Biologics in Rheumatoid Arthritis: Latest Developments and Practical Aspects

HIGHLIGHTS OF A ROUNDTABLE

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TARGET AUDIENCE: The target audience for this educational activity includes RA community-based treatment teams: rheumatologists and rheumatology nurses.

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Biologics in Rheumatoid Arthritis: Latest Developments and Practical Aspects

**ACTIVITY PURPOSE:** The purpose of this activity is to educate health care professionals on the latest developments in the treatment of patients with rheumatoid arthritis (RA), thereby improving clinical outcomes and patient quality of life.

**STATEMENT OF NEED:** Although the pathogenesis of autoimmune disorders is complex, until recently, the role of T cells has dominated research in autoimmune diseases such as RA. The well-characterized role of T cells in the pathogenesis of RA has resulted in the approval of several therapies for RA, such as tumor necrosis factor-α and interleukin-1 (IL-1) inhibitors. Despite the success of these agents, a significant minority of patients—about one third—remain unresponsive to biologic therapy.

The role of B cells in RA is not as well defined as that of T cells, but our understanding of their role has been remarkably expanded in the past few years. A B-cell–depleting antibody, rituximab, is available for the treatment of RA and other B-cell targets that have been identified.

The unprecedented number of randomized clinical trials (RCTs) in rheumatology in the past decade poses a challenge in applying the mass of clinical data to practical clinical utility in the community. It is useful from time to time for those involved in clinical research to provide a high-level review of the significance of clinical research over the past few years, and to identify critical questions that need to be answered by RCTs.

**LEARNING OBJECTIVES:** On completion of this activity, participants should be able to:

- Compare and contrast targeted therapies with regard to their adverse effects and clinical outcomes in patients with RA
- Evaluate clinical measures for defining response in patients receiving treatment for RA
- Recognize the broad implications of clinical studies over the past 10 years on clinical practice for patients with RA.

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INTRODUCTION

Arthur L. Weaver, MD, MS, FACP, MACR

The introduction of early aggressive combination therapy with traditional disease-modifying antirheumatic drugs (DMARDs) and/or biologic DMARDs has significantly altered our treatment approaches for rheumatoid arthritis (RA). The goals of therapy have evolved from merely providing symptomatic relief to preventing long-term joint damage and disability and minimizing the impact of systemic manifestations and comorbidities. Recognition of the role of B cells and identification of additional T-cell–related targets in the pathophysiology of RA have resulted in the availability of biologic agents with varying mechanisms of action that are safe and effective in patients with an inadequate response to conventional therapies or tumor necrosis factor inhibitors. Novel immune pathways, including T-cell, B-cell, and cytokine targets, are also under investigation for use in RA, and preliminary data support their efficacy.

Although recent clinical trial data provide guidance on the importance of intensive management and the efficacy and safety of switching biologic agents, additional data are needed. It is expected that data from patient registries will increasingly be available to guide clinical decisions. Furthermore, a number of clinical assessment tools and imaging techniques are available to monitor disease activity and guide treatment decisions, yet validation of these tools is needed to determine appropriate techniques and optimal intervals of use. It is important for clinicians to remain abreast of clinical trial data and emerging therapies, as it is anticipated that the treatment of RA will continue to evolve, with improved patient outcomes.

IMMUNE TARGETS IN RHEUMATOID ARTHRITIS

Mark C. Genovese, MD

A n integrated immune response of cytokine signaling pathways and cell-cell interactions underlies the pathophysiology of rheumatoid arthritis (RA). Although the initial antigen is unknown, antigen is presented in the context of a major histocompatibility complex on an antigen-presenting cell, such as a dendritic, B, T, or other innate immune cell. Ultimately, the antigen is recognized by a T cell via activation of the T-cell receptor. A redundant network of pro- and anti-inflammatory cytokines becomes involved and B cells are engaged, followed by plasma cell and autoantibody formation (Figure 1). These processes culminate in production of immune complexes and complement fixation.

Activation of the innate immune system, including macrophages and monocytes, leads to the local and systemic inflammation characteristic of RA. Interactions with chondrocytes, osteoclasts, and fibroblast-like synoviocytes lead to the production of metalloproteinases and other effector molecules which ultimately erode bone and cartilage. In contrast to the normal synovium, synovial tissue from patients with RA has thick hyperplastic layers of fibroblast-like synoviocytes, angiogenic development, cellular infiltrates, and inflammatory markers. Increased understanding of the cytokine pathways and cell lineages that damage the synovium in RA has elucidated a number of immune targets with potential for therapeutic intervention in RA. This paper will review T-cell, B-cell, cytokine, bone remodeling, and intracellular enzyme targets, and their status in the treatment of RA.
been studied in RA and autoimmune diseases. A number of other BLYs and APRIL inhibitors, and fusion proteins against the cell-surface receptors, are also in development.4

**Anti-Cytokine Targets**

It is well established that blockade of the tumor necrosis factor (TNF) α and interleukin (IL) 1 cytokines improves outcomes in RA. A number of novel cytokine targets are under evaluation in RA. For example, IL-6 plays a role in RA and other inflammatory diseases via T-cell activation and B-cell proliferation and activation. Tocilizumab, a humanized anti-IL-6 receptor mAb that binds the cell surface and soluble IL-6 receptors, is under investigation.5 Another proinflammatory cytokine target, IL-17, has effects on osteoclastogenesis, chondrocytes, and synoviocytes, suggesting the potential for targeting inflammation and joint destruction. An mAb against the p40 subunit of the IL-12/IL-23 family of heterodimeric cytokines is effective against the p40 subunit of the IL-12/IL-23 family of heterodimeric cytokines is effective in psoriasis and may be a potential target for RA. The lymphotixin beta system, a member of the TNF superfamily, has also been investigated as a means of down-regulating inflammation in RA. A heterotrimer of two lymphotixin beta subunits and lymphotixin alpha binds to a cell-surface receptor to control lymphoid microenvironments and leukocyte trafficking.

**Bone Remodeling Targets**

Increased advances in the ability to interfere with osteoclastogenesis and bone destruction elucidated novel bone remodeling targets such as RANK ligand, a receptor activator of the NF kappa B signalling system. In addition to their effects on T cells, inflammatory cytokines such as TNFα, IL-1, and IL-6 drive osteoclasts/stromal cells to activate osteoclast precursors via release of RANK ligand. Denosumab, an mAb against RANK ligand, is being studied for its ability to decrease the risk of osteoporosis and bone erosion associated with RA.

**Intracellular Enzyme Inhibition**

Intracellular targets also have significant potential as immune therapeutic approaches in RA. For example, the p38 mitogen-activated protein (MAP) kinase pathway is inducibly expressed after tissue injury (ischemia or oxidation), resulting in release of a number of inflammatory mediators, tissue inflammation, and disease progression. Janus kinase (JAK), a tyrosine kinase responsible for intracellular signalling in response to inflammatory stimuli, is involved in many cytokine signalling pathways.7 A JAK3 inhibitor with immunosuppressive properties is under investigation for a number of inflammatory diseases, including RA. Data to date also support blockade of another tyrosine kinase pathway, spleen tyrosine kinase (Syk), to inhibit degranulation, cytokine production, and other intracellular enzymes.

**Summary**

It is unknown which of the novel targets will result in pharmacotherapies that are efficacious and safe. Furthermore, it is unknown whether combination therapies with existing and novel agents will have synergistic or additive effects without toxicity. Accumulating data indicate that genetic and proteomic profiling may eventually be used to predict response and potential safety issues, thereby guiding treatment decisions. Regardless of the target, novel therapies must have improved efficacy, safety, tolerability, convenience, cost, and perhaps long-term safety compared with existing agents in order to gain acceptance in the treatment of RA.

**Discussion Question**

Is it feasible to target more than one immune pathway in clinical practice?

Current clinical practice successfully utilizes combination therapy with conventional disease-modifying antirheumatic drugs (DMARDs), such as sulfasalazine or methotrexate, or a combination of a conventional DMARD and a biologic; however, therapy with multiple biologics has not been successful because of toxicities. Increased infection rates have been observed with combination therapy of TNF and IL-1 inhibitors or a TNF inhibitor and abatacept. Dual or triple blockade of immune targets may be necessary to improve patient outcomes and increase remission rates compared with current monotherapies. Unfortunately, it is currently not possible to predict which new therapies will have additive or synergistic properties, which will be efficacious yet safe, or which patients will elicit a response without toxicity. It is hypothesized that advances in the use of proteomic and genomic signatures and other biomarkers will guide treatment decisions with current and novel immune targets.

**References**

he ability to improve the course of rheumatoid arthritis (RA) by early use of disease-modifying anti-rheumatic drugs (DMARDs) revolutionized RA treatment. Conventional and novel therapies are available to significantly lessen the impact of RA.

**Intensive Therapy**

The TICORA study sought to determine the effect of intensive treatment, meaning sustained and tight control, compared to the routine care of RA. An algorithm defined response and predetermined steps for aggressive therapy. This approach significantly improved the numbers of ACR20, 50, or 70 responders. Objective measures of response and predefined steps in disease management facilitated clinical judgment in treating RA.

**Newer Biologics**

Patients with poor response to methotrexate or tumor necrosis factor (TNF) inhibitors show response to abatacept or rituximab. The overall rates of serious infectious events (SIEs) and malignancies appear to be similar among the biologic DMARDs. All of the biologic DMARDs are associated with a risk of infection because of their immunosuppressive activity.

**ABATACEPT**

The AIM (methotrexate failures) and the ATTAIN trial (TNF inhibitor failures) each showed that patients will stay on an abatacept regimen maintaining their initial level of ACR response after 3 years of follow-up. In comparative safety analyses, patients in an abatacept clinical trial had a similar incident rate of SIEs or malignancies compared to patients in various RA registries. Proximity of prior TNF inhibitor use did not affect the rate of SIEs, adverse events, infection, or malignancies in patients in abatacept clinical trials.

**RITUXIMAB**

Patients who failed TNF inhibitors sustained their initial level of response to rituximab over a 6-month treatment course; one fourth were ACR70 responders at week 24. An epidemiologic study of TNF inhibitor failures from a patient registry showed better response to rituximab than to an alternative TNF inhibitor by both DAS28 and components of the DAS28—tender joints, swollen joints, and erythrocyte sedimentation rate. In these patients, B-cell depletion was an effective means of reducing RA disease activity following poor response to a TNF inhibitor.

The rate at which SIEs occurred per 100 patient-years remained fairly constant in patients receiving up to four courses of rituximab. In another study, the rate of SIEs per 100 patient-years increased as immunoglobulin levels decreased, specifically, IgM and IgG. More study is needed to explore whether decreased immunoglobulin is an indicator for infection risk.

**Onset of Action**

TNF inhibitors appear to have the shortest onset of action; some patients respond during the first month of therapy. Lack of response after 3 months indicates potential nonresponse to that TNF inhibitor and a switch in therapy should be considered. Adalimumab and rituximab reportedly have a longer time to onset of action; 2–3 months may pass before a response is seen. Alternative therapy may be advised if there is no improvement after 4 months with abatacept or 3–4 months with rituximab. Over time the biologics appear to have a similar proportion of ACR20 responders. Even so, response varies—patients should be assessed using objective measures of response so that there is a clear understanding of response over time.

**Emerging Therapies**

Tocilizumab is an IL-6 receptor antibody that disrupts the inflammatory response mediated by IL-6. A recent phase III study showed that tocilizumab and methotrexate resulted in ACR20, 50, and 70 responses at 24 weeks. The most common serious adverse event was infection; elevated serum lipids were seen in some patients. Atacicept is a fusion protein that neutralizes two regulators of B-cell function. A phase Ib study showed that atacicept reduced RA disease activity and was well tolerated.

**Patient Registries**

Patient registries provide insight into RA therapies outside of clinical trials by capturing data on “real world” patients. Clinical trial patients usually have more severe RA, and the profile of European patients appears to differ from that of patients in the US. Of the four main US registries (Table 1), three use patient-derived data and two retrieve data from rheumatologists. These registries will show how RA therapies are used in the clinic, and they may connect efficacy and toxicity data to biomarkers of response and genomic profiles.

**Summary**

Both comparative trials and patient registry data provide insight about the relative outcomes of various RA therapies. This may inform discussions with the patient and also set up reasonable expectations regarding therapy. Even with the success of biologic therapies, new therapies are still needed for the many patients who fail to respond to current therapy.

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**Table 1. US Patient Registries**

<table>
<thead>
<tr>
<th>Registry</th>
<th>Sponsor</th>
<th>Patients (No.)</th>
<th>Physician-Derived Data</th>
<th>Patient-Derived Data</th>
<th>Frequency of Collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administrative23</td>
<td>NIH, Arthritis Foundation</td>
<td>3500–15,000</td>
<td>No</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>National Databank20</td>
<td>Pharma</td>
<td>19,562</td>
<td>No</td>
<td>HAQ demographics</td>
<td>Every 6 mos</td>
</tr>
<tr>
<td>CORRONA20</td>
<td>Pharma</td>
<td>17,000</td>
<td>ACR, DAS28, dxa, radiographs, extra-articular manifestations, comorbidities, swollen and tender joint count, CDAI, ESR, CRP, CCP, RF, RNA, DNA for genomic “fingerprint”, demographics, ROS</td>
<td>mHAQ demographics</td>
<td>Every 3 mos</td>
</tr>
<tr>
<td>BRASS21,22</td>
<td>Millennium Pharmaceuticals</td>
<td>1000</td>
<td>ACR, DAS, dxa, radiographs, extra-articular manifestations, comorbidities, swollen and tender joint count, CDAI, ESR, CCP, CRP, CCP, RF, RNA, DNA for genomic “fingerprint”</td>
<td>MDHAQ demographics, RADAI, current meds</td>
<td>Every 6 mos</td>
</tr>
</tbody>
</table>

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ACR=American College of Rheumatology; BBRAS=The Brigham and Women’s Hospital Rheumatoid Arthritis Sequential Study; CCP=anti-cyclic citrullinated peptide; CDAI=Clinical Disease Activity Index; CORRONA=Consortium of Rheumatology Researchers of North America; CRP=CRP-Creative protein; DAS=Disease Activity Score; ESR=erythrocyte sedimentation rate; HAQ=Health Assessment Questionnaire; MDHAQ=Multidimensional Health Assessment Questionnaire; mHAQ=modified Health Assessment Questionnaire; NIH=National Institutes of Health; RADAI=Rheumatoid Arthritis Disease Activity Index; RF=rheumatoid factor; ROS-review of systems.
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Discussion Question

*Will the US registries and registries from Canada and Europe track efficacy and safety of RA drugs?* These registries could provide this information, but they are challenged by the lack of both baseline and consistent follow-up data provided by rheumatology practices. Barriers include time constraints for busy rheumatologists who may not always use metrics for evaluating RA disease activity during patient visits. While the European system requires objective documentation of patient response in order for patients to obtain RA medications, no similar system exists in the United States. Rheumatologists are encouraged to participate in a patient registry so that US-specific cost-effectiveness data will be available to guide decision making regarding the expanding choices in RA therapy.
Early, aggressive treatment of rheumatoid arthritis (RA) with combination disease-modifying antirheumatic drugs (DMARDs) and biologic therapy dramatically improves patient outcomes, with up to 40% of patients achieving remission in clinical trials. However, observations in standard clinical practice differ from clinical trial results. Registry data indicate that clinical response and remission rates with traditional DMARDs and biologic therapy in clinical practice are attenuated compared with clinical trials. Furthermore, registry data reveal residual disease activity despite treatment and also that approximately 30% of patients discontinue DMARDs or biologic therapy after 1 year, presumably because of lack of response or toxicity.

Primary inadequate response, defined as a poor or lack of response to an agent, is relatively rare. Secondary inadequate response in which patients demonstrate an early response, but subsequently experience a lack of response, is more common. It is important to note that response as defined by clinical measures may not correlate with other methods of assessment. A number of clinical measurement tools, imaging techniques, and biomarkers are available for use in the evaluation of disease activity and treatment response in patients with RA (Table 2).

Clinical Measurement Tools

The American College of Rheumatology (ACR) criteria for assessing treatment response were developed for clinical trials and are not appropriate for standard clinical care, although they are used by some practitioners. A number of clinical assessment tools have been designed to classify disease activity and define remission, visit to visit, in patients with RA. The Disease Activity Score (DAS), a computerized measure using patient global scores, tender and swollen joint counts, and either erythrocyte sedimentation rate or C-reactive protein values, is widely used in clinical practice, particularly in the European Union, but may not be feasible in some situations as it requires a laboratory value. The Simplified Disease Activity Index requires a laboratory value, but is an additive measure, making it easier to use in clinical practice. The Clinical Disease Activity Index, Global Arthritis Score, Easy Rheumatoid Arthritis Measure, and Routine Assessment of Patient Index Data (RAPID) assessments encompass a variety of patient and physician observations, and do not require a laboratory value.

These clinical assessment tools have been validated against the DAS in a significant number of patients. For example, RAPID3, an index of patient-reported outcomes, distinguished placebo from abatacept at levels comparable to DAS28 in two randomized clinical trials. Thresholds have also been established for classifying patients as being in remission or having high, moderate, or low disease activity.

Imaging Techniques

Radiographic joint damage is positively correlated with disease activity and disability. As such, radiographic imaging continues to be the standard for assessment of joint damage in RA. Ultrasound and power Doppler are rarely used in the United States despite their ability to detect early erosions, increased blood flow, and synovitis across multiple joints. Results are dependent on the experience and skill of the operator, and these technologies are untested in controlled trials. Traditional and three-dimensional magnetic resonance imaging (MRI) can be used to evaluate bone marrow edema, bone erosions, and synovitis. Although a scoring system and atlas have been developed, additional validation is needed to establish MRI as a measure of outcomes in RA. Cost is a concern with MRI, and there are a number of different types of machines available, complicating comparisons. Nonetheless, patients with continued low-grade synovitis despite normal radiographs may benefit from the use of MRI.

Accumulating data indicate that radiologic assessment may not correlate with clinical measures of response. Signs of joint damage, including the appearance of new erosions, have been observed in patients with prolonged DAS-defined clinical remission. Similarly, patients with DMARD-induced clinical remission exhibited synovitis and bone marrow edema with MRI or ultrasound evaluation. These data underscore the importance of radiographic assessments in RA patients.

Biomarkers

A number of biomarkers for inflammation, joint and cartilage damage, and bone resorption and formation have been examined as predictors of disease activity and joint damage. For example, elevated serum levels of MMP-3 and IL-6 appear to be significantly associated with disease activity. Although anti-CCP antibodies do not have clinical utility as a marker of disease activity, elevated levels are a strong predictor of incident RA and radiographic progression. Interestingly, levels of IL-6 and TNF receptor may be elevated up to 12 years prior to a diagnosis of RA. Joint and cartilage breakdown products, such as hyaluronic acid and cartilage oligomeric protein, and bone biochemical markers such as RANK ligand–OPG ratio and bone morphologic proteins, have been investigated as markers, but are not currently available for standard clinical use.

It is expected that advances in pharmacogenomics will significantly alter treatment approaches to RA. Genetic diagnostics may be used for risk profile determination, disease prediction, earlier diagnosis, and treatment selection, based on response and toxicity predictions. For instance, data on azathioprine toxicity and emerging data on methotrexate nonresponse and toxicity can be used to guide treatment.

Summary

Therapeutic decisions must be guided by clinical measures and imaging data to improve short- and long-term patient outcomes in RA. Although patients are increasingly educated about therapeutic interventions, education on the significance of radiographic damage and long-term outcomes is necessary. The most appropriate assessment tool and interval for screening in standard clinical practice must be identified in order to ensure that clinical and radiographic measures are met in patients with RA.

Discussion Question

What are the strategies for implementing clinical and radiographic assessment in community-based rheumatology practices?

Clinical trial data underscore the importance of assessing radiographic progression and clinical measures in improving short- and long-term outcomes in patients with RA.
We now understand that disease-modifying therapy is a central part of the rheumatoid arthritis (RA) treatment plan and that active disease signifies a patient with inadequately treated disease. Goals of therapy include short-term symptomatic relief, long-term prevention of joint damage and disability, and minimizing the impact of systemic manifestations of RA. Therapeutic goals may also change according to disease duration and progressive disability.

**Selecting Treatment in Early RA**

The first challenges are to accurately diagnose RA early, define disease activity upfront, and, if possible, also define the prognosis. Addressing comorbid conditions early is also important, as these may impact management and treatment choices for a patient.

Rheumatologists should consider both treatment data and patient preference when choosing first-line therapy. Patients are inevitably concerned about treatment adverse effects, questioning the type and severity that are associated with RA therapy. While uncompliacted oral regimens are easier to use, patients are also willing to consider parenteral therapies and more complex combination regimens. Patients have become more knowledgeable about RA therapies, but a trusting relationship with the physician remains a key factor in acceptance of a treatment plan.

Methotrexate is the recognized standard of care for initial therapy, supported by long experience and the fact that methotrexate is clinically effective in a significant proportion of patients. Methotrexate and tumor necrosis factor (TNF) antagonists result in similar clinical outcomes and the benefits of reducing chronic inflammation. Patients with advanced RA can have a good response to biologics. In long-standing, advanced disease inadequately controlled with methotrexate, addition of a TNF antagonist for 6 months resulted in considerable response.

**Switching Therapy**

Some patients who failed methotrexate and a TNF antagonist have responded to an alternate TNF antagonist. About one third of patients switching from infliximab to etanercept were ACR20 responders after 12 weeks, along with some ACR50 and 70 responses.

Separate studies demonstrated that adding methotrexate, 4,7,8 with more ACR70 responses were still noted after 48 weeks.

**Comorbid Conditions in RA**

Comorbid conditions may affect both the clinical outcome and treatment safety in RA. RA patients are at greater risk for atherosclerosis and cardiovascular disease (CVD). Extra-articular RA is also associated with cardiovascular and mortality. Recent investigations show that long-term use of both biologic and biologic DMARDs can reduce the risk of CVD. Registry data also suggest that methotrexate and TNF antagonists are associated with a reduction in mortality, primarily related to CVD (Figure 2).

Patients with underlying comorbidities such as lung disease or neurologic conditions could be at greater risk for infection. There is infection risk with all of the biologics and methotrexate, and RA patients should be screened for current infection or a history that might predispose to infection. In the absence of comparative studies, registry data will likely be the best source for understanding differences between the biologics. Genotyping studies may also help to define groups of patients at increased risk for infection with biologic and nonbiologic therapies.

**Summary**

Without guidance from comparative studies, strategies for selecting RA therapy include identifying therapeutic targets and patient-specific issues. Available outcomes data and clinical experience may guide the clinician when choosing therapy, but prospective data are sorely needed. While the management of RA has benefited from the many treatment options currently available, further study is needed to clarify treatment decisions.

**Discussion Question**

What issues have not been adequately addressed by clinical trials of RA therapies? There is a need for direct comparative data between the RA drugs and a need for bio-

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**Figure 2. Mortality in Patients With RA: Impact of Treatment**

<table>
<thead>
<tr>
<th>Mortality Hazard Ratio*</th>
<th>Prednisone</th>
<th>Methotrexate</th>
<th>TNF Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=19,580</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DEFINING RHEUMATOID ARTHRITIS TREATMENT SUCCESS OR FAILURE

Arthur L. Weaver, MD, MS, FACP, MACR

However, there is a lack of consensus on the most appropriate measure and frequency of use. For example, sequential radiographs should be used to monitor new and existing erosions, but there are few quantitative assessments for use in standard clinical practice and the frequency with which radiography should be performed is unclear. Most experts agree that x-rays of the hands and feet should be obtained every 6 to 12 months in patients with active disease. If there is uncertainty, ultrasound and/or MRI, which have increased specificity and sensitivity, may be useful. While DAS28 is used extensively in Europe and most clinical trials, this assessment requires acute-phase reactant data, which may not be practical in some clinical settings. This has led to the development of several validated clinical measures which do not require laboratory parameters.

Because rheumatologists are data driven, clinical trial results are often used to guide clinical and radiographic assessments in standard clinical practice. There are also a number of cytokines and extracellular matrix factors involved. Use of electronic medical records continues to expand, and patients are increasingly involved in health care decisions and monitoring disease activity. It is also important to note that RA is an individualized, heterogeneous disease such that there will be exceptions in the use of assessments. It is possible for a patient to be in DAS remission but continue to have a swollen and tender wrist. If the dominant wrist is involved and work function is severely compromised, this patient may require further treatment despite being in remission.

References
CASE PRESENTATION: PATIENT WITH INCOMPLETE RESPONSE TO TNF INHIBITOR THERAPY

Introduction
This case reviews the treatment course of a 49-year-old woman who was diagnosed with rheumatoid arthritis (RA) 2 years previously. The perspectives of two rheumatologists are presented to compare and contrast assessment approaches and treatment decisions. Viewpoints from roundtable participants are included to show the relative merits and drawbacks of the clinical decisions in this scenario.

Visit 1: Baseline Examination

<table>
<thead>
<tr>
<th>Rheumatologist A</th>
<th>Rheumatologist B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand and foot x-rays reveal no evidence of damage</td>
<td>Hand and foot x-rays reveal no evidence of damage</td>
</tr>
<tr>
<td>Anti-CCP positive</td>
<td>Anti-CCP positive</td>
</tr>
<tr>
<td>RF positive</td>
<td>RF positive</td>
</tr>
<tr>
<td>CRP: 20 mg/L</td>
<td>CRP: 20 mg/L</td>
</tr>
<tr>
<td>Multiple swollen and tender joints</td>
<td>Swollen joints: 18</td>
</tr>
<tr>
<td></td>
<td>Tender joints: 14</td>
</tr>
<tr>
<td></td>
<td>Physician global: 70</td>
</tr>
<tr>
<td></td>
<td>Patient global: 75</td>
</tr>
<tr>
<td></td>
<td>DAS28: 6.39 (severe disease activity)</td>
</tr>
<tr>
<td></td>
<td>CDAI: 46.5</td>
</tr>
<tr>
<td></td>
<td>SDAI: 48.5</td>
</tr>
<tr>
<td>Start oral methotrexate 15 mg/week and prednisone 5 mg/day</td>
<td>Start oral methotrexate 15 mg/week and prednisone 5 mg/day</td>
</tr>
</tbody>
</table>

Visit 2

<table>
<thead>
<tr>
<th>Rheumatologist A</th>
<th>Rheumatologist B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continued morning stiffness, tender and swollen joints despite 3 months of therapy with oral methotrexate 15 mg/week and prednisone 5 mg/day</td>
<td>Continued morning stiffness, tender and swollen joints despite 3 months of therapy with oral methotrexate 15 mg/week and prednisone 5 mg/day</td>
</tr>
<tr>
<td>Signs of improvement</td>
<td></td>
</tr>
<tr>
<td>CRP: 13 mg/L</td>
<td>CRP: 13 mg/L</td>
</tr>
<tr>
<td></td>
<td>Swollen joints: 8</td>
</tr>
<tr>
<td></td>
<td>Tender joints: 7</td>
</tr>
<tr>
<td></td>
<td>Physician global: 40</td>
</tr>
<tr>
<td></td>
<td>Patient global: 40</td>
</tr>
<tr>
<td></td>
<td>DAS28: 4.74 (moderate disease activity)</td>
</tr>
<tr>
<td></td>
<td>CDAI: 22</td>
</tr>
<tr>
<td></td>
<td>SDAI: 23.3</td>
</tr>
<tr>
<td></td>
<td>MRI: signs of bone marrow edema</td>
</tr>
<tr>
<td>Increase oral methotrexate to 20 mg/week</td>
<td>Increase oral methotrexate to 20 mg/week</td>
</tr>
<tr>
<td>Because increased doses of oral methotrexate are associated with variable bioavailability, parenteral methotrexate should be considered.¹</td>
<td></td>
</tr>
</tbody>
</table>

Visit 3

<table>
<thead>
<tr>
<th>Rheumatologist A</th>
<th>Rheumatologist B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continued morning stiffness, tender and swollen joints despite 6 months of therapy with methotrexate and prednisone</td>
<td>Continued morning stiffness, tender and swollen joints despite 6 months of therapy with methotrexate and prednisone</td>
</tr>
<tr>
<td>Minimal improvement</td>
<td></td>
</tr>
<tr>
<td>CRP: 11 mg/L</td>
<td>CRP: 11 mg/L</td>
</tr>
<tr>
<td></td>
<td>Swollen joints: 6</td>
</tr>
<tr>
<td></td>
<td>Tender joints: 4</td>
</tr>
<tr>
<td></td>
<td>Physician global: 30</td>
</tr>
<tr>
<td></td>
<td>Patient global: 30</td>
</tr>
<tr>
<td></td>
<td>DAS28: 4.08 (moderate disease activity)</td>
</tr>
<tr>
<td></td>
<td>CDAI: 16</td>
</tr>
<tr>
<td></td>
<td>SDAI: 17.1</td>
</tr>
<tr>
<td>Continue current regimen</td>
<td>Add etanercept 50 mg/week</td>
</tr>
</tbody>
</table>

Visit 4

<table>
<thead>
<tr>
<th>Rheumatologist A</th>
<th>Rheumatologist B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continued morning stiffness, tender and swollen joints despite 9 months of therapy with methotrexate and prednisone</td>
<td>Continued morning stiffness, tender and swollen joints despite 9 months of therapy with methotrexate and prednisone 5 mg/day, and 3 months of etanercept 50 mg/week</td>
</tr>
<tr>
<td>Minimal improvement</td>
<td></td>
</tr>
<tr>
<td>CRP: 11 mg/L</td>
<td>CRP: 11 mg/L</td>
</tr>
<tr>
<td></td>
<td>Swollen joints: 4</td>
</tr>
<tr>
<td></td>
<td>Tender joints: 4</td>
</tr>
<tr>
<td></td>
<td>Physician global: 20</td>
</tr>
<tr>
<td></td>
<td>Patient global: 20</td>
</tr>
<tr>
<td></td>
<td>DAS28: 3.81 (moderate disease activity)</td>
</tr>
<tr>
<td></td>
<td>CDAI: 12</td>
</tr>
<tr>
<td></td>
<td>SDAI: 13.1</td>
</tr>
<tr>
<td>Add etanercept 50 mg/week</td>
<td>Continue current regimen</td>
</tr>
<tr>
<td>Although the patient has experienced some improvement, her DAS28 indicates that she continues to have moderate disease activity. Her current regimen is continued because data suggest that patients with an inadequate response to etanercept at 3 months may benefit from continuing therapy for up to 6 months.²</td>
<td></td>
</tr>
</tbody>
</table>

¹ Increased doses of methotrexate are associated with variable bioavailability, and parenteral administration may be considered.
² Additional therapies may be beneficial for patients with inadequate response to current treatment.
### Current Examination

<table>
<thead>
<tr>
<th>Rheumatologist A</th>
<th>Rheumatologist B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continued morning stiffness, tender and swollen joints despite 12 months of therapy with methotrexate and prednisone 5 mg/day, and 3 months of etanercept 50 mg/week</td>
<td>Continued morning stiffness, tender and swollen joints despite 12 months of therapy with methotrexate and prednisone, and 6 months of etanercept 50 mg/week</td>
</tr>
<tr>
<td>Hand x-rays reveal joint space narrowing in MCP and PIP joints with isolated cystic changes</td>
<td>Hand x-rays reveal joint space narrowing in MCP and PIP joints with isolated cystic changes</td>
</tr>
<tr>
<td>Some improvement</td>
<td>Patient improved; not in remission</td>
</tr>
<tr>
<td>CRP: 11 mg/L</td>
<td>CRP: 8 mg/L</td>
</tr>
<tr>
<td>Swollen joints: 3</td>
<td>Tender joints: 2</td>
</tr>
<tr>
<td>Physician global: 15</td>
<td>Patient global: 15</td>
</tr>
<tr>
<td>DAS28: 3.24</td>
<td>CDAI: 8</td>
</tr>
<tr>
<td>SDAI: 9</td>
<td></td>
</tr>
</tbody>
</table>

#### Summary:
- Rheumatologist A based treatment on clinical judgment rather than clinical measures, resulting in prolonged traditional DMARD therapy, delayed initiation of biologic therapy, and uncertainty about the degree of success of etanercept. The goal of therapy is to treat to remission; this patient was clearly not in remission. Her marginal response should not be considered therapeutic success. Rheumatologist B relied on quantitative measures, and while improvement was observed, the magnitude of change was not acceptable. Although rheumatologist B also faced a number of clinical decisions, the choices were more clearly defined compared with the treatment course of rheumatologist A.

#### Viewpoint: A change in therapy is warranted
- Clinical experience suggests that if a patient does not respond to biologic therapy within 3–6 weeks, response will not improve. Without clinical measurement, this rheumatologist is unable to determine if there has been improvement. An incomplete response to one TNF inhibitor does not indicate a similar response to a second agent in this class. The patient may benefit from a TNF inhibitor with a different mechanism of action. Her therapy could also be switched to an agent with a different mechanism of action such as abatacept, rituximab, or anakinra.

#### Viewpoint: A change in therapy is warranted
- In this scenario, the clinician relies on global assessment to guide treatment decisions. Despite 12 months of therapy with methotrexate and prednisone 5 mg/day and 3 months of etanercept 50 mg/week, the patient continues to experience morning stiffness and tender and swollen joints.

#### Viewpoint: Continue current therapy
- The DAS28 continues to improve, suggesting partial response to etanercept. An adequate trial of etanercept has occurred (ie, 6 months), but the patient is not in remission. However, if the patient feels better, she may be reluctant to change therapy.

#### Viewpoint: Switch to a second TNF inhibitor
- An incomplete response to one TNF inhibitor does not predict a similar response to a second agent in this class. The patient may benefit from a TNF inhibitor with a different mechanism of action.

#### Viewpoint: Change to another biologic class
- The patient’s magnitude of response may not increase with either further exposure to etanercept or a switch to an alternative TNF antagonist. Therefore, her therapy could also be switched to an agent with a different mechanism of action, such as abatacept, rituximab, or anakinra.

### Conclusions
This case is a classic scenario of a good but incomplete response to therapy in a patient with RA. To justify continuing the current therapeutic regimen, the clinician needs to determine if the patient has exhibited adequate response. If the patient has failed to achieve sufficient response, the clinician needs to decide if a change in treatment is warranted. Rheumatologist A based treatment on clinical judgment rather than clinical measures, resulting in prolonged traditional DMARD therapy, delayed initiation of biologic therapy, and uncertainty about the degree of success of etanercept. The goal of therapy is to treat to remission; this patient was clearly not in remission. Her marginal response should not be considered therapeutic success. Rheumatologist B relied on quantitative measures, and while improvement was observed, the magnitude of change was not acceptable. Although rheumatologist B also faced a number of clinical decisions, the choices were more clearly defined compared with the treatment course of rheumatologist A.

### References
2. Kavanaugh A, Klarskog L, van der Heijde D, et al. Patients with rheumatoid arthritis who are non-responders to etanercept plus methotrexate therapy at week 12 achieve a response at week 24 and sustain the gain in response. Presented at: American College of Rheumatology Annual Scientific Meeting. November 6-11, 2007; Boston, MA.
Option 1: The DIME online credit system
A. Please visit http://biologics.cme360.net.
B. Select “Register” to the right of the title, “Biologics in RA: Latest Developments and Practical Aspects.”
C. Complete the enrollment form, posttest, and evaluation form.
D. If you receive a passing score of at least 70% on the posttest, your electronic statement of credit will be made available to you immediately.
If you have difficulty accessing the link, please contact DIME at 312-553-8000 or dmeservices@dmeded.org.

Option 2: Complete this enrollment form, posttest, and evaluation form and mail them to:
DIME 17461
222 Merchandise Mart Plaza
Suite 4-160
Chicago, IL 60654
You will receive a statement of credit within 4-6 weeks.

Evaluation Questions

Overall Enduring Material Evaluation
5=Excellent 4=Good 3=Satisfactory 2=Fair 1=Poor
Using the above scale, please evaluate this activity by marking the appropriate response:
1. Objectivity and balance
   5 4 3 2 1
2. Did you perceive any bias or commercialism in this activity (towards any product or drug)?
   Yes No
If Yes, please explain:
3. Scientific rigor
   5 4 3 2 1
4. Amount of information presented
   5 4 3 2 1
5. Level of instruction
   5 4 3 2 1

Learning Objectives
5=Strongly agree 4=Agree 3=Neutral 2=Disagree 1=Strongly disagree
Using the above scale, indicate whether after completing this activity you are better able to:
6. Compare and contrast targeted therapies with regard to their AEs and clinical outcomes in patients with RA
   5 4 3 2 1
7. Evaluate clinical measures for defining response in patients receiving treatment for RA
   5 4 3 2 1
8. Recognize the broad implications of clinical studies over the past 10 years on clinical practice for patients with RA
   5 4 3 2 1

Reason for Participation
5=Extremely 4=Very 3=Somewhat 2=Not very 1=Not at all
Using the above scale, indicate how important the following reasons are for your participation in educational activities:
9. Topics
   5 4 3 2 1
10. Faculty/Editor’s reputation
    5 4 3 2 1
11. CME/CE credit
    5 4 3 2 1
12. As a result of participating in this activity, did you learn anything that would cause you to make a change in your clinical practice? (choose only one)
   1=Yes, I am going to try to incorporate some of the information presented into my clinical practice.
   2=No, I am not going to incorporate the information into my clinical practice.
   3=I do not know
13. If Yes, how soon do you intend to incorporate changes in your practice as a result of this CME activity?
    1=Immediately 2=In 1 month 3=In 3 months 4=In 6 months 5=I do not know
14. If No, why not?
   1=I learned some new information, but the information presented is not applicable to my clinical practice.
   2=The information presented confirmed my current clinical practice.
   3=I did not find the information useful and I will not change my current clinical practice.
   4=I do not know
   Indicate your level of confidence in the following after completing this activity:
   0=Not at all confident 7=Completely confident
15. Selecting a selective costimulatory modulator as treatment for RA
   5 4 3 2 1
16. Selecting a B-cell depletion therapy as treatment for RA
   5 4 3 2 1
17. Selecting a TNFα antagonist as treatment for RA
   5 4 3 2 1
18. Selecting an alternative biologic agent for a patient with RA who responded poorly to another biologic agent
    5 4 3 2 1
19. Indicate whether you would recommend this activity to others: 1=Yes 2=No
    Please rate your interest in the following RA educational topics from 5 (highest interest) to 1 (lowest interest):
    ___ Pathophysiology of RA
    ___ Pharmacoeconomic data
    ___ Clinical trial efficacy data
    ___ Inadequate response to therapy
    ___ Monitoring treatment response
    ___ Treatment for rheumatoid arthritis
    ___ Quality of life issues
    ___ Comorbid conditions
20. Additional Comments:

Posttest

1. All of the following statements are true except:
   A. A redundant network of pro- and anti-inflammatory cytokines contributes to the pathogenesis of RA
   B. Production of metalloproteinases and other effector molecules ultimately erodes bone and cartilage
   C. The antigen that initiates the inflammatory cascade is well characterized
   D. Activation of B cells results in formation of plasma cells and autoantibodies
   1=Immediately 2=In 1 month 3=In 3 months 4=In 6 months 5=I do not know
2. Which of the following best describes the mechanism of action of the investigational agent tocilizumab?
   A. Inhibition of IL-6 via binding to cell-surface IL-6 receptors
   B. Inhibition of IL-17 via binding to cell-surface IL-17 receptors
   C. Inhibition of IL-6 via binding to cell-surface and soluble IL-6 receptors
   D. None of the above
   1=True 2=False
3. Patient registries provide insight into the treatment of RA by collecting patient data from clinical trials and patients seen in clinical practice.
   A. True  B. False
4. Which of the following is (are) true regarding the TICORA study?
   A. TICORA compared routine care of RA to sustained and tight control of RA
   B. An algorithm designed to establish tight control outlines steps for the RA regimen
   C. Treatment designed to achieve tight control of RA yields a higher proportion of patients with a more robust ACR response
   D. All of the above
   1=True 2=False
5. Which of the following is (are) a therapeutic option(s) for patients who respond poorly to TNF inhibitors?
   A. Rituximab  B. Certolizumab
   C. Tocilizumab  E. A and C
   C. Abatacept
   1=Yes, I am going to try to incorporate some of the information presented into my clinical practice.
   2=No, I am not going to incorporate the information into my clinical practice.
   3=I do not know
6. Elevated levels of which of the following biomarkers have been observed up to 12 years prior to a diagnosis of RA?
   A. TNF receptor  B. Hyaluronic acid
   C. IL-6  D. A and C
   1=Immediate 2=In 1 month 3=In 3 months 4=In 6 months 5=I do not know
7. Which clinical measurement tool does not require a laboratory test?
   A. Simplified Disease Activity Index (SDAI)
   B. Disease Activity Score (DAS)
   C. Routine Assessment of Patient Index Data (RAPID)
   D. All of the above
   1=Yes, I am going to try to incorporate some of the information presented into my clinical practice.
   2=No, I am not going to incorporate the information into my clinical practice.
   3=I do not know
8. Strategies for selecting therapy for a patient with early RA include:
   A. Encouraging communication with the patient to ascertain patient preferences and build a trusting relationship
   B. Defining disease activity and prognosis
   C. Evaluating comorbidities that might affect the course of RA
   D. All of the above
   1=Immediate 2=In 1 month 3=In 3 months 4=In 6 months 5=I do not know
9. Patients with RA are at greater risk of cardiovascular disease, which in turn may impact treatment efficacy and safety:
   A. True  B. False
   1=Immediate 2=In 1 month 3=In 3 months 4=In 6 months 5=I do not know
10. All of the following statements are true except:
    A. Patients who respond poorly to one TNF inhibitor may respond to an alternative TNF inhibitor
    B. After switching to another biologic therapy, the best reported response a patient can achieve is ACR20
    C. Further studies are needed to establish the optimal sequencing of biologic therapies
    D. TNF inhibitors are shown to reduce joint damage regardless of baseline RA activity or preexisting joint damage
   1=Immediate 2=In 1 month 3=In 3 months 4=In 6 months 5=I do not know