Rheumatoid Arthritis: Mechanisms of Autoimmunity, Immunogenicity, and Advances in Immunotherapy

The Evolving Roles of B-cells in Autoimmune Diseases, Including Rheumatoid Arthritis

Immunogenicity and Biologic Therapies: Theory and Practice

Biosimilars in Rheumatology: Present and Future

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Overview
Rheumatoid arthritis (RA) is an autoimmune disease characterized by a dysregulation of inflammatory processes leading to progressive joint destruction, systemic inflammation, and extra-articular manifestations. By understanding the underlying immunologic mechanisms driving RA progression, clinicians involved in the management of patients with RA will be better equipped to evaluate the clinical and pharmacologic safety, as well as efficacy profiles of current and emerging disease modifying antirheumatic drugs (DMARDs). This monograph integrates a discussion between the basic and clinical immunologic sciences to give learners a better understanding of autoimmunity, treatment-associated immunogenicity, and the development of biosimilars for RA management.

Target Audience
The intended audience for this activity is rheumatologists and other health care professionals involved in the treatment of patients with rheumatoid arthritis (RA).

Learning Objectives
Upon successful completion of this educational activity, participants should be better able to:
• Assess B-cell biology and its role in immune-mediated inflammatory diseases, including rheumatoid arthritis.
• Define immunogenicity in the context of biologic therapies and appraise its role in efficacy and toxicity.
• Apply clinical advances in the use of biologic therapy to optimize the treatment of rheumatoid arthritis.

CME Questions?
Contact us at CME@VindicoCME.com
Introduction

The treatment of rheumatoid arthritis (RA) has undergone major changes in the last 2 decades, largely attributable to the increased understanding of the immune and inflammatory pathways involved in RA pathogenesis. The multiple roles of B-cells and other cell types in the pathogenesis of RA are increasingly apparent, and results of ongoing research to understand their mechanisms and identify potential therapeutic targets are constantly emerging. The increase in biologic treatment options has been accompanied by reports of anti-drug antibodies (ADA) that can develop in response to these immunogenic treatments, which can potentially compromise treatment effectiveness and decrease tolerability. In the 17 years since the first biologic drug for RA became available, in addition to continuing efforts to develop more effective agents, the development of biosimilar agents has recently become a global phenomenon.

To provide an opportunity for practitioners to assure they are up-to-date on the status of and developments in these dynamic aspects of RA pathology and therapy, Vindico Medical Education provided a forum on immunological approaches to RA management, inviting experts in the field to share their expertise on the pathogenesis of RA, focusing on the involvement of B-cells and their interaction with other key players that produces the sustained autoimmune environment characteristic of RA; reviewed factors associated with the development of ADA and their consequences, focusing on treatment with tumor necrosis factor inhibitors; and introduced the concept of biosimilars, summarizing global regulatory policies, current research status, and concerns and considerations related to the potential inclusion of biosimilars in the RA treatment armamentarium.

I thank the panelists for their contribution to the discussion and the preparation of this monograph. Readers can expect to improve their understanding of these salient aspects of RA disease and its management, and become better equipped to critically appraise new developments as they become available.

Leonard H. Calabrese, DO
Activity Chair
The Evolving Roles of B-cells in Autoimmune Diseases, Including Rheumatoid Arthritis

Gregg J. Silverman, MD

The pathogenesis of rheumatoid arthritis (RA) is characterized by a continuous interaction of numerous cells, molecules, and processes. A striking pathological change is the transition of the synovial lining from 2 to 3 layers of fibroblast-like synoviocytes (FLS) into several layers of macrophage-like cells. In health, the synovial lining is a single-cell layer, while in RA, there are hypertrophic and hyperplastic changes of the FLS to assume a frond-like appearance. The abnormal growth and survival of these synovial fibroblast-like cells are supported by the neoangiogenesis promoted by ongoing inflammation. There are several features of these cellular changes within the RA synovium that have been likened to the cells in a metastatic tumor.

The complex processes leading to cartilage loss and synovial inflammation that occurs in RA involves, at a minimum, B-cells, T-cells, as well as cells from the innate immune system (dendritic cells, macrophages, and mast cells), and the cytokines and chemokines that these cells express. B-cells infiltrating the synovium play a number of roles in the pathophysiology of RA, where they can differentiate into autoantibody-producing plasma cells. B-cells are also involved with T-cell activation, antigen presentation, and cytokine production. Activated T-cells stimulate B-cells directly and through their membrane-associated and soluble-proinflammatory mediators. The activated B-cells can then differentiate into antibody-producing plasma cells, and produce a range of soluble-proinflammatory mediators that include IL-6, TNF-α, IFN-γ, and lymphotixin.

The proinflammatory mediators from both T-cells and B-cells activate macrophages, which produce IL-6, TNF-α, IL-1, and IFN-γ, and secrete metalloproteinases and other proteolytic enzymes that damage synovial tissue. TNF-α, IL-1, and IL-6 produced by dendritic cells attract additional cells to the inflammatory infiltrate in the synovium. Mast cells, also derived from monocytes, may be part of the triggering process that initiates the inflammatory response leading to self-perpetuating synovitis.

Figure 1. Integrated Immune Response During the Pathogenesis of Rheumatoid Arthritis

An array of cell types are drawn into the downstream effector mechanism, including synoviocytes and endothelial cells, which are induced to undergo morphologic changes. The process results in an inflamed, hyperplastic synovium and leads to joint damage and destruction. These damaged chondrocytes are unable to repair the injured matrix and cartilage is lost. Osteoclasts are multi-nucleated myeloid cells that acquire the ability to resorb cortical bone, and due to imbalances with osteoblasts, are major contributors to joint destruction. Following a chemokine trail into the joint, osteoclasts fuse to become multicellular structures that promote progressive bone erosion.

On a functional level, the inflammatory cytokine mediators facilitate cell interactions through 2 major pathways. Cell membrane-associated receptors may react with a ligand on another cell, or they may produce autocrine effects on the same cell. T-cell activation cannot be completed without a second signal involving other costimulatory molecules. For example, when a T-cell encounters an antigen in the context of a major histocompatibility complex (MHC) protein on an antigen presenting cell (APC), costimulatory molecules, such as CD28 on the T-cell, with its CD80 and CD86 ligands, allows the T-cell to become fully activated. Accordingly, abatacept, a CTLA-4 fusion protein, was approved in 2005 for the treatment of RA, as this agent mediates interruption of T-cell stimulation during the pathogenesis of this autoimmune disease.

Activated T-cells proliferate and secrete other cytokines that induce further proliferation. When cytokines, such as TNF, are locally produced in excess levels, enzymatic cleavage from the cell membrane releases them to enter the circulation, where they can cause remote effects, including stimulatory effects on bone marrow cells. Hence, the effects of cytokine blockade extend beyond cells in the synovium.

The autoantibodies that characterize RA include rheumatoid factors (RF) and anti-citrullinated peptide antibodies (ACPA). Both RF and ACPA antibodies form immune complexes that can activate complement and attract other inflammatory cells to the synovium. Levels of these autoantibodies may be reduced following treatment with CTLA4-Ig and TNF blockade.

B-cell Involvement in Rheumatoid Arthritis

In adults, B-cells are continuously generated from bone marrow, with sequential stages of differentiation, including stem cells that produce Pro-B and Pre-B precursor cells from which mature B-cells will later arise. Each cell stage has different surface receptors and follows different activation pathways in vivo, nurtured by local signals that can lead to the next differentiation stage. Differentiation of immature B-cells continues in peripheral lymphoid tissues, with entry of naive cells into a germinal center where, with cooperation of CD4⁺ T-follicular cells (TFH), selected B-cells acquire antigen specificity, and are banked in memory.

In the autoimmune disease setting, these normal physiologic functions can become distorted, and the adaptive immune system, that evolved to defend from infections, instead can attack the body itself. Several B-cell functions can contribute to the pathogenesis of autoimmune disorder, and these may all contribute to the pathogenesis of RA.

Lymphoid Organogenesis

When activated inappropriately at sites of a lesion, B-cells can be a source of chemokines, such as lymphotxin-β, that recruit other cells to the site of inflammatory disease. Ectopic lymphoid results, for example, can have many of the features of a lymph node. This can occur in joints such as the knee in RA, or in the salivary and lacrimal glands in Sjögren's Syndrome.

Figure 1: Integrated immune response during the pathogenesis of rheumatoid arthritis.
Antigen Presentation and Costimulation

In this pathological setting, immune tolerance is bypassed and expansion of damaging autoreactive clones can occur. When an antigen triggers the antigen-receptor of a B cell, a complex is formed which becomes internalized and this is directed to a lysosomal compartment where enzymes degrade B-cell antigen complexes into their constituent peptides. Some of these antigenic peptides can potentially become loaded onto MHC Class II molecules that enable self-peptide presentation to autoreactive follicular helper T cells (THF). B-cells can thereby present antigen to T-cell receptors (TCRs), and also provide costimulatory signals to T cells.9,10 The activated T cells may produce proinflammatory cytokines that contribute to activation of other local cells including macrophages.9,11

Inflammatory Cytokines

Inflammatory cytokines produced by activated B-cells, including IL-6, TNF-α, IFN-γ, and lymphotoxin can also directly affect T cells and other cells downstream. Although each B cell may not produce as much of the inflammatory cytokines as other innate cells, such as macrophages, by initiating the production of these factors B-cells may start a process with downstream amplification. For this reason, the potential role of B-cells as cytokine producers may be very important in autoimmune pathogenesis. B-cells can polarize into separate types, expressing either Th1- or Th2-like cytokines, and there are recent reports that some B-cells may also be producers of IL-17 that may be an important driver of autoimmune injury.

Autoantibodies

Many autoantibodies have been identified in patients with RA, including rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), as well as anti-glucose-6-phosphate isomerase (anti-GPI), and anti-RA33.12,13,14 These autoantibodies may act as stimuli for immune complex formation that are further contributors to the self-perpetuation phase of this chronic condition.11,14 In fact, autoantibodies are not always directly pathogenic through their binding activity. In clinical practice, these autoantibodies may be sufficiently specific that they aid diagnosis as they serve as disease markers. There are probably only a handful of cases in which the autoantibodies themselves are directly toxic. For example, antibodies produced in Graves’ disease can stimulate the excessive release of thyroid hormone, and antibodies in myasthenia gravis can have pathological effects by directly interacting with the neuromuscular junction. In addition, autoantibodies produced in pemphigus vulgaris interact with desmoglein 1 and 3, desmosomal adherens proteins in the skin, producing a blistering disease that can result in skin loss over major portions of the body.

Immune Complexes

As mentioned, most of the antibodies that contribute to disease diagnosis are not destructive in themselves. Rather, they form immune complexes that can change the properties of the IgG constant region, acquiring the capacity to trigger Fc receptors inducing an inflammatory response. These autoantibody immune complexes also can contribute to RA pathogenesis through activation of the complement cascade. Therefore, there are several roles for B-cells that are very relevant in the pathogenesis of RA. Rituximab, a chimeric murine-human monoclonal antibody that binds to and depletes CD20-positive B-cells, was the first monoclonal antibody approved for cancer treatment (non-Hodgkin’s lymphoma), and in 2006 this B-cell depleting agent was FDA-approved for RA patients with inadequate response to TNF blockers.5,13

Fundamental Roles of BLYS/BAFF in B-cell Survival

The B-lymphocyte stimulator/B-cell activating factor of the TNF family (BLYS/BAFF) is potentially expressed by multiple immune cells and levels are often increased in response to inflammation.16,17 BLYS (TNFSF13B) exists in membrane-bound and soluble forms, and is genetically and structurally related to another TNF family member called the A Proliferation Inducing Ligand (APRIL, TNFSF13). Three molecules bind together to form the trimeric soluble protein.16,18 BLYS participates in ensuring that new B-cells mature, survive, and differentiate. BLYS/BAFF is expressed by THF to select germinal center B-cells.

RA Pathogenesis: Putting It All Together

The RA pathogenesis often extends beyond the local synovitis; rather, this chronic condition requires the continuous trafficking of cells and molecules into and out of the disease site.19 We believe that disease initiation is triggered by breaches in immunologic tolerance with antigen presentation to self-reactive T cells. Affected joints are then subjected to the interactions of diverse cell types. A consequence of disease is the local release of inflammatory cytokines, such as TNF-α, that then enters the circulation to enter other sites, such as the bone marrow where it can cause the premature release of activated neutrophils and B-cell precursors. These cells may then home to inflamed joints in response to the local release of chemotactic factors. Inflammatory factors in the joints also cause synoviocytes and leukocytes, such as neutrophils and dendritic cells, to release additional factors that include the B cell survival factors, such as BAFF and APRIL, and also IL-6 and stromal cell-derived factor 1 (SDF-1). There are similar pathways for T cells, and similar differentiation factors for monocytes to become macrophages or osteoclasts. Together these contribute to the active synovitis of this common autoimmune disease.

Genetic Susceptibility and Risk of RA

The participation and interaction of genetic and environmental factors that result in RA is not clearly understood; however, despite an uncertain initiation mechanism, there are now an increasing number of genetic factors that have been reported to have a role in RA development through a complex mode of inheritance. There are also variants of several candidate genes that have been reported to be associated with an increased risk of RA.20,21 The best documented genetic susceptibility factor for RA is with Class II MHC human leukocyte antigen- (HLA)-DRB1 alleles, including *0401 and *0404.22 This subset of HLA II alleles is called the “shared epitope” subset because of its similar amino acid sequence in the third hypervariable region that are directly involved in presentation of peptide epitoones to T-cells. While the shared epitope hypothesis was first published in 1987, a genome-wide association study (GWAS) more recently confirmed that the strongest association with RA was with the MHC region of chromosome 6.21 Carriers of 1 or 2 of these specific shared epitope alleles have a 3- to 10-fold increased risk of developing RA. SNPs at the TRAF1-C5 locus on chromosome 9 were also significantly associated with a diagnosis of RA, as was a variant of the regulatory cell signaling phosphatase, PTPN22.

Citrullinated Antigens

New clues regarding the nature of the causative autoantigens in RA have been linked to the discovery that enzymes released by an inflammatory cell can modify proteins to have a neutral citrulline amino acid molecule in place of a positively charged arginine in the peptide chain of a protein.23,24 When processed by antigen presenting cells (APCs), some citrullinated peptides bind with high affinity to the RA associated MHC II alleles expressed by a APC. A common belief is that these citrullinated autoantigens thereby cause APC-induced T cell activation and clonal expansion of autoreactive T cells against the citrullinated antigens. Autoreactive B-cells may then be activated by these T cells to produce ACPA autoantibodies in a self-perpetuating cycle of lymphocyte co-stimulation (Figure 2).

In support of this postulated disease associated pathways, certain citrullinated peptides were shown to have a 20- to 100-fold higher binding affinity for certain RA associated HLA-DRB1 alleles on APCs.25 In surveys of patient populations, the presence of serum ACPA have greater diagnostic specificity for RA than RFs, which are also produced in several unrelated conditions associated with chronic antigen exposure. In addition, patients who are seropositive for ACPA autoantibodies are more likely to have radiographic progression and a worse long-term prognosis compared with seronegative RA patients (ie, those without RF or ACPA).

There remain many aspects about early RA pathogenesis that are poorly understood. Serum samples taken before and after disease manifestation were analyzed for ACPA autoantibodies to investigate the development of recognition to citrullinated antigens in relation to symptomatic disease development.26 The number of recognized antigens was shown to increase in the years before synovitis developed, which has suggested that the initial breach of immune tolerance, and start of the ACPA-associated autoimmune
state, in many patients may start long before the disease is detectable from a clinical perspective. Therefore, it may be difficult to turn off the central drivers of this autoimmune disease.

**ACPA: RA Classification Criteria**

Better clinical outcomes require earlier treatment before there is substantial joint damage. Towards this goal the 2010 ACR/EULAR RA classification criteria were developed, which incorporate 4 scored domains. A definite diagnosis of RA requires a total score of ≥6 in a clinical setting in which there is also: (1) ≥1 specified joint with synovitis; and (2) absence of an alternative diagnosis that better explains the synovitis (Table 1). A score of ≥3 in the ACPA serology domain contributes 1 of the 4 domains, and can provide up to one-half of the required diagnostic score, which illustrates the importance of clinical RF and ACPA results.

**B-cell and T-cell Infiltrates**

Studies of synovial biopsies have shown that patients with RA may have predominance of either B-cell or T-cell infiltrates, or both, but it has been unclear whether the nature of these infiltrates can influence prognosis or response to therapeutic intervention. In a recent report, data from immunohistology, synovial transcripts, and potential serum biomarkers were examined. The authors proposed that RA could be divided into 4 major molecular phenotypes: lymphoid, myeloid, low inflammatory, and fibroid. However, these findings will require independent validation as it is currently uncertain if these different phenotypes are related to different disease stages or represent specific forms of the disease; however, treatment data suggested different therapeutic effectiveness among phenotypes. Specifically, patients with the lymphoid pattern were more responsive to the IL-6 receptor blocker tocilizumab, while the myeloid pattern was more responsive to a TNF blockade. Serologic biomarkers were also postulated to correlate with these different synovial patterns, and this topic is currently being examined in a number of laboratories.

**Emerging Approaches to Eliminate B-cells in Autoimmunity**

In RA, the immune-mediated pathogenesis involves the complex contributions of many different lymphoid and innate immune cells types. As the disease progresses, the rheumatoid synovitis can assume an organization that emulates features of lymph nodes, with evidence of coordinated activities of the cells and cytokines that are involved in driving RA pathogenesis. However, the detection of a cell type and/or a particular soluble inflammatory factor at the site of disease is insufficient to prove there is a critical role in the disease process. Like firemen at the site of a crime, correlation does not prove causation, and some of these cells and factors may even be working to resolve the insult. With the advent of targeted biologic therapy, which typically removes only one cell or cytokine from the process, we can now test for the central disease drivers, as we can unmask whether removal of a candidate cell/factor may cause disintegration of the synovitis and significant clinical improvement.

We are also gradually learning about the greater biologic implications of effective treatments. In RA, there is now evidence that the clinical benefits observed with the approved biologics abatacept, anakinra, tocilizumab, and rituximab may also be accompanied by down-modulation of pathologic autoimmune memory B-cell responses. In contrast, the targeting BAFF/BlyS by agents, such as belimumab and TACI-Ig (atacicept), failed to provide significant clinical benefits in RA trials. These findings therefore indicate that some B-cell associated targets do not necessarily provide relevant therapeutic approaches for the treatment of RA.

**Summary**

Rheumatoid arthritis is a complex inflammatory autoimmune process. Emerging research has suggested there may be major histopathologic subsets that could be driven by the interactions of different cell types and pathways; however, in patients with ACPA seropositive disease, it is clear that B-cells play dominant roles in the pathologic autoimmune.

Targeted B-cell therapy with an anti-CD20 antibody can have dramatic effects on pathogenesis, which can lead to amelioration of synovitis through secondary effects on many other cells and factors. Effective clinical treatment with biological agents with several other mechanisms of action can also correlate with normalization of B-cell abnormalities and reduced autoantibody production. Future investigations are needed to develop practical biomarkers to identify subsets of patients with RA that are more amenable to treatment with individual biologic agents. The ultimate goal should be to find effective and safe approaches to reset the adaptive immune system and wipe out all remnants of the pathogenic autoimmune state.

**Table 1. ACR/EULAR 2010 Rheumatoid Arthritis Classification Criteria**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Score</th>
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<tbody>
<tr>
<td>Swollen/Tender Joints</td>
<td>(0-5)</td>
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<tr>
<td>1 large</td>
<td>0</td>
</tr>
<tr>
<td>2-10 large</td>
<td>1</td>
</tr>
<tr>
<td>1-3 small</td>
<td>2</td>
</tr>
<tr>
<td>4-10 small</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10</td>
<td>5</td>
</tr>
<tr>
<td>Serology</td>
<td>(0-3)</td>
</tr>
<tr>
<td>Negative RF and ACPA</td>
<td>0</td>
</tr>
<tr>
<td>Low-positive RF or ACPA</td>
<td>2</td>
</tr>
<tr>
<td>High-positive RF or ACPA</td>
<td>3</td>
</tr>
<tr>
<td>Symptom Duration</td>
<td>(0-1)</td>
</tr>
<tr>
<td>&lt;6 weeks</td>
<td>0</td>
</tr>
<tr>
<td>≥6 weeks</td>
<td>1</td>
</tr>
<tr>
<td>Acute Phase Reactants</td>
<td>(0-1)</td>
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<tr>
<td>Normal CRP and ESR</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal CRP or ESR</td>
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Key: ACPA=anti-citrullinated protein autoantibodies, CRP=C-reactive protein, ESR=erythrocyte sedimentation rate, RF=rheumatoid factor.


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**Figure 2. Potential Pathogenic Roles of ACPAs in RA**

![Image used with permission. Source: Catrina AI, et al. Nat Rev Rheumatol. 2014. Doi:10.1038/nrrheum.2014.115.](image-url)
Bioengineering of the Drug

Antibodies are comprised of 2 heavy and 2 light chains connected by disulfide bonds, each with constant and variable regions. The variable amino acid sequences of the antibody Fab portions define the antigen binding site. The Fc portion that defines the immunoglobulin isotype and subclass can bind to the Fc receptor on effector cells and activate immune mediators including complement.

In 1975, the production of monoclonal antibodies that bind to the same epitope was described, which led to their becoming an important research tool and novel class of biotherapeutic agents. The initial mouse antibodies were highly immunogenic in humans, which can affect treatment tolerance as well as efficacy. Subsequently, chimeric antibodies were made that substituted the variable regions of human antibodies with the relevant mouse sequences. Reducing the foreign component of the antibody further by grafting murine hypervariable, or complementarity-determining, regions to a human antibody framework resulted in a humanized antibody. Further advancements in genetic engineering allowed removing all xenogenic components, or use of a transgenic mouse model to produce human antibodies.

Each antibody binds with idiotypic specificity. Within the antigen-binding pocket, the specific hypervariable portion of light and heavy chains, known as the paratope, is a unique set of amino acids that binds directly to the epitope, its cognate ligand on the antigen. Anti-idiotypic antibodies can be produced in response to monoclonal antibodies that contain foreign idiotypes. Aggregated therapeutic antibodies can also induce ADAs, as can nonhuman glucosylation or pegylation. In addition, patients with alternative allotypes compared with the single polymorphic IgG allotype comprising the treatment biologic may generate ADAs against these allotypes.

Among the 5 available TNFi, infliximab, adalimumab, and golimumab are full-length monoclonal antibodies (Figure 1). Infliximab contains approximately 25% of mouse-derived amino acids in its variable domains, while adalimumab and golimumab have framework regions that are approximately 98% human. Certolizumab is a humanized protein, containing murine complementarity-determining regions from a mouse TNF monoclonal antibody inserted into the variable domains on a humanized antibody Fab fragment that is conjugated to polyethylene glycol. Etanercept is the only TNFi that is not a TNF monoclonal antibody or fragment. Etanercept comprises a genetically engineered dimeric fusion protein from the ligand binding extracellular portions of human TNF receptor 2, which is fused to the Fc portion of human IgG.

These structural differences can be related to the immunogenicity of the TNFi(s), although other factors can contribute to varying immunogenicity among agents. ADAs can be induced against mouse epitepopes on the variable regions of chimeric antibody constructs; theoretically, therefore, they would be the most immunogenic, which is usually the case. Approximately one-half of patients with an initial response to the chimeric

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**Table 1. Currently Available TNF Inhibitors for Treating Rheumatoid Arthritis**

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Structure</th>
<th>RA Treatment</th>
<th>Other Indications</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>Recombinant human dimeric fusion protein linked to Fc portion of human IgG1</td>
<td>First-line monotherapy or in combination with MTX</td>
<td>JIA, PsA, AS, Ps</td>
<td>1998</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Chimeric murine-human IgG1 monoclonal Ab</td>
<td>First-line only in combination with MTX</td>
<td>PsA, AS, A/P CD, A/P UC, PsA</td>
<td>1999</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Fully human IgG monoclonal Ab</td>
<td>First-line monotherapy or in combination with MTX</td>
<td>JIA, PsA, AS, A/P CD, UC, PsA</td>
<td>2002</td>
</tr>
<tr>
<td>Golimumab</td>
<td>Fully human IgG monoclonal Ab</td>
<td>First-line only in combination with MTX</td>
<td>PsA, AS, UC</td>
<td>2009</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>Fc-free humanized pegylated anti-TNF Fab fragment</td>
<td>First-line monotherapy or in combination with MTX</td>
<td>AS, CD, PsA</td>
<td>2009</td>
</tr>
</tbody>
</table>

**Key:** Ab=antibody, A/P=adult/pediatric, CD=crohn’s disease, IgG=immunoglobulin G, JIA=juvenile idiopathic arthritis, MTX=methotrexate, Ps=plaque psoriasis, PsA=psoriatic arthritis, RA=rheumatoid arthritis, TNF=tumor necrosis factor, UC=ulcerative colitis.

**Source:** Meier FMP, et al. Immunotherapy. 2013;5:955-974; see prescribing information for each biologic.
antibody infliximab experience disease flare after several months, with TNFi antibodies associated with the secondary response failure.12 Immunogenic epitopes remain in human and humanized monoclonal antibodies, primarily in the hypervariable regions of the binding site. Exemplifying the contribution to immunogenicity of other than a xenogenic origin of antibody components, ADAs were observed within 28 weeks of treatment in over half of patients with RA who were treated with the fully human monoclonal antibody adalimumab.15 Almost all of the antibody response was specific for the adalimumab idiotype, and resulted in functional neutralization of the drug.

The dimeric fusion protein etanercept is the least immunogenic of the TNFi. When ADAs were detected they were nonneutralizing, and not associated with a loss of treatment effectiveness.16

Patient-related Factors
Not all patients develop ADA. Genetic susceptibility may have a role, as patients who developed ADAs against infliximab were more likely to develop ADAs against adalimumab, and were less likely to respond.13 Conversely, treatment response assessed in switchers from infliximab or adalimumab to etanercept in 1 study revealed that the response to etanercept was similar between switchers who had ADAs and TNFi-naïve patients (P=0.74); while switchers without ADA had a reduced response to etanercept compared with TNFi-naïve patients (P=0.001) and switchers with ADAs (P=0.017).17

A possible association between IL-10 polymorphisms and anti-adalimumab antibody development has been reported.14 Higher baseline disease has also been reported to be associated with ADA development, suggesting a role of inflammation in the ADA response.16 Similarly, infections that trigger the immune response may increase the likelihood of ADA development. Patients with RA are more likely to produce antibodies to TNFi compared to patients with ankylosing spondylitis who are being treated following the same regimen.19

Treatment-related Factors
Drug dose, route, frequency, and duration are often associated with sensitization risk. Lower doses administered intermittently are generally considered to be more immunogenic compared with larger bolus doses.16 Although increased immunogenicity is typically associated with subcutaneous compared with intravenous administration, subcutaneous tocilizumab used to treat RA was not more immunogenic than intravenous tocilizumab.20

Effects of Immunosuppressants on Antidrug Antibodies
Concomitant treatment with methotrexate (MTX) and other immunosuppressive disease-modifying treatments has been shown to reduce the immunogenicity of TNFi. Among the available TNFi, infliximab and golimumab are indicated for treatment of RA in combination with MTX.

The development of ADA has been reported to be inversely associated with MTX use and dosage for infliximab, adalimumab, and golimumab.21 An early study reported 53%, 21%, and 7% ADA after 26 weeks in patients with RA treated with 1, 3, or 10 mg/kg infliximab.22 Patients receiving concomitant MTX had 15%, 7%, and 0% ADA at the 3 infliximab dose levels. Studies have also reported an MTX dose-dependent decrease in ADAs during adalimumab treatment. In 4 patient subgroups based on receiving no MTX to high-dose MTX, ADAs were less frequent with MTX compared with patients without MTX (odds ratio [OR] 0.20; 95% confidence interval [CI]: 0.12, 0.34; P<0.001), with ADA development inversely proportional with increasing MTX.23 In addition, the incidence of adverse events was not increased when immunosuppressants were added to the TNFi treatment.

Detection of Antidrug Antibodies
Interpretation of ADA development data must consider the assay that was used, as ADA detection results vary widely among assays, and with TNFi and ADA levels.12,13 This variation complicates making valid comparisons among studies. Many assays do not distinguish between functionally active and inactive antidrug antibodies. ELISA, antigen-binding test (ABT), and PIA (pH-shift anti-idiotype antigen binding) test detect free ADA but not free TNFi; accordingly, a pharmacokinetic (PK) assay is necessary to determine the amount of functional drug; however, a PK assay will not detect free ADA. Results are less predictable in the presence of ADA-drug complexes, and separating them for assay purposes is laborious, reassociation may occur, and the process itself may introduce artifacts.

Clinical Consequences of Antidrug Antibodies
Increasing ADA are associated with decreased levels of drug, and may correlate with decreased treatment effectiveness.23-25 Immune complexes may form that are also immunogenic. Data are emerging that support an association between ADA and toxicity, including hypersensitivity and infusion reactions.

Variability of Response to Anti-TNF Agents
From 30% to 40% of patients with RA, inflammatory bowel disease (IBD), juvenile idiopathic arthritis, and spondyloarthritis (SpA) treated with a TNFi fail to derive a significant benefit.26 In addition, some patients experience a relapse, or secondary failure, after an initial response. Failure may also occur due to toxicity. The mechanism of treatment failure is incompletely understood, and may be related to several factors including the drug mechanism of action, pharmacokinetics, toxicity, host factors such as a non-TNF-driven disease, and immunogenicity.

In a meta-analysis of 17 qualifying studies of infliximab, adalimumab, and etanercept in patients with RA, SpA, psoriasis, and IBD, ADA was compared with drug response.27 Anti-etanercept antibodies were not detected. In the presence of ADA against infliximab or adalimumab, drug response was reduced 68%, which was attenuated by concomitant MTX treatment. Concomitant MTX or azathioprine/mercaptopurine reduced ADA frequency by 37% when assessed by ELISA, and 64% when assessed by RIA.

One etanercept study in patients with RA that failed to observe ADA reported that low circulating etanercept levels were a nonresponse predictor.28 Another study reported 6% ADA positive patients, and the nonneutralizing antibodies did not have an effect on clinical response or tolerance; however, patients with concomitant MTX had a better clinical response.
Therefore, the variability in response to TNFi can be partly explained by ADAs; however, there may be alternative causes of relapse that are not yet clearly defined. For example, there may be an immunopatho-
genic breach, where the disease transitions from a TNF mechanism to an
IL-17 mechanism.

ADA and Drug Safety
Many studies show a correlation between ADA and specific acute adverse
events (AEs). A meta-analysis with 60 qualifying studies in chronic
immune-mediated inflammatory conditions reported ADA seropositive
patients had a significantly higher risk of hypersensitivity reactions (OR
3.75; 95% CI: 2.36, 6.67; P<0.001) compared with seronegative patients.28

When 3 patients who developed severe venous and arterial thromboem-
bolic events during treatment with adalimumab were shown to have ADA,
data from 272 adalimumab-treated RA patients were reviewed for pres-
ence of ADA and thromboembolic events.30 Over one-fourth (28%) of
patients had anti-adalimumab antibodies. Eight thromboembolic events
were observed, with an increased incidence rate in seropositive (26.9/1000
person-years) compared with seronegative (8.4/1000 person-years) patients
that approached significance by univariate analysis (hazard ratio [HR] 3.8;
95% CI: 0.9-15.3; P=0.064). After adjusting for duration of follow-up, age,
BMI, ESR, and prior thromboembolic events, seropositive patients had a
significant 7.6-fold increased risk of a thromboembolic event compared
with seronegative patients (HR 7.6; 95% CI: 1.3, 45.1; P=0.025).

Therapeutic Drug Monitoring
Therapeutic drug monitoring may assist with patient management and
contribute to understanding of individual variability of immune responses.31
Robust, standardized assays are necessary for this to be feasible. Therapeutic
drug monitoring has traditionally been used for small drug molecules, such
as seizure medications and antimicrobials. Therapeutic drug monitoring can
be beneficial when used for agents with the following characteristics:
- Clinically difficult to assess efficacy or toxicity
- Established therapeutic window
- Narrow therapeutic range
- No active metabolites

An algorithm for monitoring serum TNFi levels and ADAs in patients
with TNFi failure has been proposed to provide a predictive tool for
choosing biologics (Figure 2).7 In the proposed model, when a patient is
not responding to a TNFi, drug concentration and ADA are measured,
which can yield 1 of 4 results based on TNFi concentration (optimal/
suboptimal) and ADA seropositivity status (positive/negative).

Patients with low TNFi without ADA may be hypermetabolizing, or
this situation may represent a sink effect. Increasing the injection dose
or frequency can be appropriate for these patients. A switch to another
TNFi, or to another drug class, may be warranted for ADA positive
patients with suboptimal TNFi levels, and for ADA negative patients
with optimal TNFi levels. If patients are seropositive and have optimal
TNFi levels, a switch to a biologic with another mechanism of action may
be the best treatment strategy.

Summary
Biologics are important tools in the therapy of immune-mediated inflam-
matory diseases. Although factors leading to both failure and toxicity
remain poorly understood, ADAs are reported to contribute to drug failure
and increased toxicity, primarily infusion hypersensitivity reactions. ADAs
have been observed with all TNFi in RA and non-RA disorders. There
is variability in ADA development among the TNFi, which is low with
tanercept treatment, and higher with infliximab; however, ADAs are also
observed following treatment with totally human antibodies.

Several studies have shown a correlation between ADAs and reductions
in serum drug concentrations and clinical responses. High-dose tolerance
has been suggested as a possible explanation for decreased immunoge-
nicity at higher treatment doses,13,32 and the decrease in immunogenicity
observed in the setting of concomitant MTX use is most likely related to
the immunosuppressive activity of MTX.14

ADA and therapeutic monitoring may be able to improve clinical
decision-making. However, assays for treatment monitoring lack uniform-
ity and robust predictive power to justify routine use. Strategies to reduce
the development of ADA and its associated undesirable effects are an
important research objective.

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    suppressive therapy in suppressing the formation of antibodies to infliximab in Crohn’s disease. Gut.
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    inadequate response to tumour necrosis factor inhibitors: a systematic review. Rheumatology.
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Figure 2. Patients With Failure of TNFi Therapy

![Diagram of Patients With Failure of TNFi Therapy](image)

Suboptimal TNFi Inhibitor

Drug Concentration and ADA Measurement

Suboptimal TNFi Inhibitor

Switch to another TNFi inhibitor

Switch to biologic with another mechanism of action

Key: ADAb= antidrug antibody


continued on page 14
Biosimilars in Rheumatology: Present and Future

Jonathan Kay, MD

The term "biosimilar" implies the same general meaning worldwide; however, its regulatory definition varies among global markets (Table 1). Terminology also varies across countries and agencies, including "subsequent entry biologic" (Canada), "similar biologic" (India), and the World Health Organization (WHO) term "similar biopharmaceutical product." The European Union (EU) was the first to develop a distinct regulatory pathway for biosimilar product approval, and similar guidelines became adopted standards in several other countries. In the EU, a biosimilar is defined as "a biologic medicinal product that contains a version of the active substance of an already authorized original biologic medicinal product (reference medicinal product). A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biologic activity, safety, and efficacy based on a comprehensive comparability exercise." In some countries, such as India, the approval process for biosimilars is less rigorous than it is in the EU, United States, and other highly regulated countries.

In the United States, an abbreviated licensure pathway for biosimilars was implemented through the Biologics Price Competition and Innovation Act (BPCIA) of 2009. Although modeled on the Hatch-Waxman generic act, the BPCIA additionally describes requirements for establishing "similarity" between biological products, made necessary because biological drugs are never exact copies of the reference biopharmaceutical. According to the FDA, similarity means "that the biologic product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biologic product and the reference product in terms of the safety, purity, and potency of the product." Biosimilars are not second-generation biopharmaceuticals, which are structurally different from the originally licensed biopharmaceutical. Second-generation biopharmaceuticals are intended to improve performance while preserving the mechanism of action of the first-generation biologic. For example, adalimumab was intended to be an improvement on infliximab, because it is humanized. Accordingly, adalimumab is a second generation TNF-inhibition biotherapeutic.

Biosimilars also are not biomimics, or intended copies, as biomimics are not developed, assessed, or approved according to a regulatory pathway for biosimilars. Similarity with the reference biopharmaceutical has not been demonstrated by a stepwise and comprehensive comparability exercise. Biosimilars may differ from the reference product in primary structure, as well as in formulation, dose/dosing regimen, efficacy, safety, and immunogenicity. Biomimics of rituximab and etanercept have been developed and manufactured in India, Mexico, and China. These are not biosimilars, as they have not been reviewed following a stringent regulatory pathway.

### CT-P13: Biosimilar Infliximab

In 2013, CT-P13 was the first biosimilar monoclonal antibody approved by the European Medicines Agency (EMA). Approvals in other countries followed, and it is now available in more than 70 countries worldwide as an approved biosimilar. Approved indications include those for which infliximab was approved: rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), Crohn's disease (CD; adult and juvenile), and ulcerative colitis (UC; adult and juvenile). Canada and Japan did not extrapolate approval to all of these disease indications. CT-P13 is currently under FDA review in the United States. Other agents have been approved as biosimilars in South Korea and India (Table 2).

Several additional biosimilars are in clinical trials (Table 3; see Clinicaltrials.gov), while others are in preclinical development. In March 2015 the FDA approved the leukocyte growth factor biosimilar filgrastim-sndz, marking its first approval of a biosimilar product. The EU allows biosimilars to use the same international nonproprietary name as their reference products; however, the United States policy has not yet been established. As an interim measure, the FDA required the biosimilar manufacturer to add the "-sndz" suffix to facilitate differentiation between the originator and biosimilar products. Applications have been filed with the FDA for 4 other biosimilar products, including CT-P13, between August 2014 and February 2015; however, the CT-P13 advisory committee meeting was postponed pending receipt of additional information requested from the sponsor.

All biopharmaceuticals, including biosimilars and the reference products (originators), are subject to variability over time, as posttranslational modifications of a protein change coincident with modifications in the manufacturing process. These differences can be due to physical changes that include protein-folding variants, misfolding, aggregation, enzymatic cleavage, and degradation. Biochemical changes, including glycosylation, disulfide bond formation, phosphorylation, deamidation, oxidation, and amino acid substitution may also contribute to variation. Any of these changes can affect the function of the biopharmaceutical. However, subtle changes that occur over time do not make a product a biosimilar of itself, because these versions of the reference product never undergo comparative evaluation according to a regulatory pathway for biosimilars.

Biosimilar data are submitted for approval to the FDA through an Abbreviated Biological License Application. The process requires evaluation of the biosimilar against a single reference biological product.

### Table 1. Terminology by Country/Organization for Biosimilar

<table>
<thead>
<tr>
<th>Country/Organization</th>
<th>Terminology</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO</td>
<td>Similar biotherapeutic product (SBP)</td>
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<tr>
<td>EU</td>
<td>Similar biological medicinal product</td>
</tr>
<tr>
<td>US</td>
<td>Biosimilar</td>
</tr>
<tr>
<td>Australia</td>
<td>Biosimilar</td>
</tr>
<tr>
<td>Mexico</td>
<td>Biocomparable</td>
</tr>
<tr>
<td>Brazil</td>
<td>Biologic product</td>
</tr>
<tr>
<td>Canada</td>
<td>Subsequent-entry biological</td>
</tr>
<tr>
<td>India</td>
<td>Similar biologic</td>
</tr>
</tbody>
</table>

### Table 2. Global Biosimilar Approvals

<table>
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<th>Product</th>
<th>Active Substance</th>
<th>Country</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOW015</td>
<td>Infliximab</td>
<td>India</td>
<td>September 15, 2014</td>
</tr>
<tr>
<td>HD203</td>
<td>Etanercept</td>
<td>Korea</td>
<td>November 11, 2014</td>
</tr>
<tr>
<td>ZRC-3197</td>
<td>Adalimumab</td>
<td>India</td>
<td>December 9, 2014</td>
</tr>
</tbody>
</table>
The biosimilar and reference product must have the same presumed mechanism of action, route of administration, dosage form, and potency. The reference product must be reviewed and approved by the FDA for the indications applied for by the biosimilar.

Data demonstrating that the biosimilar is highly similar to its reference product must be submitted. These must be obtained from analytical studies, toxicology studies, pharmacokinetic (PK) and pharmacodynamic (PD) studies, and at least one clinical trial performed in patients who have a disease for which the reference product has an existing license. The “totality of evidence” from these studies must demonstrate safety, purity, and potency of the biosimilar. There also must be an assessment which establishes that the biosimilar is not more immunogenic than the reference product. If there is a Risk and Evaluation Mitigation Strategy (REMS) for the reference product, the same REMS must be applied to the biosimilar.

The objective of a biosimilar development program is to establish biosimilarity based upon the “totality of evidence,” not to re-establish benefit. Research and development activities for an originator begin with analytical studies to characterize the biopharmaceutical, followed by preclinical studies, including in vitro assays and animal studies to characterize the mechanism of action and toxicology of the drug. After appropriate preclinical studies have been conducted, PK and PD studies are undertaken in human subjects. For an originator biopharmaceutical, at least 2 large randomized, placebo-controlled trials are required to provide efficacy and safety data in each disease for which approval is being sought.

In contrast, the biosimilar approval pathway is based upon an extensive and robust analytical data package, which compares the biosimilar to its reference product. Comparative preclinical in vitro assays are performed, followed by clinical pharmacology to demonstrate that the biosimilar has the same PK and PD characteristics as the reference product. Finally, at least one clinical trial comparing the biosimilar to its reference product is conducted in patients with the disease that is most responsive to treatment with that biopharmaceutical, as a bioassay to confirm safety and efficacy of the biosimilar. Since the biosimilar must be highly similar to the reference biopharmaceutical, comparative efficacy must be shown to be within a prespecified equivalence margin. If the biosimilar were to be superior to its reference biopharmaceutical, it would not be biosimilar. Thus, a non-inferiority trial design is not adequate to assess biosimilarity. The biosimilar must be studied at the same dose that is licensed for the reference biopharmaceutical; accordingly, dose-ranging Phase 2 trials are not needed. Dose-ranging (Phase 2) studies are not necessary, since the biosimilar must have the same potency and dosage form as the reference product. FDA scientists integrate the submitted data to formulate an overall assessment that a biologic is biosimilar to its approved reference product.

Table 3. Biosimilar Agents in Development to Treat Rheumatologic Diseases

<table>
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<tr>
<th>Drug</th>
<th>Manufacturer Location</th>
<th>Clinical Trial Status</th>
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<tbody>
<tr>
<td>Adalimumab biosimilar</td>
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<td>ABP 501</td>
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<td>Phase 3</td>
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<td>BI695501</td>
<td>Germany</td>
<td>Phase 3</td>
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<tr>
<td>SB5</td>
<td>South Korea</td>
<td>Phase 3</td>
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<td>PF-06410293</td>
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<tr>
<td>Etanercept biosimilar</td>
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<td>SB4</td>
<td>South Korea</td>
<td>Phase 3</td>
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<tr>
<td>TuNEX (ENIA11)</td>
<td>Taiwan</td>
<td>Phase 3</td>
</tr>
<tr>
<td>CHS-0214</td>
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<td>Phase 3</td>
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<td>LBEC0101</td>
<td>South Korea</td>
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<td>DWP422</td>
<td>Daewoong Pharmaceutical Co. Ltd. (South Korea)</td>
<td>Phase 1</td>
</tr>
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<td>Infliximab biosimilar</td>
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<td>CT-P13</td>
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<td>Phase 3</td>
</tr>
<tr>
<td>SB2</td>
<td>South Korea</td>
<td>Phase 3</td>
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<td>PF-06438179</td>
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<td>GS-071</td>
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<td>BCD-020</td>
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<td>Phase 3</td>
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<td>CT-P10</td>
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<tr>
<td>SAIT101</td>
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<td>Development halted in 2012</td>
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<tr>
<td>TL011</td>
<td>Israel</td>
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<tr>
<td>PF-05280586</td>
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<td>Phase 1/2 completed</td>
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<tr>
<td>GP2013</td>
<td>Switzerland</td>
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</tr>
<tr>
<td>MK-8808</td>
<td>United States</td>
<td>Phase 1 completed</td>
</tr>
</tbody>
</table>

Table 3. Biosimilar Agents in Development to Treat Rheumatologic Diseases

The objective of a biosimilar development program is to establish biosimilarity based upon the “totality of evidence,” not to re-establish benefit. Research and development activities for an originator begin with analytical studies to characterize the biopharmaceutical, followed by preclinical studies, including in vitro assays and animal studies to characterize the mechanism of action and toxicology of the drug. After appropriate preclinical studies have been conducted, PK and PD studies are undertaken in human subjects. For an originator biopharmaceutical, at least 2 large randomized, placebo-controlled trials are required to provide efficacy and safety data in each disease for which approval is being sought.

In contrast, the biosimilar approval pathway is based upon an extensive and robust analytical data package, which compares the biosimilar to its reference product. Comparative preclinical in vitro assays are performed, followed by clinical pharmacology to demonstrate that the biosimilar has the same PK and PD characteristics as the reference product. Finally, at least one clinical trial comparing the biosimilar to its reference product is conducted in patients with the disease that is most responsive to treatment with that biopharmaceutical, as a bioassay to confirm safety and efficacy of the biosimilar. Since the biosimilar must be highly similar to the reference biopharmaceutical, comparative efficacy must be shown to be within a prespecified equivalence margin. If the biosimilar were to be superior to its reference biopharmaceutical, it would not be biosimilar. Thus, a non-inferiority trial design is not adequate to assess biosimilarity. The biosimilar must be studied at the same dose that is licensed for the reference biopharmaceutical; accordingly, dose-ranging Phase 2 trials are not needed. Dose-ranging (Phase 2) studies are not necessary, since the biosimilar must have the same potency and dosage form as the reference product. FDA scientists integrate the submitted data to formulate an overall assessment that a biologic is biosimilar to its approved reference product.

Figure 1. Comparative Pathways to Regulatory Submission

Source: Macdonald J. 2013 APEC Harmonization Center Biotherapeutics Workshop; Seoul; September 25, 2013.
Antidrug antibodies (ADA) can develop in patients treated with either the reference product or the biosimilar. Small differences between the biosimilar and reference biologic may result in increased immunogenicity, if patients are switched repeatedly between the two. Therefore, both animal and clinical studies of the biosimilar should include assessments of immunogenicity. In the clinical study, evaluation of immunogenicity should assess the incidence and nature of the immune response (eg, anaphylaxis, induction of neutralizing antibodies) and its severity and clinical relevance (eg, loss of efficacy, adverse events) in the population studied. If the biosimilar manufacturer aims to extrapolate immunogenicity findings from one indication to others, the population chosen for study should be adequately sensitive to predict a difference in immune responses across indications. Because AS and RA patients may have a lower incidence of ADAs to infliximab than patients with Ps, CD, or UC, these may not be the ideal populations from which to extrapolate immunogenicity data.

CT-P13 Immunogenicity

The development of ADAs is complicated and can vary among conditions and treatment doses. The Phase 1 PLANETAS study randomized patients with active ankylosing spondylitis (AS) to receive 5 mg/kg CT-P13 (n=125) or infliximab (INX; n=125) without concomitant MTX. The Phase 3 PLANETRA study randomized patients with active RA that was inadequately responsive to MTX to receive 3 mg/kg CT-P13 (n=302) or INX (n=304), in combination with MTX and folic acid. ADA were assessed by an electrochemiluminescent immunoassay.

Follow-up data through 60 weeks revealed that approximately 25% of patients with AS receiving 5 mg/kg CT-P13 (22.9%) or INX (26.7%) as monotherapy developed ADA, compared with approximately 50% of patients with RA taking 3 mg/kg CT-P13 (52.3%) or INX (49.5%) in combination with MTX (Figure 2). The reason for this discrepancy is not clear. Patients with AS are not predisposed to form clinically detectable autoantibodies, whereas many with RA have circulating autoantibodies. However, this difference may be affected more by the dose administered, with the higher dose inducing immunologic tolerance, than by concomitant treatment with MTX.

Interchangeability

Switching and substitution may be similar. Switching occurs when a patient is transitioned to a biosimilar after initial treatment with the reference product. The consequences of such transitioning can be investigated in a single-switch study, such as takes place in the open-label extension phases of most biosimilar trials when subjects treated initially with the reference product are switch to receive the biosimilar while those treated initially with the biosimilar continue to receive that product. Substitution occurs when a different product is substituted for that initially prescribed. This may result in a single switch or in repeated switches, which constitute “interchange.”

The BPCI indicates that the FDA can judge a biologic product to be interchangeable. This additional standard can be met if the product is biosimilar to the reference product and it is expected to produce the same clinical outcomes as the reference product in any given patient. In addition, if it is given more than once, the risk in terms of safety or decreased efficacy of alternating between the reference product and the biosimilar must not be greater than the risk of using the reference product without such repeated switching. By definition in the Act, the designation of interchangeability would allow the biosimilar product to be substituted for the reference product without involving the health care provider who prescribed the reference product. Accordingly, to support this designation, a study design with repeated switching would be appropriate; however, a single switch study could fulfill the current statutory requirement.

The BPCI offers 1 year of exclusive marketing rights to the first biosimilar shown to be interchangeable with its reference product. However, the FDA has not yet provided specific guidance as to the trial design necessary to achieve the designation of “interchangeability,” and the logistics of conducting such a trial are cumbersome which may be prohibitive to its successful conduct.

Biosimilars: Looking Forward

The justification for biosimilars assumes that the potential risk to the individual patient of switching to a lower cost biosimilar is outweighed by the potential benefit to society of expanding access to care. Currently marketed biosimilars are priced considerably lower than their reference products. If a biosimilar is approved according to a regulatory pathway designated for biosimilar products, approval will be based on the biosimilar being as effective and safe as the reference product. The designation of “interchangeability” is unlikely to be granted in the near future because a clinical trial adequate to support such a designation is unlikely to be accomplished. However, in the United States, insurance carriers and pharmacy benefit management companies will likely dictate switching between the originator and a biosimilar or between 2 biosimilars.

Figure 2. CT-P13: Immunogenicity

<table>
<thead>
<tr>
<th>Week</th>
<th>PLANETAS</th>
<th>PLANETRA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Planetary % Subjects</td>
<td>MTX + CT-P13 3 mg/kg (n=302)</td>
</tr>
<tr>
<td>0</td>
<td>9.1%</td>
<td>52.3%</td>
</tr>
<tr>
<td>10</td>
<td>11.0%</td>
<td>48.4%</td>
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The lack of standardization among regulatory approval pathways for biosimilars makes regulatory submissions to multiple national regulatory agencies challenging. This may inhibit biosimilar manufacturers that are targeting international markets. In addition, the unified International Committee on Harmonization authorized reference standard could facilitate the development of effective and safe biosimilars.

Conclusions

Biosimilars are highly similar to their reference products. The objective of biosimilar development programs is to establish biosimilarity, not to reestablish benefit. A stepwise and comprehensive comparative approach to claim biosimilarity must demonstrate highly similar physicochemical characteristics, biologic activity, pharmacokinetics, and clinical safety and efficacy. The biological license application submitted for approval of a biosimilar is abbreviated, compared with applications submitted for approval of an originator biopharmaceutical. However, in the EU, United States, and several other countries, biosimilars undergo a rigorous regulatory approval process in which regulators assess the “totality of evidence.” Many biopharmaceuticals will be going off-patent in the near future; accordingly, the opportunity exists to expand patient access through the availability of lower-cost biosimilars.

References


14. FDA. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. April 2015.


17. McCormick M. Effect of naming on competition and innovation. FTC Biosimilars Workshop on Nomenclature and Impact on Competition; December 10, 2013; Washington, DC.


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References


1. Which of the following best describes the mechanism of action for anakinra?
   A. IL-1 recombinant human IL-1 receptor antagonist
   B. Recombinant humanized anti-human IL-6 receptor monoclonal antibody
   C. CTLA-4 fusion protein
   D. CD28 antibody

2. Which of the following best describes the mechanism of action for tocilizumab?
   A. IL-1 recombinant human IL-1 receptor antagonist
   B. Recombinant humanized anti-human IL-6 receptor monoclonal antibody
   C. CTLA-4 fusion protein
   D. CD28 antibody

3. Which of the following best describes the mechanism of action for abatacept?
   A. IL-1 recombinant human IL-1 receptor antagonist
   B. Recombinant humanized anti-human IL-6 receptor monoclonal antibody
   C. CTLA-4 fusion protein
   D. CD28 antibody

4. Which of the following drugs is a chimeric murine-human monoclonal antibody that binds to and depletes CD20-positive B-cells?
   A. Etanercept
   B. Rituximab
   C. Golimumab
   D. Infliximab

5. Which of the following drugs is a fully human IgG monoclonal Ab?
   A. Etanercept
   B. Certolizumab
   C. Methotrexate
   D. Golimumab

6. Among the available TNF inhibitors, which one is indicated for treatment of RA only when used in combination with MTX?
   A. Adalimumab
   B. Etanercept
   C. Golimumab
   D. Certolizumab

7. According to the FDA, biosimilarity means that:
   A. The biologic medicinal product contains a version of the inactive substance of an already authorized original biologic medicinal product.
   B. The biologic medicinal product is slightly similar to the reference product notwithstanding minor differences in clinically active components.
   C. The biologic medicinal product is highly similar to the reference product notwithstanding minor differences in clinically inactive components.
   D. The biologic medicinal product is identical to the reference product notwithstanding minor differences in clinically active components.

8. Which of the following statements is true concerning biosimilars?
   A. Biosimilars are biomimics.
   B. Biosimilars are intended copies.
   C. Biosimilars are developed, assessed, or approved according to the same regulatory guidelines as biomimics.
   D. Biosimilars are not second-generation biopharmaceuticals.

9. Which of the following statements is true concerning biomimics?
   A. Biomimics may have differences in primary structure compared with the reference product.
   B. Biomimics never differ from the reference product in formulation or doses/dosing regimen.
   C. Biomimics never differ from the reference product in efficacy.
   D. Biomimics never differ from the reference product in safety and immunogenicity.

10. You are treating a 45-year-old male with rheumatoid arthritis with a TNF inhibitor. He continues to experience painful flares that impair his quality of life. Blood tests reveal low levels of the TNF inhibitor with no antidrug antibodies. Which of the following would be the best recommended approach to treatment?
   A. Stop the TNF inhibitor and begin the patient on high-dose prednisone
   B. Switch to another TNF inhibitor
   C. Increase the dose or frequency of the TNF inhibitor
   D. Switch to a biologic with a different mechanism of action
CME Registration Form

Activity Evaluation

Your evaluation of this activity is extremely important as it allows for us to plan for future educational programs. Please take a moment to answer the following questions.

Please indicate your profession/background:
- MD/DO
- NP
- RN/BSN/MSN
- PhD
- RPh/PharmD
- Other; specify _______________________________________________

How many years have you been treating patients with rheumatoid arthritis (RA)?
- 0-5 years
- 6-15 years
- 16-25 years
- 26-30 years
- 31+ years

Approximately how many patients with RA do you see per week?
- Less than 10
- 10 to 20
- 21 to 30
- More than 30
- N/A

Please rate the overall educational quality of this activity (from 1=Poor; 5=Excellent)
- 1
- 2
- 3
- 4
- 5

Yes No

1. Overall, the activity supported achievement of the identified learning objectives.
- □
- □

2. This activity better prepared me to care for my patients.
- □
- □

3. The content covered was useful and relevant to my practice.
- □
- □

4. Future activities concerning this subject matter are necessary.
- □
- □

5. The activity addressed and provided strategies for overcoming barriers to optimal patient care.
- □
- □

6. The activity reinforced my current practice patterns.
- □
- □

7. The activity was presented objectively and was free of commercial bias.
- □
- □

*If you indicated that the activity was not free of commercial bias, please provide additional comments here:

Approximately what percentage of the activity’s content was NEW to you?
- □0%
- □25%
- □50%
- □75%
- □100%

Would you recommend this activity to your peers?
- □ Yes
- □ No

Yes No N/A

Do you believe this activity:
- Increased your knowledge about the subject matter?
- Increased your competence in managing these patients?
- Will improve your performance in caring for your patients?
- Will improve patient outcomes in your practice?
- Provided you with resources to use in your practice and/or with your patients?

Yes No N/A

Planned Changes to Practice

I plan to make the following changes to my practice:
- Monitor patients on biologics for the clinical aspects of immunogenicity.
- Implement pharmacologic strategies to help reduce the development of antidrug antibodies in patients treated with biologics.
- Discuss treatment safety, efficacy, and preferences with patients.
- Clinically evaluate patients for treatment with new and emerging biosimilars.

Barriers to Practice

These are the barriers I face in my current practice that impact my ability to provide optimal care (select all that apply):
- Lack of evidence-based guidelines
- Lack of applicable guidelines for my current practice/patients
- Lack of time to spend with my patients
- Organizational/institutional limitations
- Insurance/financial restrictions
- Patient adherence/compliance issues
- Treatment-related adverse events

How confident are you in your ability to manage your patients with RA (select ONE)?
- Extremely Confident
- Very Confident
- Somewhat Confident
- Not at All Confident

Return the CME Registration Form before the test expires to:
Vindico Medical Education
PO Box 36
Thorofare, NJ 08086-0036
Or Fax to: 856-384-6680

Questions about CME?
Contact us at CME@VindicoCME.com or
Call us at 856-994-9400 ext. 504

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