INTRODUCTION

The term biologics have been used as a collective term for biological therapies. Therapeutic agents with biologic properties, including monoclonal antibodies and soluble cytokine receptors have been in use against rheumatic diseases for some time now. Treatment of rheumatic diseases has undergone a remarkable change over the last 10 years. This can be credited to an increased understanding of the immune system and the mechanisms and causes of rheumatic diseases which has enabled us to treat the underlying cause aggressively and early. The use of biologics has become essential along with DMARDs in treatment of autoimmune diseases.

The success of early biologics, especially etanercept and infliximab for the treatment of rheumatoid arthritis, has strongly influenced researcher and manufacturers to develop a new generation of biologic agents that inhibit cytokine behavior, cellular activation and inflammatory gene transcription by various means. Some of these novel therapies in development are not antibodies, soluble receptors or natural antagonists, but are rather small molecules that specifically inhibit intracellular, cell-cell and cell-matrix interactions intrinsic to systemic inflammatory and autoimmune diseases.

Therefore, the term biologic therapies may better be replaced with a more accurate term, such as biologic response modifier or targeted therapy that differentiates these finely tuned immunomodulators and anti-inflammatory agents from less specific immunosuppressive drugs such as cytotoxic agents and corticosteroids.

TILL DATE WITH BIOLOGICS

The use of biologic agents has revolutionized the treatment of rheumatic diseases overall. Early aggressive therapy and tight control seem to produce significant positive outcomes in patients.

RHEUMATOID ARTHRITIS:

The introduction of agents that inhibited the key proinflammatory cytokine, tumor necrosis factor (TNF), ushered in a new era in the treatment of RA in the late 1990s. TNF inhibitors and B-cell inhibitors are approved in many other countries for the treatment of RA and a number of other autoimmune systemic inflammatory conditions: (1) etanercept, which is a soluble TNF receptor-immunoglobulin IgG Fc fusion construct; (2) infliximab, which is a chimeric anti-TNF monoclonal antibody (mAb); (3) adalimumab, which is a human anti-TNF mAb; (4) certolizumab pegol, which is a PEGylated Fab fragment of a humanized mAb; and (5) golimumab, which is a human anti-TNF mAb and (6) rituximab, a CD-20 receptor inhibitor mAb. Recently, IL-6 inhibitor (Tocilizumab) and CTLA 4 blockers (Abatacept) have been also quite successfully being used in RA. The success of these agents has not only provided an opportunity to achieve better outcomes for patients with RA, but it also has had a dramatic impact on the overall approach to the treatment of RA and the goals of therapy. However, approximately 30-40% of patients with established disease fail to respond to TNF-α antagonists and the majority of those that respond initially do not achieve complete remission. Concerns have also been raised about the short- and long-term tolerability of these agents.
SYSTEMIC LUPUS ERYTHEMATOSUS

The pathogenesis of systemic lupus erythematosus (SLE) involves aberrancy in multiple components of the immune system including B cells, T cells, cytokines and growth factors. Therapeutic agents targeting these mediators selectively have been tested for the treatment of SLE. The two large phase 3 trials of belimumab, the monoclonal antibody against B-lymphocyte stimulator (BLyS), showed significant clinical benefit. Response rates were 57.6 and 43.2% for 10 mg/kg belimumab, compared with 43.6 and 33.8% for placebo in BLISS-52 and BLISS-76, respectively. On the contrary, large phase 2/3 randomized placebo-controlled trials of B-cell depletion, using anti-CD20 antibody, rituximab, in SLE, reported unexpected negative results. Studies of a costimulation blocker (abatacept), tumor necrosis factor inhibitor (infliximab), and interleukin-6 inhibitor (tocilizumab) also showed either negative results or were associated with high rates of adverse events.

Studies of T cell and interferon inhibition remain in the early developmental phase. However, a recent multicenter double blind placebo controlled study was conducted using a fully human anti-IFN α monoclonal antibody, sifalimumab, with fairly positive non-adverse results.²

SPONDYLOARTHRITIS

The spondyloarthritis (SpAs) have five subtypes: ankylosing spondylitis, reactive arthritis, and major parts of the arthritis and spondylitis spectrum associated with psoriasis, inflammatory bowel disease, undifferentiated SpA. Ankylosing spondylitis is the most frequent subtype of SpA, more prevalent than undifferentiated SpA. Based on the high prevalence of psoriasis, psoriatic arthritis is also quite frequent, whereas reactive arthritis and inflammatory bowel disease are relatively rare.

Therapeutic options for more severe forms of spondyloarthritis have been rather limited in the last decade. From accumulating evidences it is evident that anti-TNF therapy is the most suitable for treating spondyloarthritis. Unlike rheumatoid arthritis, where DMARDs are an effective measure for treatment, in spondyloarthritis specially in Ankylosing spondylitis DMARDs can offer no remedy to severely affected patients. Therefore, anti-TNF could be the first line of defence in such patients.

ANKYLOSING SPONDYLITIS

The TNF-α blockers are biologic medications that have shown great promise in treating ankylosing spondylitis. They have been shown to be highly effective in treating not only the arthritis of the joints but the spinal arthritis associated with ankylosing spondylitis and related diseases. In the open pilot study performed in Berlin, Germany, infliximab in a dosage of 5 mg/kg improved the disease activity of patients with severe ankylosing spondylitis, with short mean disease duration of 5 years. Nine of 10 patients showed an improvement of greater than 50% in disease activity as measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI); the median improvement of the BASDAI after 4 weeks was 70%. The efficacy of infliximab in ankylosing spondylitis has been proved from a randomized, double-blind, controlled trial performed in Germany, a highly significant effect of infliximab treatment (5 mg/kg body weight given at weeks 0, 2, and 6), with the primary outcome parameter of a 50% improvement of disease activity (BASDAI), was achieved in 53% of the patients treated with infliximab compared with 8% on placebo.

Treatment of ankylosing spondylitis with the soluble TNF-α receptor, etanercept, has now been studied to a larger extent. The primary outcome parameter was a 50% or greater improvement of the BASDAI. Treatment with etanercept resulted in a 50% regression of disease activity in 57% of these patients, versus 6% on placebo at week 6 (P = 0.004). Large trials with this drug are in progress.

PSORIASIS

Currently six biologics are approved for psoriasis and/or psoriatic arthritis treatment and are being used regularly, viz., etanercept, adalimumab, infliximab, alefacept, golimumab and ustekinumab. There are strong evidences that both etanercept and infliximab work in psoriasis and psoriatic arthritis. At the end of 12 weeks, 87% of patients in the etanercept group had achieved a Psoriatic Arthritis Response Criteria response, compared with 26% in the placebo group. In another study with infliximab, patients achieved a 20% improvement according to the American College of Rheumatology criteria (ACR20) in all patients by week 2, 8 patients improved 70% (ACR70) at week 10; 6 patients maintained this level of improvement after week 54. At week 10, MRI revealed an 82.5% mean reduction in inflammation from baseline. Taken together, both agents seem to work favorably in psoriasis and psoriatic arthritis.

Even as these biologics transform many lives, others continue to suffer. Some patients cannot access these treatments due to their high cost and/or insurance coverage issues; some are precluded from using them due to preexisting conditions (TB, HIV, cancer, etc.); some are concerned about side effects or long term uncertainties; and some are simply not aware of these new treatments. For still others, their first try with a biologic does not work. After all, no biologic can work in 100% of cases.

NEW EMERGENCES

In the past, any improvement with treatment was considered good; however, now there is a growing interest in maintaining a tight control and achieving as low a disease state as possible. Most of the above discussed biologics rarely result in disease
remission and provide clinical benefits in some sporadic cases of rheumatic diseases. Therefore, alternative therapies are needed and inhibitions of small molecules like kinases, transcription factors, chemokines etc were the most suitable targets.

However, issues remain in regard to how to predict who will respond to which agents and how to monitor disease activity while using these agents. Looking to the future, biosimilars (or generic biologics) and a number of new small molecules are being developed that may have an important impact on the treatment.

BIOSIMILARS

Biosimilars is the term used for generic versions of biologic agents. These biologic agents are often manufactured in cell lines, and thus are subject to modifications -- such as glycosylation -- that may potentially alter the efficacy and safety of the product. There are examples of biologic agents with identical primary sequences in which changes in the manufacturing processes have led to important differences in safety and efficacy.

A multicenter observational before-after study with Etanar, a recombinant TNF receptor: Fc fusion protein has been shown to be effective in suppressing disease activity in patients with RA who fail to respond to DMARDs.\(^3\) Etanar can effectively control disease activity in real-life patients with active RA and poor responses to not only MTX but also other DMARDs.

Introduction of biosimilars requires a specifically designed pharmacovigilance plan. In order to be released to the public, biosimilars must be shown to be as close to identical to the parent biological product based on data compiled through clinical, animal and analytical studies. Moreover, it is difficult and costly to recreate biologics because the complex proteins are derived from living organisms that are genetically modified.

In contrast, small molecule drugs made up of a chemically based compound can be easily replicated, orally administered to patients and are considerably less expensive to reproduce. Therefore, research and development of small molecule therapeutic targets was the need of the hour.

SMALL MOLECULES

Inhibition of T-Cell Co stimulatory Pathways

Binding of a T-cell surface co stimulatory molecule with its ligand expressed on the surface of an antigen-presenting cell (APC) provides a second signal to the T cell in addition to the signal generated from T cell receptor (TCR) recognition of antigen/MHC complex. The second, co stimulatory signal promotes T cell activation in response to antigen recognition. In the absence of co stimulatory signals, T-cell responsiveness is impaired.

The possible roles of the various co stimulatory pathways like including the CD40-CD40 ligand (CD-40L), CD28-CTLA4-B7, CD11a/CD18 (LFA-1)-intracellular adhesion molecule-1, OX40 (CD134)-OX40L and CD2-LFA3 pathways has been reviewed in autoimmune disease.

- CTLA4 Immunoglobulin

The B7 family of cell surface molecules delivers stimulatory signals to T cells through interaction with a common ligand, CD28, present on T-cell surfaces and suppressive signals through binding with T-cell surface-expressed CTLA4 (CD154). A soluble chimeric molecule, CTLA4 immunoglobulin has been developed to inhibit T-cell costimulation by B7-family molecules. CTLA4 immunoglobulin consists of the extracellular component of CTLA4 fused to human IgG Fc. The affinity of CTLA4 for B7 molecules is greater than the affinity of CD28, permitting CTLA4 immunoglobulin to prevent B7-mediated CD28 signaling. Costimulatory blockade has also been considered in the management of chronic plaque psoriasis, RA and systemic lupus erythematosus (SLE).

- Anti-CD40 Ligand Monoclonal Antibody

Interaction between CD40 on APC surfaces and its ligand on T-cell surfaces, CD40L, generates c-stimulatory signals for T-cell activation. This ligand-receptor pair also induces B-cell proliferation and formation of germinal centers when CD40L present on activated T cells binds CD40 expressed on B cells. Two monoclonal antibodies against CD40L have been developed and tested in patients but have failed to demonstrate the same success in human subjects with RA and SLE as has been observed in animal models of arthritis and autoimmune disease. However, a mechanistic study of B cells obtained from five patients with SLE who participated in an open-label study of this anti-CD40L antibody, found that anti-CD40L treatment induced a persistent reduction in the frequency of anti-dsDNA antibody-producing B cells.\(^4\)

- Anti-CD11a Monoclonal Antibody

The T-cell surface complex CD11a/CD18 (also termed LFA-1) interacts with its ligand, intercellular adhesion molecule-1 (ICAM-1), as part of a costimulatory pathway for T-cell activation. LFA-1-ICAM-1 interaction also serves to form a tight junction adjacent to the TCR that enhances the interaction between the TCR and antigen/MHC complex on APCs. Efalizumab, a humanized, monoclonal antibody against CD11a, has been developed to disrupt this interaction. Efalizumab treatment of psoriasis has resulted in consistent clinical and histologic improvement in several clinical trials.\(^7\) A phase II,
randomized, controlled trial of efalizumab for the treatment of subjects with RA on concurrent methotrexate is underway.

INTRACELLULAR TARGETS

Signal transduction pathways provide an intracellular mechanism by which cells respond and adapt to environmental stress. Inflammatory mediators including TNF and IL-1 activate numerous intracellular signaling cascades, resulting in transcription of various mediators of the inflammatory process including chemokines and proinflammatory cytokines. Pro-inflammatory stimuli engage these pathways to direct a response that can either be physiologic, as with exposure to pathogens, or harmful to the host, as in chronic autoimmune diseases. Thus studying these signal transduction mechanisms have led us to a greater understanding and identification of potential therapeutic targets. All these cascades have been subjected to intense investigational efforts to develop pathway-specific inhibitors.

MITOGEN ACTIVATED PROTEIN KINASES

The mitogen-activated protein kinases (MAPK) are members of a highly conserved serine/threonine protein kinase family that regulate gene expression, cell survival, proliferation, cytokine expression, and metalloproteinase production. These kinases phosphorylate serine, threonine, or tyrosine residues on intracellular proteins and are divided into three major classes in mammals, the c-Jun N terminal kinase (JNK), extracellular signal-related kinases (ERK), and p38 MAPKs.

- p38 MAPK

The p38 MAPK pathway has attracted considerable attention as a potential therapeutic target because of its ability to regulate the production of proinflammatory cytokines in vitro as well as in vivo. Four isoforms of p38-MAPK (α, β, γ, and δ) have been identified, and p38α appears to be a critical factor for cytokine expression and regulation in macrophages and other cell types in the joint. Inhibition of p38 MAPK by p38 MAPK inhibitor such as RWJ-67657 blocked the expression of cyclooxygenase-2 (COX-2), TNF-α, IL-1 and IL-8 in cultured macrophages. More recently, the potent p38 MAPK inhibitor FR167653 prevented CIA from developing in rats and also suppressed joint destruction when treatment was initiated after the onset of arthritis.7 As the p38 MAPK inhibitors such as RWJ-67657, BIBB-796, VX-745, VX-702, SCIO-469 etc. were also effective when tested in a therapeutic protocol, these data suggest that p38-MAPK inhibitors may have therapeutic potential and have been developed and tested in clinical trials.7

- Extracellular Signal Related Kinases

Extracellular Signal Related Kinases (ERKs) have critical role in cell proliferation, induction of proinflammatory cytokines like IL-1β, TNF-α, IL-6 and MMPs thus promoting inflammation, lymphocyte activation and tissue destruction. Thus this signaling cascade is an important target for therapy where inflammatory diseases are concerned.

Several small-molecule inhibitors of MEK (MAPK-ERK Kinase) 1 and 2 like PD184352 and ARRY-162 have shown efficiency in controlling ERK in animal models. Oral administration of PD184352 to mice with CIA suppressed synovitis, pannus formation and cartilage and bone destruction whereas ARRY-162 significantly reduced inflammation in CIA and AIA rats.9 Administration of ERK 1 and 2 inhibitors (FR180204) to mice reduced clinical signs of arthritis.10

- c-Jun N-Terminal Kinase

The development of small molecule inhibitors of c-Jun N-terminal kinase (JNK) is also underway. JNKs play an important role in the transcriptional activation of some matrix metalloproteinases (MMPs) that degrade articular cartilage and promote joint destruction in RA. This is supported by the studies showing that the broad spectrum JNK inhibitor SP600125 suppressed the IL-1 induced MMP-1 expression in vitro as well as bone erosion in a mouse model of arthritis in vivo.11 In preclinical studies, a c-Jun N-terminal kinase inhibitor reduced clinical synovitis and blocked radiographic joint damage in adjuvant-induced arthritis in rats.12

JANUS KINASES

Janus kinases (Jaks) play a very important role in innate and adaptive immunity. Though Jak1 and Jak2 are ubiquitously expressed, it is Jak3 which is primarily involves in cells of immune system and is critical in lymphocyte activation, function and proliferation. Given this multifactorial role in innate and adaptive immunity, it was expected that Jaks are involved in pathogenesis of rheumatic diseases.

It was first observed that Jak3 reduced clinical signs of inflammatory arthritis by more than 90% and protected against joint damage in mice models of RA. Thus small molecule Jak inhibitors – CP690550 and INCB18424 – were therapeutically tested and found to be efficacious and well tolerated in phase II trial in RA patients with considerably reducing ACR 20, ACR 50 and ACR 70 when compared to placebo.13,14 In fact Tofacitinib (CP690550) has gone under a large phase III monotherapy trial as reported in EULAR 2011.15

Thus, Jak inhibitors are arguably, at this moment, the best-performing small-molecules drugs under investigations and are also being tried against other rheumatic diseases than RA.
NF-κB is considered the master regulator of inflammation and immunity. It plays a pivotal role in inflammatory and autoimmune diseases. Several drugs primarily corticosteroids have been successfully controlling inflammation by depending largely on inhibition of NF-κB transcriptional activity.

The NF-κB transcription factor is regulated by the upstream IKK complex, consisting of the kinases IKK1 and IKK 2 and the regulatory component NEMO (NF-κB essential modulator). IKK2 is dominant kinase in the activation NF-κB pathway, thus its selective inhibition can be explored as potential future therapeutic targets. Some orally bioavailable small molecule inhibitors of IKK2 have been shown to suppress development and progression of inflammation in animal models.16,17

Another approach to inhibit NF-κB pathway could be the use of a cell-permeable peptide similar to NEMO-binding protein (NBD) of IKK2 thus disrupting the interaction of IKK2 with NEMO, thereby blocking the formation of IKK complex. This inhibitory peptide has been shown to suppress inflammation and bone destruction in joints of mice with collagen-induced arthritis not causing any toxicity.18

**Table 1**

<table>
<thead>
<tr>
<th>Type</th>
<th>Molecule</th>
<th>Agent</th>
<th>Mechanism or development</th>
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<tbody>
<tr>
<td>Chemokines</td>
<td></td>
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<tr>
<td>CCR1</td>
<td>Antibody</td>
<td>Increased ACR 20 responses in treated patients in phase Ib trial.19</td>
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<tr>
<td>CXCL 12/13</td>
<td>Inhibitors</td>
<td>Potential role in decreasing inflammation in RA synovium20 and CIA21 respectively.</td>
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<tr>
<td>IL-17/IL-17R</td>
<td>Antibody Secukinumab</td>
<td>Targets IL-17A; preliminary efficacies in RA and psoriasis, now being tried in Ankylosing spondylitis.22</td>
<td></td>
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<tr>
<td>Cytokines</td>
<td>Antibodies or recombinant proteins</td>
<td>Effectively reduce inflammation in preclinical studies in animal models.23</td>
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<tr>
<td>IL-18</td>
<td>Antibody Secukinumab</td>
<td>Inhibits Th17 differentiation, thus blocks secretion of IL-17.PHOENIX trial in psoriatic arthritis (phase III) and plaque psoriasis (approved).</td>
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<tr>
<td>IL-12/23</td>
<td>Antibody Ustekinumab Briakinimab</td>
<td>Inhibits Th17 differentiation, thus blocks secretion of IL-12/23. PHOENIX trial in psoriatic arthritis (phase III) and plaque psoriasis (approved).</td>
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<tr>
<td>Adhesion mole-</td>
<td>Antibody VCAM-1</td>
<td>Reduced the number of inflamed joints in CIA models.</td>
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<tr>
<td>cules</td>
<td>Antibody E-selectin</td>
<td>Trail on chronic plaque psoriasis but failed to reduce the PASI score in patients.24</td>
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**STRENGTHS**

- The availability of several well-established and broadly applicable methods for antibody generation and development.
- A growing repertoire of technologies to redesign antibodies with modified or new properties to enhance their clinical potential.
- A high success rate compared to other drugs: 17% for humanized antibodies from the first human trial to regulatory approval [*].
- Well-established and broadly applicable production technologies [*].
- Often, but not invariably, well tolerated by patients.

**LIMITATIONS**

- Expensive, reflecting high production costs and commonly large doses [*], potentially limiting patient access or clinical applications.
- Clinical applications currently limited to cell surface or extracellular targets.
- Cannot be orally administered.
CONCLUSION

Biologics have revolutionized the treatment of autoimmune diseases due to their efficacy, speed of onset and tolerability. A careful dissection of a targeted pathway is needed so that novel therapeutic interventions designed to specifically block inflammatory signaling may be developed. The development of new agents and expanded use of existing agents continues to be a highly active area of investigation among the rheumatic diseases with a multitude of innovative therapeutic strategies in various stages of development.

Although development of treatments continues at a rapid pace, therapeutic research in some diseases is hindered by the rarity of the disease, variation in phenotype, and concerns about toxicity. These issues make trial design challenging. In the coming years developments in this area are going to be exciting and will influence the therapeutic approaches for the effective suppression of rheumatic diseases.

However, overall, biologic therapies represent an exciting advance in the treatment of autoimmune diseases. For millions of patients, treatment success may translate to rapid suppression of inflammation, prevention of disability, improved quality of life and the goal of complete disease remission – something unthinkable a decade ago.

REFERENCES

3. Rondon F. Etanercept therapy in real-life patients with rheumatoid arthritis. Program and abstracts of the American College of Rheumatology (ACR) 2010 Annual Scientific Meeting; November 7-11, 2010; Atlanta, Georgia. Abstract 11811.