TNF-α to its cell surface receptor and can bind to two TNF molecules. It inhibits the biological function of TNF-α by preventing the receptor stimulation. It binds primarily to soluble TNF-α as well as TNF-B (lymphotoxin-α) by cell surface TNFRs (Feldman & Maini, 2001; Immunex Corporation, 2013).

- **Dosage** Recommended dosage is 50 mg given once a week. MTX, salicylates, glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs) or analgesics may be continued during treatment.

- **Adverse events** Common side effects include injection site reactions, upper and lower respiratory infections, urinary tract and skin infections, allergic reactions, and so on (Feldman & Maini, 2001; Immunex Corporation, 2013).

- **Clinical efficacy** In patients with early, active RA etanercept as monotherapy slowed radiographic progression, and improved the disability index score significantly better than MTX monotherapy did over a 2-year period (Genovese et al., 2002). The TEMPO (Trial of Etanercept and Methotrexate with radiographic and Patient Outcomes) study compared the combination of etanercept and MTX with either etanercept or MTX monotherapy in patients with active RA in whom previous treatment with DMARDs other than MTX had failed. The 2-year data demonstrated that combination therapy was significantly better than either monotherapy in reducing disease activity, improving function and slowing radiographic progression (van der Heijde et al., 2006). The COMET (COmbination of Methotrexate and ETanercept in early rheumatoid arthritis) study compared the clinical efficacy and safety of etanercept and methotrexate combination therapy with methotrexate alone on clinical disease activity and progressive joint damage in patients with early active RA. According to 2-year results from this trial treating RA patients with a combination of etanercept plus methotrexate leads to better results (gives better performance) than methotrexate alone (Emery et al., 2008).

### 2.3 Receptor Antagonists for Treatment of RA

#### 2.3.1 Anakinra

- **Indications** For RA patients who have failed one or more DMARDs.

- **Structure** Anakinra is a recombinant, nonglycosylated form of the human interleukin-1 receptor antagonist (IL-1ra), which is produced in E. coli expression systems by recombinant DNA technology (Calabrese, 2002; Arend, 2002).

- **Mechanism of action** Anakinra blocks the biologic activity of interleukin-1α (IL-1α) and interleukin-1β (IL-1β) by competitively inhibiting their binding to interleukin-1 type I receptor (IL-1RI). IL-1 is an inflammatory mediator that binds to the IL-1RI
and triggers the inflammatory response. (Calabrese, 2002; Arend, 2002)

- **Dosage** For moderate to severe active RA patients the recommended dosage of anakinra is 100 mg/day subcutaneously.

- **Adverse events** Most common and frequently reported side effect is injection site reaction and lasts for 15 days to 1 month. Other frequent side effects may include bacterial infection such as cellulitis, bone and joint infections, rather than unusual, opportunistic, fungal or viral infections. Serious infections may develop such as pneumonia or infections of the skin. (Fleischmann et al., 2006; Mertens & Singh, 2009)

- **Clinical efficacy** In a study, 1,207 patients received 100 mg of anakinra in addition to DMARD (MTX, sulphasalazine or hydroxychloroquine) for up to 36 weeks (Le Loet et al., 2008). Relevant improvement in the HAQ (Health Assessment Questionnaire) was seen in 51 %, with a DAS28 (Disease Activity Score-28) amelioration of 1.5 at the end, without significant differences between the three DMARD patient groups. An assessment of using anakinra in RA involving 2,846 patients, of whom 781 and 2,065 were randomized to placebo and anakinra, respectively, concluded that anakinra demonstrated relative safety and modest efficacy in RA, although data for the long-term use are still being collected (Mertens & Singh, 2009).

Several biologics are already approved for the treatment of RA; however, no data are available/published on any large study on head-to-head clinical trials to support using one agent over another. Nowadays, RA has an expanded range of available therapies and these provide a greater chance of controlling this disease. It is too early to say which molecule will be the most relevant target to hit for RA treatment. Early diagnosis of RA combined with early start of an appropriate treatment regimen is acknowledged as an important factor in improving clinical outcomes in patients with RA. Unfortunately, early diagnosis has been challenging because of the non-specific signs and symptoms associated with many polyarthropathies. However, with the advent of biologic drugs new imaging tools should be developed for selecting patients that may respond to one or other biological therapy.

### 3 Biosimilars and Intended Copies

Biologics, because of their complex structures, are variable and can never be duplicated, unlike small molecule drugs (generics) that are chemically synthesized (Zuñiga & Calvo, 2010). As the patents of biologics are expected to expire within the next few years, an opportunity has arose for the “biosimilars” to be marketed. A biosimilar is a biologic medicine that is similar but not the same to an already registered innovator biologic in terms of quality safety and efficacy. These molecules are also called as follow-on biologic (USA); subsequent entry biologic (Canada); similar biotherapeutic product (WHO) (Dranitsaris et al., 2011).

Because the biosimilar manufacturers have no access to the production data of
patented biologics, it is not possible to replicate the innovator. Variations in glycosylation, purification, formulation and storage may alter its safety, immunogenicity and efficacy profiles (Dorner et al., 2013). Currently, several products labelled as “biosimilars” are approved for treatment of RA in a number of countries that, at the time of approval, did not have stringent regulatory processes in place to ensure comparability as defined by EMA (European Medical Agencies) and FDA. While these products apparently meet local regulatory requirements, they should be called “intended copies” (Dorner et al., 2013). Thus any copy version of a biologic not developed and assessed in accordance with a strictly comparative development program should not be termed biosimilar (Weise et al., 2011). Table 2 shows the intended copies of an Innovator biologic available in different parts of the world.

<table>
<thead>
<tr>
<th>Biologics</th>
<th>Manufacturer</th>
<th>Intended Copy</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>Dr. Reddy’s Laboratories (India)</td>
<td>Reditux</td>
<td>Bolivia, Chile, Peru, India</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Probiomed (Mexico)</td>
<td>Kikuzubam</td>
<td>Bolivia, Chile, Peru and Mexico</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Shanghai CP Goujian Pharmaceutical Co (China)</td>
<td>Etanar</td>
<td>Colombia</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Shanghai CP Goujian Pharmaceutical Co (China)</td>
<td>Yisaipu, Etacept</td>
<td>China and India</td>
</tr>
</tbody>
</table>

**Table 2**: Intended copies* of available biologics (Dorner et al., 2013). * - Not as per EMA and FDA standards for biosimilars at time of approval

Though biosimilars may improve access to expensive biologics, their clinical benefit is still a question mark (Dorner et al., 2013). While efficacy issues have been documented (Misra, 2012), the primary safety concern for biosimilar agents is their potential immunogenicity (Kessler et al., 2006). Immune reactions like allergy, serum sickness, anaphylaxis as well as reduced or enhanced drug efficacy can occur (Schellekens, 2003). Quality (Misra, 2012) and interchangability (Sensabaugh, 2011) issues also need to be addressed. Practically, substitution of the innovator with a biosimilar can have clinical consequences as patients could respond differently to the two products. Thus, certain regulators like the EMA and the authorities in France, Germany, Greece, Italy, Slovenia, Spain, Sweden and UK do not permit substitution or interchangeability. Storage is a critical issue with biopharmaceuticals, particularly for when used and stored in conditions where temperature control could be a problem (Seshiah et al., 2013). The same holds true for biosimilars (De Groot & Scott, 2007).

Because biosimilars are quite recent, clinicians should be aware of issues that have cropped up during their development and approval (Sekhon & Saluja, 2011). The use of biosimilars is essentially a change in clinical management (Combe et al., 2005). They should be looked at more cautiously than generics. In addition, pharmacovigi-
lance will be the need of the hour to track down any safety and efficacy problems with biosimilars. However, the wind of change is blowing in rheumatology. Rheumatologists are slowly getting exposed to “biosimilars”. The role of biosimilars in the management of rheumatoid arthritis, however, will be based on the confidence gained by the treating rheumatologist. Rheumatologists will, sooner or later, be utilizing a wide range of alternative options to many patented originator biologics. It is likely that the implementation of biosimilars in the management of different rheumatic diseases will change the treatment algorithms we currently use, and this will be mainly based on the cost saved. Only hands-on experience will prove if many current beliefs will hold true (Noaiseh & Moreland, 2013). It is hoped that biosimilars will help improve patient access to expensive biologics. The success of an individual biosimilar will ultimately depend on the clinical data generated to support the product. However, it is important that clinicians distinguish between biological “intended copies” and biosimilars. Proper regulatory protocols need to be followed for getting a biosimilar approval. Issues regarding the safety, efficacy and similarity of biosimilars as compared to the innovator biologics have raised potential concerns regarding their use and should be addressed before giving them approval. Also, intended copies which do not comply to the regulatory standards for biosimilars have gained access in some countries which may lead to hazardous consequences. Patient safety and interchangeability of biosimilars will depend on establishment of stringent regulatory processes that best manage the potential benefits and risks associated with this newer drug category.

4 Clinical Considerations for Biological Therapy in RA

In the therapy for RA, the goal is to achieve and maintain remission or to minimize the disease activity. This may be possible by treating the patient to target, and maintaining tight disease-control. Regular monitoring of the disease activity, at 3 monthly intervals, is essential to evaluate the appropriateness of therapeutic approach. Early initiation of DMARDs facilitates the retardation of disease progression, and induction of more remissions. Synthetic DMARDs like methotrexate remain the agents of choice for initiation of therapy. Evidence supports the possibility of good initial control with biological agents, when used as first-line therapy. Improved initial control is also possible when biological agents are combined with synthetic DMARDs; however, the long-term sustenance of such benefit is not proven. In fact, this approach is considered to result in over-treatment, in a significant proportion of patients (van Vollenhoven, 2009). In early RA of < 6 months duration, the American College of Rheumatology (ACR) recommends the use of anti-TNF agents as first-line therapy, when the disease activity is high and prognosis is poor (ACR, 2012). In this scenario, the anti-TNF agents may be used with or without methotrexate; however, infliximab must always be used in combination with methotrexate. In established RA of ≥ 6 months’ duration, the disease activity should be monitored every 3 months, to assess the influence of treatment. Inadequate control with synthetic DMARDs (monotherapy or combination therapy) should prompt the initiation of biological therapy.
4.1 Considerations for Initiating a Biological Therapy

Screening for latent tuberculosis infection, is suggested for all patients of RA (ACR, 2012). Screening may be carried out with Tuberculin Skin Test (TST) or Interferon Gamma Release Assays (IGRAs). IGRAs may be preferred over TST, as TST may give false-positive results in presence of BCG vaccination. In immunocompromised patients, screening tests may be falsely negative, and may be repeated after an interval of 1 to 3 weeks. Positive screening test result may prompt further assessment for active tuberculosis, with chest X-ray and sputum examination. In presence of latent tuberculosis, biological therapy may be considered after 1 month of anti-tuberculosis treatment, whereas in active tuberculosis, biological therapy may be considered only after completing the course of anti-tuberculosis therapy. When the risk of exposure to tuberculosis is present, periodic screening for tuberculosis infection may be considered, while continuing the biological therapy.

In patients with comorbidities like Hepatitis B or C, malignancy or congestive heart failure (CHF), the ACR has made special recommendations (ACR, 2012). For patients with hepatitis C, the use of etanercept is recommended. For patients with hepatitis B infection, the choice of biological agent is not conclusive. Biological therapy is not recommended if chronic hepatitis B is untreated, or even in treated cases, if the Child Pugh ranking is class B or higher. For patients with CHF with NYHA class III or IV, or when ejection fraction <50%, therapy with anti-TNF agents is not recommended. In patients with previously treated solid cancers, skin cancers or lymphoproliferative cancers, rituximab may be used. If 5 years have elapsed after treatment for solid cancers or non-melanoma skin cancers, any biological agent may be considered.

4.2 Factors that Influence the Decision of Switching

In the biological therapy for RA, primary treatment failure following initiation, or secondary treatment failure after an initial response, are commonly encountered. For such cases, switching between biological agents is a reasonable option. The ACR recommends switching to different biological agents, in cases of observed loss or lack of benefit with the initial agents, or adverse reactions to the initial agents (ACR, 2012).

Safety profile of biological agents is an important consideration, and appearance of adverse effects is a valid reason to consider switching. TNF receptor fusion protein is known to be associated with lesser risk of reactivation tuberculosis, relative to anti-TNF monoclonal antibodies. Infusion reactions occurring with infliximab are common reasons for discontinuation and switching. In case of a serious adverse reaction developing to an anti-TNF agent, switching to a non-TNF agent must be considered. For serious or non-serious reactions developing to a non-TNF agent, switching to another non-TNF agent or to an anti-TNF agent may be considered.

Within the anti-TNF options, switching can result in improved outcomes owing to the different biological structures, affinities and half-lives. Appearance of neutralizing antibodies, against the therapeutic monoclonal antibodies, frequently results in loss of efficacy, over a period of time. This is a common reason to consider a switch to an-
other biological agent, like a receptor fusion protein. Generally, such antibodies that develop against the fusion proteins are non-neutralizing, whereas those developing against the monoclonal antibodies possess the capacity of neutralization.

Primary treatment failure with any biological agent may indicate the active existence of different pathological mechanism(s). In such cases, it is prudent to switch to a biological agent, which acts on a different pathological target.

4.3 Achieving Remission and Tapering of TNF Therapy?

Sustained remission is the ideal goal of therapy in RA. The definitions of remission of RA for clinical practice, evolved by the ACR/EULAR task-force, are described in the Figure 1 (Zhang, et al., 2012). Evidence to address the considerations of tapering DMARDs is not conclusive. Persistent remission for at least 12 months may be observed, for any considerations of therapeutic adjustments.

<table>
<thead>
<tr>
<th>a) Boolean-based definition</th>
<th>b) Index-based definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>At any time point, patient must satisfy all of the following:</td>
<td>Clinical Disease Activity Index (CDAI) score of ≤ 2.8.</td>
</tr>
<tr>
<td>• Tender joint count (28) ≤ 1</td>
<td>CDAI comprises of tender-28 joint count, swollen-28 joint count, patient global disease activity and evaluator’s global disease activity.</td>
</tr>
<tr>
<td>• Swollen joint count (28) ≤ 1</td>
<td></td>
</tr>
<tr>
<td>• Patient global assessment ≤ 1 (on a 0 – 10 scale)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1: Definition of Remission for Clinical Practice in RA (Zhang, et al., 2012). Definitions adapted from the ACR/EULAR definitions of remission in rheumatoid arthritis (Zhang et al., 2012).

5 Lessons from the Biologics Registries

Clinical trials of TNF inhibitors (TNFi) have several limitations such as relatively fewer number of patients, limited exposure; exclusion of patients with co-morbidities; etc. Meta-analyses of Randomised controlled trials (RCT) have highlighted the “short term” safety profile of biologic therapies approved for RA. Since some of the adverse effects of interest are rare but severe, and occur during long-term use of biologics, we need to also look at non-randomized observational/registry studies to fully address the safety issues of biologic therapy for RA (Rawlins & De Testimonio, 2008). Also in the absence
of head-to-head trials; questions regarding treatment comparisons may not be adequately answered by RCTs. (Rawlins & De Testimonio, 2008; Silman et al., 2000; Zink et al., 2009). Information from different national registries provides real-life, long-term data in patients with co-morbidities relevant to safety, efficacy and long-term outcomes (Zink et al., 2009). Registries provide feedback on the management of rheumatic conditions in real life that can inform clinical decision making (Zink et al., 2009). The growing importance of the registries is underlined by the fact that regulatory agencies, as well as the pharmaceutical industry, have identified the registries as useful post-marketing drug surveillance tools (Rawlins & De Testimonio, 2008). Long-term observational studies should be seen as complementary to RCTs and not as inferior data sources (Silman et al., 2000; Zink et al., 2009). Agreeing on a standardized reporting system for serious adverse events, and the ongoing discussions on methodological issues, have ensured that the registries have improved quality of data that is reported to regulatory agencies (Silman et al., 2000). Regulatory authorities in certain parts of the world now require patients on new drugs to be included in existing registries. This means that although the biological registries began as an academic enterprise with voluntary support from different pharmaceutical companies, they have evolved into official pharmacovigilance tools (Silman et al., 2000). Primarily, registries obtain data on the real-life clinical use of TNFi to investigate long-term safety and efficacy. Registries provide real life feedback on the management of RA that can inform clinical decision making. A major advantage of the registries over industry-driven observational post-marketing studies is that all registries follow up with patients irrespective of whether they continue treatment with a specific drug (Rawlins & De Testimonio, 2008).

However, there may be challenges to methodology of registries. Channeling bias or confounding by indication are obvious limitations and may be because treatment guidelines in some countries that limit the prescription of TNF inhibitors to patients with severe disease, a bad prognosis or those who have failed to respond to DMARD therapy (Zink et al., 2009). Methods for controlling these biases and adjusting for confounding must be applied at several stages of the research process: selection biases have an influence not only at the start of biological treatment but also at clinical decision time points regarding “switching” to alternative drugs (Zink et al., 2009). Choosing an adequate control group is difficult – matching on many different criteria is important and statistical methods need to be used to minimize confounding by indication when the data are analyzed (Zink et al., 2009). Table 3 highlights the registries set across the world.

5.1 Safety Results for Registry Studies

5.1.1 Infections

The CORRONA database showed that in RA patients, higher disease activity was associated with a higher probability of developing infections (Au et al., 2011). Askling and colleagues showed that RA patients are at increased risk of hospitalisation due to infection but this risk decreases as time from initiation of TNFi treatment increases. Within
the RA cohort studied, the overall response rate (RR) for TNF inhibitor-associated infection, adjusted for comorbidity and use of inpatient care, was increased by approximately 30% during the first year of treatment. Importantly, however, beyond the first year of follow-up on first TNF inhibitor treatment, no significant increase in infection risk was noted. Rates of severe infections were similar across the biologic treatment groups (Askling et al., 2007). Compared with the DMARD-treated cohort; data from BSRBR reported no increased risk of all-site serious infection for any of the 3 TNF inhibitor therapies. There were 8,973 patients included in the analysis: 7,664 in the anti-TNF cohort (3,596 etanercept, 2,878 infliximab, 1,190 adalimumab) and 1,354 in the comparison cohort (Dixon et al., 2006). Galloway and colleagues compared the risk of serious infections between 11,798 patients treated with infliximab, adalimumab, or etanercept and 3598 synthetic DMARDs patients using data from 2001 to 2009 in the British Society for Rheumatology Biologics Register (BSRBR) and the data suggest that anti-TNF therapy is associated with a small but significant overall risk of serious infection (Galloway et al., 2011). The Dutch Rheumatoid Arthritis Monitoring (DREAM) register of 2157 RA patients showed the risk of serious infection in RA patients treated with either adalimumab or infliximab was similar (unadjusted hazard ratio of 3.31 and 4.13, respectively) (van Dartel et al., 2011). However, risk of serious infection in RA patients treated with etanercept was significantly lower (unadjusted hazard ratio of 2.13) (van Dartel et al., 2011). Even in the RATIO registry Patients on etanercept had lower

<table>
<thead>
<tr>
<th>Country</th>
<th>Name of Registry</th>
<th>Started</th>
<th>Total TNFi Treated Patients (year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK (Mercer et al., 2009)</td>
<td>BSRBR</td>
<td>2001</td>
<td>11,757 (2009)</td>
</tr>
<tr>
<td>Germany (Zink et al., 2013)</td>
<td>RABBIT</td>
<td>2001</td>
<td>7000 (2009)</td>
</tr>
<tr>
<td>Spain (Gomez-Reino et al., 2003; “Spanish registry”, 2014)</td>
<td>BIOBADASER</td>
<td>2000</td>
<td>5493 (2009)</td>
</tr>
<tr>
<td>Norway (Kvien et al., 2005)</td>
<td>NOR-DMARD</td>
<td>2000</td>
<td>4683 (2005)</td>
</tr>
<tr>
<td>Denmark (Hetland, 2005)</td>
<td>DANBIO</td>
<td>2000</td>
<td>3056 (2005)</td>
</tr>
<tr>
<td>Netherlands (Kievit et al., 2007)</td>
<td>DREAM</td>
<td>2003</td>
<td>546 (2007)</td>
</tr>
<tr>
<td>Italy (Marchesoni et al., 2009)</td>
<td>LORHEN</td>
<td>1999</td>
<td>1114 (2009)</td>
</tr>
<tr>
<td>Switzerland (Pan et al., 2009)</td>
<td>SCQM</td>
<td>1997</td>
<td>2364* (2009)</td>
</tr>
<tr>
<td>Greece (Flouri et al., 2009)</td>
<td>HRBT</td>
<td>2004</td>
<td>715 (2009)</td>
</tr>
<tr>
<td>Japan (Komano et al., 2011)</td>
<td>REAL</td>
<td>2005</td>
<td>1144 (2010)</td>
</tr>
<tr>
<td>France (Salliot et al., 2007)</td>
<td>RATIO</td>
<td>1997</td>
<td>1571 (2004)</td>
</tr>
</tbody>
</table>

Table 3: Worldwide Established Registries.
rates of opportunistic infections vs. infliximab or adalimumab. (Salmon-Ceron et al., 2011)

**Tuberculosis (TB)**
The data from the BSRBR registry showed that the rate of TB in patients with RA treated with anti-TNF therapy was three to fourfold higher in patients receiving infliximab or adalimumab than in those receiving etanercept (Dixon et al., 2010). Similarly the French Research Axed on Tolerance of Biotherapies (RATIO) registry showed that the risk of TB is higher for patients receiving anti-TNF mAb therapy than for those receiving soluble TNF receptor therapy. The increased risk with early anti-TNF treatment and the absence of correct chemoprophylactic treatment favor the reactivation of latent TB (Tubach et al., 2009).

**Serious Viral Infections**
While the RABBIT registry showed that the incidence of Herpes zoster increased in rheumatoid patients treated with infliximab or adalimumab but not etanercept (Strangeld et al., 2009). No significant association with herpes zoster was found for etanercept use (HR, 1.36 [95% CI: 0.73-2.55]) (Strangeld et al., 2009); the BSRBR registry showed that Varicella Zoster Virus (VZV) infections are increased in Patients with Rheumatoid Arthritis (RA) Treated with Anti-TNF Therapy (Galloway et al., 2010). A similar pattern of risk was seen for each anti-TNF therapy with no statistical difference between etanercept and the monoclonal antibodies (Galloway et al., 2010). Thus reactivation of herpes zoster is the most common viral problem associated with TNFi treatment. Data from BIOBADASER and BRSBR show very low rates of Listeria infection in TNFi treated rheumatoid patients (Pena et al., 2008). Data from RATIO and BSRBR show very low rates of Legionella infection in TNFi treated patients (Tubach et al., 2006).

**5.1.2 Malignancies**
According to ARTIS Registry data, RA patients in general have a marginally increased risk of solid cancers. The risk of cancer in RA patients varied by cancer site, with non-melanoma skin cancer at the highest increased risk (70%), and smoke-related cancers at the next highest (20-50%). However, RA patients have a decreased risk of both breast and colorectal cancers (20% and 25%, respectively) (Askling et al, 2005). However, data from Swedish and US registries and observational meta analyses show no overall increased risk of new cancers has been associated with TNFi treatment (Askling et al., 2005; Wolfe & Michaud 2007). Observational meta analysis data indicate patients treated with TNFi have a significantly increased risk of both non melanoma skin cancer and melanoma (Wolfe & Michaud 2007). Risk of lymphoma is elevated in RA, particularly in patients with more severe disease (Greenberg et al., 2011). Generally, TNFi are not associated with any major further increase in the already elevated lymphoma occurrence in RA (Baeklund et al., 2006).
5.1.3 Cardiovascular Risk

TNFi use is associated with reduced risk of cardiovascular events in RA patients (Greenberg et al., 2011; Askling & Dixon, 2011). In the CORRONA registry cohort, anti-TNF use resulted in a reduction in myocardial infarction, Transient ischaemic attacks (TIA)/stroke, cardiovascular-related death, and composite cardiovascular events compared to DMARD and Methotrexate treated patients (Greenberg et al., 2011; Askling & Dixon, 2011). After adjusting (for age, gender, smoking status, diabetes, hypertension, dyslipidemia, previous Myocardial Infarction (MI) or stroke and modified health assessment questionnaire score, aspirin use, naproxen use, non-selective non-steroidal anti-inflammatory drug use, and cyclooxygenase-2 inhibitor use.); TNF antagonist use was associated with a reduced risk of the primary composite cardiovascular endpoint compared with non-biological DMARD use. However, methotrexate was not associated with a reduced risk (Greenberg et al., 2011; Askling & Dixon, 2011). There have been postmarketing reports of worsening of congestive heart failure (CHF), with and without identifiable precipitating factors, in patients taking soluble TNF receptor (Immunex Corporation, 2013) There have been rare reports of new onset CHF, including CHF in patients without known preexisting cardiovascular disease. Physicians should exercise caution when using soluble TNF receptor in patients who also have heart failure, and monitor patients carefully (Immunex Corporation, 2013).

5.1.4 Demyelinating Disease Risk

All confirmed cases of demyelinating disease, optic neuritis, and multiple sclerosis (MS) in patients with rheumatic diseases treated with TNF-α antagonists were reviewed from 3 different sources: (1) the Spanish Registry of biological therapies in rheumatic diseases (BIOBADASER); (2) the Spanish Pharmacovigilance Database of Adverse Drug Reactions (FEDRA); and (3) a systematic review (PubMed, EMBASE, and the Cochrane Library). However, it is not clear whether TNF antagonists increase the incidence of demyelinating diseases in patients with rheumatic diseases. It is estimated that the rate of demyelinating diseases in patients with rheumatic diseases treated with TNF antagonists does not clearly differ from the expected rate in the population (Cruz Fernandez-Espatero et al., 2011).

5.2 Discontinuation Rates of Biologic Therapy

Marchesoni et al. used data from the Lombardy Rheumatology Network (LOHREN) registry to evaluate drug survival in 1064 patients treated with either infliximab, adalimumab, or etanercept. Data showed that long-term survival of etanercept was better than that of both infliximab and adalimumab. The risk of discontinuing infliximab was mainly due to primary or secondary loss of efficacy, whereas the risk of discontinuing adalimumab was mainly due to adverse events (Marchesoni et al., 2009). Markenson et al. performed a retrospective analysis of the data from the RADIUS registry, a 5-year observational registry of patients with RA, to determine time to first- and second-
course discontinuation of etanercept, infliximab, and adalimumab. This analysis included 2418 patients. Discontinuations due to adverse events were significantly lower ($P = 0.0006$) for etanercept than for infliximab (etanercept, 14%; infliximab, 22%; adalimumab, 17%) (Markenson et al., 2011). Similarly, Hong Kong registry data showed that drug retention is higher in patients treated with etanercept compared to those treated with infliximab. Patients treated with infliximab had a lower cumulative probability of drug retention due to lack of efficacy or due to adverse events compared with patients treated with etanercept (Mok, 2011).

5.2.1 Drug Survival

In the DANBIO Registry: drug survival; among etanercept, adalimumab, infliximab treated patients, infliximab had the lowest drug survival. This trend was observed at 24, 48, 72, and 96 month follow-ups (Hetland et al., 2010). Similarly in the GISEA Registry; at 4 years etanercept survival was significantly higher than infliximab or adalimumab survival ($P < 0.0001$). At this time-point, 51.4% of etanercept -treated patients were remaining on therapy, 36.4% of adalimumab-treated patients were remaining on therapy, and 37.6% of infliximab-treated patients were remaining on therapy (Iannone et al., 2011). ATTRA registry data demonstrated that Ankylosing Spondylitis patients were more adherent to anti-TNF therapy than RA patients (Pavelka et al., 2009).

While registries provide valuable real life treatment information their observational nature, lack of controls and randomization require complex analysis to avoid confounding factors (Kievit et al., 2007; Markenson et al., 2011; Mok, 2011).

6 Future Perspectives in the Treatment of RA

Biologics go a long way towards meeting the needs of many RA patients. However there are patients who can fail biologics. Cost is an overriding factor in the development of newer molecules for targeted therapy of RA (Van Vallenhoven, 2010). Clinicians look for are therapies that are targeted; affordable and with an improved safety profile.

There are a large number of possible targets for modulating the immune response. Hence the current developments include biologics with different specific targets. Many novel biologics are undergoing development in RA e.g. newer IL-1 inhibitors, B-cell depleting agents osrelizumba, ofotumumab, TRU015, targeting cytokines in B-cell maturation Bly5 inhibitor, AORUK inhibitor, briobacept, atitacept (Kukar et al., 2009).

Another entirely new approach to treat RA is related to the development of small molecule compounds with similar targeted action and therapeutic efficacies (Van Vallenhoven, 2010). These include JAK-3 inhibitors (tofacitinib), Syk inhibitors (tamatinib, fosdium, lymphotoxinB, and LIGHT pathway inhibitors (baminercept), p38 MAP inhibitors (VX 702, SB-6811323) (Kukar et al., 2009). Of these tofacitinib is marketed in many countries across the world.
Small molecule derivatives that target signal pathways that subserve the cytokine effector pathways are also attracting attention. Other approaches include the inhibition of factors that promote angiogenesis and those that promote osteoclast activation (anti-RANKL [anti-receptor activator of nuclear factor-kB ligand]) and modulate adipocytokines.

7 Conclusions

Biological therapy has undoubtedly been a subject of immense clinical interest, over the past few years. The resultant developments have engendered various perspectives for consideration, towards optimizing the therapeutic approach to RA. As a routine practice, biological agents are initiated following inadequate response to synthetic DMARDs. However, supportive evidence does prompt considerations for early use of biological agents, in the course of disease. An increase in the variety of available biologics has broadened the choice, propelling the approach towards personalized medicine. Long-term observations with biological therapies are now available, to help address some essential questions. Facilitated by the advent of more affordable biosimilar agents, improving the therapeutic access is now a real possibility.

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