Updates in Improving Care of Patients With Rheumatoid Arthritis

Insights from the 2016 ACR/ARHP Annual Meeting

BEGIN
Program Title

Updates in Improving Care of Patients With Rheumatoid Arthritis
Insights from the 2016 ACR/ARHP Annual Meeting

Course Description

Rheumatoid arthritis (RA) remains a clinically challenging autoimmune disorder for rheumatologists to manage. Effective patient care is critical: an estimated sixty percent of people with inadequately treated RA are unable to work 10 years following onset of the disease. The American College of Rheumatology (ACR) has endorsed the use of several quality improvement measures in RA management, including recommended screening, disease activity assessment, and treatment guidelines. However, clinical care of patients with respect to guideline recommendations continues to be suboptimal.

A major reason for gaps in care of patients with RA is the ever-increasing amount of data being reported. The management paradigm for RA is evolving; increases in knowledge of RA pathophysiology, enhanced assessment tools, and the emergence of biologic and nonbiologic therapies targeted to key pathways in RA result in an overwhelming amount of new information. Rheumatologists must assess key information and decide which to apply in clinical practice.

This activity is intended to provide rheumatologists with critical updates in care of patients with RA reported at the 2016 ACR Annual Meeting. Areas of focus include tracking and measuring disease progression, as well as predicting positive outcomes of RA, and updates on integration of biosimilars into clinical practice. Early use of traditional or biologic disease-modifying antirheumatic drugs (DMARDs) has now made disease remission a realistic goal for many patients. The possibility of tapering RA therapy in patients with low disease activity will be discussed. Finally, the activity will address multimorbidity, taking the concept of comorbidity in patients with RA and refining it to focus care upon the patient, rather than the disease.

Target Audience

This activity has been designed to meet the educational needs of health care professionals involved in the diagnosis, treatment, or management of patients with RA.

Educational Objectives

Upon completion of this activity, participants will be better able to:

• Describe methodologies and factors that can be used to predict disease progression, comorbid disease, response to treatment, and clinical outcomes in patients with RA
• Discuss considerations in the expanding clinical use of biosimilars as biologic DMARDs in RA treatment
• Explain how and when to stratify patients with low RA disease activity as potential candidates for tapering therapy
• Define multimorbidity and how it differs from comorbidity in approaches to patient care

Faculty

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<table>
<thead>
<tr>
<th>Faculty</th>
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<td>Dr. Shmerling has no financial interest to disclose.</td>
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2. Complete the pre-activity questions.
3. Read or review the activity content.
4. Complete the post-activity test questions and evaluation.
5. Physicians who receive a grade of 70% or better on the post-activity test questions and who complete the evaluation will receive a CME certificate.
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Release date: May 15, 2017
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Introduction

This is a time of exciting changes in the field of rheumatoid arthritis (RA). Unprecedented advances in genomics, molecular biology, and protein engineering are leading to earlier detection of disease and an increasing armamentarium of effective treatment options, all of which combine to improve the care of our patients with RA. As the quality movement has taken hold here in the US and the government has revised policies and payment models with the goal of improving the quality of healthcare, we, as clinicians, are now almost continuously advancing the standards by which we deliver care to our patients. Advancing knowledge to support these efforts is critical. Educational activities such as this one are designed to assist us by providing both scientific updates as well as practical advice for how and when they can be applied to our patients in the clinic.

In this activity, some of the salient advances in RA assessment and management of the past 2 years will be highlighted, including data presented at last year’s Annual College of Rheumatology (ACR) meeting in Washington, DC. For those of you who could not attend, I believe this information will be educational, and if you did attend as I did, a useful reinforcement of some of the key issues discussed there.

• A key question for us continues to be in the area of early detection of RA. Early intervention leads to better patient outcomes in RA, and we will discuss some of the latest information on molecular and cellular biomarkers, imaging approaches that can help us identify and track RA disease and its progression, and some initial insights into predicting which patients may respond better to specific therapeutic approaches.

• As more biosimilars enter our disease management toolbox, we need to understand how these agents are designed to be similar, and potentially interchangeable, with the existing, original biologic therapies, to be able to effectively integrate them into clinical use. We will discuss the process by which biosimilars are developed and some of the key issues we should understand as we consider their use. One of the most common questions I am asked by patients with RA when they attain low disease activity is whether they need to stay on their RA medications. We will discuss some of the arguments for and against tapering or withdrawing disease-modifying antirheumatic drug (DMARD) therapy, balancing the risk of relapse with the potential benefits of not taking medications.

• Clinical trials are restrictive in the types of patient they enroll, and as such some of the information is difficult to apply to our patients, who often have multiple other diseases managed in tandem in the rheumatology clinic and other practices. We will describe here ideas on how we shift our focus away from RA as the index disease and toward our patient as the focal point of quality care. The concept of multimorbidity is central to this topic, something that doesn’t always align with clinical trial data.
Updates in Improving Care of Patients With Rheumatoid Arthritis

Quantifying Disease Progression and Response to Treatment

Biomarkers

The increasing investigation into biomarkers in RA has been driven primarily by the need to identify patients earlier in the disease course. The 2010 ACR and European League Against Rheumatism (EULAR) criteria attempted to classify RA earlier in the time course and help clinicians identify patients sooner. Follow-up analyses suggest that the 2010 criteria did indeed improve diagnostic performance; however, limitations remain, particularly in their ability to identify patients who are negative for the autoantibodies anti-citrullinated protein antibody (ACPA) and rheumatoid factor (RF). Currently, only C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are regularly used as inflammatory biomarkers clinically. A recent study suggested that CRP levels may vary in men or women with RA in different body mass index (BMI) categories. Morbid obesity was associated with increasing CRP in women with RA, as with the control population; however, in men this correlation did not hold true, and in fact in one Veteran’s Administration population cohort was reversed—a higher CRP level being associated with lower BMI. Hence, there is a need for additional objective biomarkers to support clinically-assessed measures of RA diagnostic classification.

One of the most promising is calprotectin, a pro-inflammatory leukocyte S100 family protein that has been demonstrated previously to be elevated in RA, and substantially increased in inflamed synovium. In two separate studies, serum calprotectin outperformed both CRP and ESR as markers of treatment response as defined by swollen joint counts and ultrasound-assessed synovitis. In the ARCTIC study, an intensive treat-to-target trial, all markers were high before treatment onset, but after 12 months of DMARD therapy, only calprotectin retained a significant association with ultrasound markers of synovitis.

Other markers of RA disease activity that have been investigated include metabolites produced as part of bone or cartilage turnover; these have the potential to indicate disease activity even in presymptomatic individuals. Some biomarkers of interest are MMP3 (a member of the matrix metalloproteinase family), thrombospondin-5 (cartilage oligomeric matrix protein, or COMP), and a TNF receptor superfamily member, osteoprotegerin (OPG). The GREAT study looked at 140 patients with DMARD-naïve early RA (symptoms less than 2 years), treated for 6 months with synthetic DMARDs (mostly methotrexate), and looked at markers of bone and cartilage turnover as potential biomarkers. Among the markers studied, only elevated baseline MMP-3 and OPG identified a group of patients resistant to therapy at 6 months, as defined by a Simple Disease Activity Index (SDAI) score>11, and low baseline levels of OPG predicted better control of disease activity. These types of bone and cartilage biomarkers may prove useful in stratifying patients according to therapy responsiveness, such as patients who may need early intensification of management.

Thinking beyond molecular and toward cellular markers, a recent prospective cohort study has identified a potential role for B-cell clonal development in the onset and progression of RA. Analysis of B-cell clones obtained from 21 patients without RA but defined as at-risk (ACPA+ and RF+) identified a number of B-cell clones that were expanded beyond 0.5% of the total population, none of which were isolated from control groups. Five or more of these dominant clones in peripheral blood from an independent prospective cohort of similar patients was associated with a 5-fold increase in relative risk for developing RA. Interestingly, in patients that developed overt RA, these clones were no longer observable in peripheral blood, but rather were now localized to the inflamed synovium, suggesting a direct role for these cells in disease pathology and progression. Another recent pilot implicated T-helper lymphocytes, specifically T17 types, as potential markers; low levels at baseline were associated with a good response to bDMARDs.
Imaging

In addition to molecular and cellular biomarkers, imaging techniques also continue to be investigated for their utility in quantifying RA disease progression and response to treatment. X-ray techniques to assess joint damage have been in use for many years, but are limited by needing large numbers of patients to provide a quantitative assessment of treatment response even at 12 months from baseline. Imaging techniques such as MRI have become of increasing utility because of the ability to see the joint in 3-D (although typically viewed as a series of 2-D slices), but limitations in quantitative imaging exist due to reader interpretation and scoring of images. This can be of particular concern in analyzing large multi-center trials, where data has to be pulled together from different machines and can vary based on the interpretation and scoring of the individual reader. Some recent automation using newer imaging software and analytic techniques is helping to overcome this issue, as well as beginning to help us more fully understand individual patient disease progression. One of these is RAMRIQ (RA-MRI quantification), an image analysis that builds on the existing RAMRIS (reader-based scoring system) but removes the need for subjective scoring (Figure 1).¹³,¹⁴ This analysis software is based on the same programming used in facial recognition techniques; the software learns the 3-D shape of all the bones in the hand by reading a high volume of test data, which allows it to create a fully 3-D image of the patient’s hand skeleton and surrounding tissue. It is accurate to around 0.2mm, more sensitive than reader interpretation and scoring of images, and fully automated, which removes inter-reader variability and allows high-level statistical analysis.
The predictive power of RAMRIQ was investigated using post-hoc data from a study (30 patients per arm) of tofacitinib plus methotrexate (MTX) versus either tofacitinib or MTX alone, assessed by radiographic and RAMRIS-measured joint damage over a 12-month period.\textsuperscript{13,14} RAMRIQ scoring of synovitis and bone marrow edema/osteitis at months 1 and 3 could effectively predict significant erosion progression of the joint at month 12. Although few study patients developed radiographic progression at the 12-month mark in the original study, what was measurable radiographically was predictable by RAMRIQ. This radiographic progression at 12 months was not predictable using RAMRIS at 1 and 3 months, showing the limitations of reader-assisted subjective measures with only 30 patients.\textsuperscript{14} If confirmed in other settings with a larger number of patients, this study could have implications for clinical trials and clinical practice; with the substantial increase in sensitivity and specificity of these techniques, it is possible that trials could be of shorter duration and still be meaningful for regulatory authorities with a smaller number of patients in each study arm.

Another imaging technique that has gained attention is the use of whole-body positron emission tomography (PET) scanning, in particular with respect to cardiovascular aspects of RA.\textsuperscript{15} 18F-fluorodeoxyglucose (FDG) is a marker of glucose uptake that has been used in different diseases to identify sites of abnormal glucose metabolism. This technique has been used in the evaluation of cardiomyopathies for almost 20 years. In patients with RA, FDG-PET has been used traditionally to identify clinically inflamed joints, but has the potential to track cardiovascular aspects of RA as well. The RHYTHM study looked at 113 patients with moderate-to-severe RA, current lower disease activity (Clinical Disease Activity Index (CDAI) score<10, mean DAS28=3.78), and no history of cardiovascular disease; 30% of these patients showed myocardial inflammation using FDG-PET.\textsuperscript{16,17} Higher BMI and higher disease activity positively correlated with myocardial inflammation, and use of tumor necrosis factor inhibitor (TNFi) therapy was negatively correlated. A small group of these patients (n=12) enrolled in a 6-month step-up therapy trial, and a decrease in mean DAS28 score in these patients (4.57 to 3.51) was paralleled by a decrease in myocardial inflammation.\textsuperscript{17} This is an encouraging sign, as it supports the idea that if we treat to target with anti-RA therapy, we may have a positive impact on cardiovascular disease outcomes.

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Predicting Positive Clinical Outcomes in RA

While biomarkers are beginning to provide insight into how we track and measure disease progression, predicting which patients will respond to a specific class, or mechanism of action, of drug therapy is still quite unclear. Data from the ORBIT study, in which patients were randomized to either rituximab or TNFi therapy and switched to the alternate therapy if they did not respond, showed that roughly 25% of patients needed to switch in either study arm, and those who did switch achieved an average DAS28 score reduction of around 1.4 units on the second treatment.18,19 If we could better identify patients who would respond to one therapeutic mechanism of action or other, could we better tailor treatment plans?

The ORBIT study attempted to use gene expression profiles of the enrolled patients to answer this question. RNA analysis of patient blood gene expression at baseline versus 3 months identified groups of genes which could predict general or class-specific responsiveness with high sensitivity and specificity (Figure 2).19

**Figure 2.** Ability of Peripheral Blood Transcriptional Biomarkers in the ORBIT Cohort to Predict Subsequent Response/Non-response to Biologic Therapy

<table>
<thead>
<tr>
<th></th>
<th>Training Set</th>
<th>Test Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>General responsiveness</td>
<td>82.0% (81.1–82.8)</td>
<td>91.1%</td>
</tr>
<tr>
<td>Response to TNFi</td>
<td>82.7% (81.6–83.8)</td>
<td>88.7%</td>
</tr>
<tr>
<td>Response to rituximab</td>
<td>95.4% (94.8–96.0)</td>
<td>91.7%</td>
</tr>
</tbody>
</table>
The ability of these gene expression profiles to predict response to therapy was modest at 3 months. By 12 months this expression profile predictor had lost a significant amount of its power, possibly due to the switching that took place in the study over that 12-month period. However, if we look at stratification of the data at 3 months, the profiles can identify the 10% of patients who will not respond to either therapy, and for these patients, one might consider pharmacologic agents with alternate mechanisms of action. The profiles can also identify the roughly 40% of patients who would respond to either therapeutic approach used in ORBIT as well as those who would respond best to either rituximab or TNFi therapy.

This technology is still several years away from clinical utility; however, it is encouraging as a clinician to note that a significant group of patients will respond to either one or both of these classes of therapy. Starting from this positive baseline, we could be more aggressive sooner and switch therapies if patients do not attain early response, maximizing our chances of response. Support for this hypothesis comes from an analysis of data from the CORRONA patient registry, in which the authors attempted to understand how poor prognosis at baseline may influence treatment decisions. The use of a high number of poor prognostic factors as a guide to treatment was previously removed from the ACR guidelines. Data was collected from patients with baseline prognostic factors, who were biologic-naïve, and who had a follow-up visit at 12 months. Their data suggested that currently the presence of 3 or more poor prognostic factors at baseline does not influence clinical decision-making, as determined by initiation of any DMARD at 12 months. However, an increased number of poor prognostic factors was strongly correlated with a lower responsiveness to initial therapy by CDAI scores. This suggests that patients with more advanced disease at treatment initiation are less likely to respond to first-line therapy, supporting an argument for more aggressive treatment in these patients, including switching earlier to DMARDs with an alternate mechanism of action.

Outside of genetic or biomarker predictors, other recent studies have provided some insight into factors that may predict response to therapy and thereby drive our clinical decision-making. A combined post-hoc analysis of two adalimumab/MTX trials, OPTIMA and PREMIER, attempted to identify factors predicting poor response and rapid radiographic progression in patients taking MTX. Health Assessment Questionnaire (HAQ) score at baseline, along with time-averaged HAQ and DAS28 scores through 12 weeks, were the biggest predictors of MTX-IR (insufficient responders) and rapid radiographic progression. SIRROUND-D was a phase 3 trial of sirukumab, an anti-IL-6 biologic, in patients refractory to other DMARDs; a post-hoc analysis to identify predictors of radiographic nonprogression showed that patients with poor prognostic factors at baseline, including high baseline radiographic damage and ACPA seropositivity, were the strongest predictors of radiographic nonprogression for sirukumab over placebo. The ESPOIR cohort is a prospective observational multicenter study conducted in France in the early 2000s including early RA patients in an attempt to better understand disease progression and response to treatment. Data from recent analyses of these patients’ treatment response with conventional synthetic DMARDs suggests that, rather than conventional prognostic factors, the most significant parameter affecting response to treatment was a delay in treatment initiation. Treating patients within 3 months of first joint swelling was 2.5-times more likely to result in good or moderate response at 1 year.
Clinically suspect arthralgia (CSA) is a term recently defined by EULAR to describe patients without clinically apparent synovitis but with arthralgia symptoms suggestive of RA (Table 1). Patients with CSA are among those considered at high risk of progressing to overt RA. Two recent reports in this population of patients are of interest. First, there appears to be only minimal, if any, correlation of ACPA and RF autoantibodies in this patient population with those who will go on to develop RA, extending and reinforcing the theme that autoantibodies alone are insufficient to predict which patients will develop RA. Second, and of more interest, in patients with CSA who progressed to RA, only a HAQ>1.0 correlated positively with progression, suggesting that patients in the early phases of RA already have functional limitations.

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**TABLE 1.** (A) EULAR-defined characteristics of clinically suspect arthralgia; (B) Sensitivity and specificity for clinically suspect arthralgia for the number of positive characteristics

**(A) EULAR defined characteristics describing arthralgia at risk for RA**

These parameters are to be used in patients with arthralgia without clinical arthritis and without other diagnosis or other explanation for the arthralgia.

**History taking:**
- Joint symptoms of recent onset (duration <1 year)
- Symptoms located in MCP joints
- Duration of morning stiffness ≥60 min
- Most severe symptoms present in the early morning
- Presence of a first-degree relative with RA

**Physical examination:**
- Difficulty with making a fist
- Positive squeeze test of MCP joints

**EULAR, European League Against Rheumatism; RA, rheumatoid arthritis.**

**TABLE 1.** (B) Sensitivities and specificities for the presence of arthralgia at risk of RA with the clinical expertise on CSA as reference

<table>
<thead>
<tr>
<th>Number of parameters present</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1</td>
<td>100.0</td>
<td>14.1</td>
</tr>
<tr>
<td>≥2</td>
<td>98.4</td>
<td>53.8</td>
</tr>
<tr>
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<td>70.5</td>
<td>93.6</td>
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<td>≥6</td>
<td>16.4</td>
<td>100.0</td>
</tr>
<tr>
<td>≥7</td>
<td>1.6</td>
<td>100.0</td>
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Left-ventricular diastolic dysfunction (LVDD), or the lack of ventricular filling due to increasing myocardial stiffness and inadequate myocardial relaxation during diastole, underlies many cases of heart failure in patients with RA. A 5-year study of patients using echocardiography attempted to identify factors predicting LVDD progression. Major factors correlated with echocardiographic evidence of LVDD progression included high disease activity and severity at baseline, and use of prednisone. This correlates well with a recently developed expanded risk score calculator for cardiovascular disease (CVD) in patients with RA (ERS-RA), which identified disease activity, disability (HAQ score), prednisone use, and disease duration >10 years as modifiable factors which may lower CVD risk in patients with RA when reduced. It is worth noting, however, that these factors are not entirely independent of one another: high disease activity may lead to corticosteroid therapy and corticosteroid therapy may reduce disease activity. This points out the challenge of relying on these variables to assess cardiovascular disease risk and the importance of controlling disease activity with therapies other than corticosteroids.

Prednisone use >10 mg per day was also associated with higher rates of infection in patients with RA and interstitial lung disease in one study. This data highlights some of the potentially significant risks associated with corticosteroid use, which must be carefully balanced against their benefits in clinical use.

Viewed together, the take-home message from these and other studies is a clear benefit of early treatment initiation on disease prognosis, particularly prior to overt functional limitations, in patients with RA. Of course, this is not a new concept; multiple previous studies have shown a similar benefit from early treatment initiation. As biomarkers and other methods to earlier identify those patients at risk for developing RA emerge and move into clinical use, the time to treatment initiation may be reduced and patients can receive effective treatments with appropriate intensity to achieve optimal outcomes.
Biosimilars: Regulatory and Practice Considerations

Molecular Engineering of Biosimilars

Over the past 30 years, improved understanding of the molecular detail of immunoglobulins and the function of the immune system have been the primary drivers for the antibody engineering that has underpinned biologic therapy in RA. Notably, the modular domains of both the light and heavy chains in monoclonal antibodies, each of which are encoded by separate exons at the DNA level, has facilitated rapid advancements in antibody engineering. Initial work with mouse-generated antibodies to specific therapeutic targets has given way to therapies that are either chimeric, in which entire domains are replaced with human ones; humanized, in which only the hypervariable complementarity-determining regions (CDRs) are remaining from the original mouse antibody; and fully-human antibodies, generated by more modern molecular engineering techniques. Each of these antibody types has its own conventional nomenclature in biologic therapy (Figure 3).

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Much of this molecular engineering has focused on the variable region (Fv) of the antibody, which confers specific binding to a target such as TNF. Keeping this region specific to the target while maintaining a low immunogenicity is critical for an effective biologic. Antibody molecules also have a second function, however, and that is the linkage of these targets to an effector function, such as complement activation or cell-mediated cytotoxicity. This is accomplished via the constant region (Fc), which is also known to play a role in prolonging antibody half-life; the neonatal Fc receptor is a ubiquitously expressed cell surface protein that rescues antibodies from lysosomal degradation when they are endocytosed from the blood.\(^3\) Selectively mutating specific amino acids within these regions can improve binding or reduce unwanted effector function activation; for example, RA biologic therapies have no need for activating natural killer cells via the complement pathway, and so molecules such as abatacept have these binding regions mutated to reduce the likelihood of unwanted cell death.\(^4\)

One of the major complexities with biologics, as well as biosimilars, is that these are large, complicated molecules produced by living cells rather than an \textit{in vitro} chemical synthesis, as is the case with manufactured pharmacologics.

\textbf{FIGURE 4: Variation in Glycosylation Patterns of Asparagine-297 of the Immunoglobulin Heavy Chain}

These living cells modify the protein product by various mechanisms, including glycosylation, methylation, deamidation, and oxidation, which are only partly determined by the amino acid sequence of the antibody. One well studied example is Asparagine-297 of the immunoglobulin heavy chain; glycosylation at this residue has a fairly consistently structured backbone of glucosamine and mannose, but can also have fucose, galactose, and sialic acid moieties attached in different cell types and lineages (Figure 4). When all potential glycosylation sites in any particular antibody are taken into account, a large number of possible structural conformations and heterogeneity in the pool of antibody species can be obtained from any given cell type.\(^6\) These post-translational modifications matter clinically, as they can impact effector function, structural stability, and pharmacokinetics. There are also many steps along the pathway to development and generation of a final clinical product in which post-translational modifications may impact the outcome and molecular properties, and they are not always predictable; as such, regulatory agencies mandate control of the post-translational modification profile in biologic agents.
The development and integration of biosimilars into clinical practice presents new challenges for the rheumatologist. The processes of antibody engineering to create biologics and biosimilars is very different from that associated with small-molecule pharmacologics. With the knowledge of these processes, the challenges of producing biosimilars, as well as obtaining regulatory approval, become clear. The consensus definition of a biosimilar is a **biotherapeutic product which is similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product, or bio-originator**. The phrase “similar to” defines the absence of a clinically relevant difference in the parameter of interest; the US Food and Drug Administration (FDA) refers to safety, purity, and potency as the parameters of interest. Small-molecule pharmacologics are chemically synthesized, easily replicated, and their identity is able to be readily confirmed; as a result, regulatory approval of generic versions requires demonstrating only an identical structure *in vitro*, by mass spectrometry for example, and identical pharmacokinetics using healthy volunteers. A typical monoclonal antibody is over 1000-times larger and more complex than a small molecule such as aspirin, and as such, determining similarity becomes significantly more challenging. Starting with the same amino acid sequence, post-translational modifications and a heterogeneous antibody product can result in a markedly different biologic from the bio-originator. These can be affected by the cell line, any genetic modifications the cell line may have, the culture medium in which the cells are grown, or specific growth conditions; and much of this information for the bio-originator is either proprietary or commercially sensitive. The challenge with producing a biosimilar is therefore two-fold; comprehensive analysis of the bio-originator, and subsequent replication of that development process.

When demonstrating similarity between products to the FDA, the first item is an extensive physicochemical and biological characterization of the product, described as a “fingerprint-like” analysis (Figure 5). The biosimilar and the bio-originator data should be superimposable, at the levels of:

- Primary amino acid sequence
- Higher order folding structures, including secondary, tertiary, quaternary structure, and aggregation
- Enzymatic post-translational modifications
- Other potential variants, including protein deamidation and oxidation

**FIGURE 5. Approval Processes for Bio-originators versus Biosimilars**
Following this, the binding and function of the two products must be compared non-clinically and in a side-by-side approach. It is important to demonstrate that the biosimilar binds to its antigenic target as well as the bio-originator, and that the Fc domain binds to all relevant receptors and complement, along with any appropriate activation of downstream signaling cascades and functions. *In vivo* non-clinical animal testing of the biosimilar is usually not required, unless there are clear and significant differences from the bio-originator, such as use of a different cell expression system, incompletely characterized impurities, or formulation differences. Following this, there must be at least one pharmacokinetic study in healthy volunteers to demonstrate that the body handles the biosimilar in the same way as the bio-originator, and at least one randomized controlled trial to demonstrate clinical equivalence; the margins of similarity are defined using meta-analysis data from the bio-originator clinical trials. Safety and immunogenicity must be comparable for the biosimilar, and it is a regulatory requirement that immunogenicity continues to be monitored using post-marketing surveillance programs.\(^3^8\)

Immunogenicity is a concern for both biosimilar and bio-originator products. Even with fully humanized antibodies, immunogenicity can arise in about a third of patients, as seen in studies of adalimumab.\(^3^9\) Fortunately, immunogenicity does not always lead to side effects or loss of efficacy.

Beyond the antibody engineering process itself, which can produce glycosylation events recognizable by our immune systems and thereby have immunogenic potential, patient factors including underlying genetics, comorbid disease and concomitant medications, dosing schedule, and route of administration all can influence immunogenicity. Since biosimilars are licensed with relatively few patient exposures as compared to the bio-originator, registries and surveillance are required to monitor not only immunogenicity, but rare adverse events and long-term safety and efficacy data, which will be lacking with the shortened regulatory process.

Another issue under debate is that of interchangeability, which defines the situation in which a pharmacist may substitute a biosimilar for the bio-originator. A biosimilar product is interchangeable if it is expected to produce the same clinical result as the bio-originator in any given patient, and the FDA’s draft guidance has required at least one suitably designed switching study to effectively demonstrate interchangeability.\(^4^0\) Similar to the process whereby a patient may receive a generic small-molecule pharmaceutical instead of a branded product at their pharmacy (unless the prescribing physician specifically requests the brand name version), and with the same cost considerations (as biosimilars are predicted to be significantly less expensive than bio-originators), if a biosimilar has demonstrated interchangeability with the bio-originator, substitution with a biosimilar will not specifically require the prescribing physician’s approval. None of the biosimilars approved to date in the US have demonstrated interchangeability.
The naming convention for biosimilars is important for prescribers to understand. With the amount of ongoing post-marketing surveillance, the ability to accurately identify a product is critical, and the International Non-proprietary Name (INN) will be insufficient for that task. The FDA currently requires a four-letter suffix for the INN to distinguish different products; for example, the biosimilar of infliximab (Remicade) is infliximab-dyab (Inflectra). A concern is that this naming difference implies these products are not interchangeable (which is currently true), when they may be in the future. In Europe currently, the INN is used identically for both products, which may inappropriately imply interchangeability. Both of these scenarios emphasize the importance of understanding the current nomenclature used for biosimilars, and the degree to which interchangeability is appropriate now and in the future.

The final issue in ongoing discussion of biosimilars is that of extrapolating indications. The operating principle is that if the bio-originator was efficacious and safe in multiple diseases, and the biosimilar has been determined to be clinically equivalent for one of those diseases, it should be equivalent for them all. However, for this to hold true, clinical efficacy must rely on a similar mechanism of action in the extrapolated indication. For example, infliximab in RA and psoriatic arthritis works by neutralizing TNF in the joint; this has led to the extrapolated indication for infliximab-dyab to both diseases. For the clinician, it is therefore important to understand that biosimilars have not been extensively characterized clinically as much as chemically. As far as we know, they should perform identically to the bio-originator, but we should be aware that they have not been tested as extensively in patients, and so increased vigilance on our part is worthwhile.
Managing Patients With Low RA Disease Activity: Can We Taper Therapy?

For patients with RA who have low disease activity, it makes sense to consider reducing the dose of a medication or to stop it altogether. Perhaps disease control will be just as good with a lower dose; in addition, there may be cost savings and safety advantages to consider. Cytokine levels in the target organ may also justify reducing medication dosage. When TNFi therapy is initiated, TNF levels in the joint synovium are usually high, as disease activity is high. These local levels of TNF tend to fall as therapy proceeds successfully, and it therefore stands to reason that the amount of agent needed to inhibit specific cytokines may be reduced. Another important reason to taper therapy is patient preference. Patients in remission rarely see why they may need to continue aggressive therapy when they feel well, and as clinicians we often err on the side of continuing treatment lest the patient flare. But this is only logical if the patient actually needs continued exposure to therapy to maintain disease control, and this is the crux of the discussion around whether to taper.

DMARD tapering/withdrawal studies can shed some light on management strategies in patients with low RA disease activity. However, heterogeneity of patient populations, definitions of remission, and low disease activity across many studies make it difficult to come up with clear take-home recommendations. One group of patients who might have the best success with tapering are those who reach remission early in the disease course.

Pilot data has suggested early remission is a prerequisite for successful therapy withdrawal (Figure 6). This small study (47 patients) also suggested a basis for assessing patients’ ability to regain low disease activity following flare.

**FIGURE 6: Early Remission May be a Prerequisite for Successful TNFi Therapy Withdrawal**

<table>
<thead>
<tr>
<th>Early (MTX naïve) Treatment Group</th>
<th>N = 27</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Flare</strong></td>
<td>N = 11</td>
</tr>
<tr>
<td>Time to flare:</td>
<td>median 14 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Remission regained with DMARD escalation</th>
<th>N = 8</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sustained Remission</strong></td>
<td>N = 16</td>
</tr>
<tr>
<td>Time to flare:</td>
<td>median 4 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Delayed (MTXIR) Treatment Group</th>
<th>N = 20</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Flare</strong></td>
<td>N = 17</td>
</tr>
<tr>
<td>Time to flare:</td>
<td>median 4 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TNF Blocker therapy stopped</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Flare</strong></td>
<td>N = 17</td>
</tr>
<tr>
<td>Time to flare:</td>
<td>median 4 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Remission regained</th>
<th>N = 15</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TNF Blocker restarted</strong></td>
<td>N = 3 (11%)</td>
</tr>
<tr>
<td>All regained remission</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sustained Remission</th>
<th>N = 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TNF Blocker restarted</strong></td>
<td>N = 17</td>
</tr>
<tr>
<td>(85%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Remission regained</th>
<th>N = 15</th>
</tr>
</thead>
</table>

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For patients early in the RA disease course (MTX-naïve in this study), more than half sustained remission over the 2-year study period after TNFi therapy was stopped; all patients continued MTX therapy. The patients in this arm who relapsed did so with a significantly longer median time to flare than the control group of MTX inadequate responders (MTXIR), and most also re-attained remission with escalation of a DMARD alone, rather than having to restart TNFi therapy. For MTXIR patients, substantially fewer patients maintained remission once TNFi therapy was stopped, and all of those flared needed to restart TNFi therapy to have a chance of regaining remission; even with TNFi therapy, not all of these patients regained remission. In conclusion, this pilot study suggested that successful cessation of TNFi therapy is achievable if remission is achieved quickly following early treatment initiation.

Looking at data from some studies that have considered dose reduction, rather than withdrawal of therapy, in early disease, a pattern appears (Table 2):

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Information</th>
<th>Outcome Following Dose Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGREE</td>
<td>Randomized, double-blind study extension following patients who reached remission (DAS&lt;2.6) Evaluated maintenance of response to half-dose (5mg/kg) versus continuation on full dose (10mg/kg) of intravenous abatacept</td>
<td>Relapse (flare) over time and proportion of patients relapsing were similar in both groups (31% vs 34%)</td>
</tr>
<tr>
<td>PRIZE</td>
<td>Patients with 12 weeks of sustained, low disease activity (DAS&lt;2.6) on etanercept and methotrexate following 52 weeks of treatment were randomized to: • Half-dose etanercept plus full-dose methotrexate • Full-dose methotrexate alone, or • Placebo for a further 40 weeks</td>
<td>Patients who maintained combination therapy through the full 92 weeks of the trial showed sustained remission through the final 40 weeks on half-dose etanercept</td>
</tr>
<tr>
<td>C-EARLY</td>
<td>Patients with sustained low disease activity (DAS28≤3.2) during weeks 40–52 while taking standard dose certolizumab pegol were randomized to either continue standard dose certolizumab, a reduced frequency of dosing, or placebo for a further 52 weeks</td>
<td>Patients who maintained combination therapy through the full 104 weeks of the trial showed sustained remission through the final 52 weeks on reduced-dose certolizumab, comparable to that observed in the full-dose patient group</td>
</tr>
</tbody>
</table>

Based on these initial trial results with different therapeutics, a case can be made that, if a patient in early stages of the disease can attain remission on pharmacotherapy for a sustained period of time (e.g., 3 months), dose reduction of the biologic may be possible with little risk of adverse impact. Additional data comes from the PRESERVE study, in which patients had persistent, moderate disease activity (rather than being early in the disease course); after reaching low disease activity with full-dose etanercept plus methotrexate, they were randomized to either continued full-dose etanercept, half-dose etanercept, or placebo. At the conclusion of the 88-week study, there was little difference by disease activity measures between patients in the full-dose versus the half-dose etanercept arms. Data from these studies therefore suggests that dose reduction in patients with sustained low RA disease activity is feasible and well-tolerated among patients with either early or well-controlled disease.
The studies discussed previously all considered dose reduction; additional data is available on stopping therapy altogether. In the 2-year TNF-20 trial, researchers showed sustained benefit of 1 year of infliximab treatment followed by withdrawal of therapy, as measured by quality-of-life and HAQ scores. Long-term follow-up of these patients over 8 years showed maintained low disease activity in the infliximab-treated cohort versus placebo (DAS28 score 2.7 vs 4.3) and 44% of infliximab patients were in remission versus none in the placebo group. Patients who stopped etanercept therapy in the second arm of the PRIZE study (Table 2, previous page) did not maintain remission as well as those patients who remained on half-dose etanercept, but still about 80% maintained remission. It is of note that the PRIZE study had a third phase, during which patients in all three study arms who were still in remission went completely drug-free for a further 28 weeks, including stopping MTX. Fifty percent of patients who took etanercept through the first two phases and then went completely drug-free were still in remission at the end of this phase. Applying this study to clinical practice may be met with resistance, however, as the ACR guidelines recommend against discontinuation of all therapy. In C-EARLY, patients who stopped therapy in the second phase did show some increase in disease activity compared to patients continuing on certolizumab, but their mean DAS score was still rather low (around 3.0) after 104 weeks.

The OPTIMA study was a complex multi-arm study over 78 weeks; for the purposes of discussing termination of therapy only two arms are relevant. Patients in the first phase were given full-dose adalimumab plus MTX, and if they had sustained DAS28≤2.8 at weeks 22 and 26, they were randomized blindly to either continue on the same therapy or to withdraw adalimumab. Using DAS and SDAI scores, roughly 90% of patients maintained remission when adalimumab was continued, and there were around 10% fewer patients maintaining low disease activity when the agent was stopped. Given an estimated recapture rate in excess of 75% (P Emery, pers. comm.), the risk of potential harm to patients with low disease activity from tapering therapy seems quite low.

On the other hand, there are some valid reasons to not taper therapy. From an immunopathologic standpoint, we know that endothelial cells of the affected synovium have altered morphology and gene expression patterns that persist across the disease course, implying disease processes and inflammatory processes may still be present, even for patients treated to low disease activity. One longitudinal real-world study using patients in the CORRONA Registry who voluntarily decided to discontinue their TNFi therapy found that roughly 50% of patients had restarted their TNFi by around the 18-month mark, and at the end of the study over 90% of participants had flared.

Flares have long-term consequences for patient health and quality-of-life. Ten-year data from the BeST study, in which patients were treated to target DAS≤2.4 and then tapered to maintain MTX monotherapy demonstrated that the more flares a patient experienced, the higher the HAQ score at year 10, and the greater the radiographic disease progression from baseline to year 10. Flares were also associated with patient-scored factors, including perception of pain and disease activity, morning stiffness, and functional deterioration, suggesting that treatment intensification may outweigh the possible risks in select patients. Other studies have also suggested that patients on tapered regimens experience more adverse events, including infections, and require more corticosteroid, DMARD, and pain medications as a result. Hence, if we consider an economic argument for tapering, we must balance the reduced cost of primary pharmacologic therapy with the potential increased costs of using other agents, as well as indirect costs including those associated with side effects, increased office visits, or other contact with the healthcare system.
Key issues in considering tapering or termination of therapy are the definitions of remission and determining how to predict who will tolerate less medical therapy. Patients with the same low disease activity score are often quite different in terms of their global RA disease state, their overall health and wellness, their serologic status for certain biomarkers, their RA disease and treatment history, and different dimensions of remission, including imaging, immunologic measures, and clinical status. In OPTIMA, for example, when the patients who continued adalimumab were compared to those who stopped it, there were small but discernable differences in radiographic progression and ACR-70 scores (Figure 7). Among these patient groups, the only predictor of maintaining remission after stopping adalimumab was a lower HAQ score at baseline. Patients in the early stages of disease typically have less functional impairment, and based on these data may have an increased likelihood of maintaining remission when therapy is stopped; but this needs to be evaluated on a case-by-case basis, and dose reduction would present a lower-risk scenario. In order to be better able to predict who would tolerate termination of therapy, data samples that analyze outcomes for predictive factors must be larger; so, while these data are helpful, it is worth remembering that current guidelines recommend caution when tapering and recommend that patients with RA not stop all therapy.

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Treatment of RA When the Patient Is Unwell

Multimorbidity is the term used to describe patients with two or more chronic medical conditions. Multimorbidity differs from comorbidity in that comorbidity involves the relation of an index disease (in this case RA), to one other specified disease such as diabetes or heart disease. As rheumatologists, we have traditionally focused on treating RA with the hope that at least some comorbidities (such as heart disease) might benefit as well.

The concept of multimorbidity considers how all identified disease states may interrelate, with the focus on the patient as the center of care. This requires adding an extra dimension to our thinking: beyond measures of RA disease activity as our primary outcomes, with the patient as the primary treatment focus we should include more global measures such as overall quality of life (Figure 8).

FIGURE 8: Refocusing Treatment to Patient-centered Outcomes Is the Key Principle of Managing Multimorbidity

Click on the figure to see Multimorbidity
Regardless of the disease states, multimorbidity is associated with poorer patient outcomes, including:

- Reduced quality of life
- Reduced socioeconomic status
- Increased mortality rates
- Increased rates of polypharmacy and high treatment burden
- Increased rates of treatment-emergent adverse events
- Increased health system utilization, including emergency room visits

The number of multimorbid conditions increases with age; in one large analysis, by the median age of onset of RA (45 to 49 years), 43.2% of the population had 1 or more chronic morbidity, and 23.2% had 2 or more. By ages 50 to 60, more patients will have 2 or more diseases than those with 1 or none, and these make up a substantial proportion of the patients with RA that we treat. The number of comorbid conditions also increases for any given age with reducing socioeconomic status, adding an extra dimension of burden to the management and the potential for poorer patient outcomes.

Yet, due to exclusion criteria, these are not patients represented in clinical trial populations. Therefore, we face challenging treatment decisions on a daily basis. When considering RA, it is not one clearly defined disease as studied in clinical trials, but an amalgamation of complex chronic diseases, all of which we should be considering in our management approach. Multimorbidity is present in almost two-thirds of patients with RA, as compared with around 20% of the general population. Currently it is unclear why there is such an increased prevalence; shared genetic or lifestyle factors (such as smoking or a sedentary lifestyle) could be contributors.

Time plays an important role for patients with RA and multimorbidity. We may treat a patient with RA over many decades and over that period of time, development of new conditions or exacerbations of existing diseases are common. Considering that disease activity and treatment can trigger or worsen other medical conditions, early decisions in RA management are among the most critical.

Even when in remission, individuals with RA may experience functional impairment. Patients with 4 or more multimorbidities, who were in remission according to the CDAI, had a significantly higher HAQ score than those without any comorbid disease. In patients with higher disease activity, increasing multimorbidity also correlated strongly with increasing HAQ scores, indicating that patients with RA and multimorbidity have worse function regardless of current RA disease activity.

When thinking about managing patients with multimorbidity, we as clinicians should offer an approach that maximizes quality of life. The 2016 National Institute for Health and Care Excellence (NICE) guidelines offer useful items for a clinician to focus on:

- How the patient’s health conditions and their treatments interact and how this affects quality of life
- The patient’s individual needs, preferences for treatments, health priorities, lifestyle and goals
- The benefits and risks of following recommendations from guidance on single health conditions
- Improving quality of life by reducing treatment burden, adverse events, and unplanned care
- Improving coordination of care across services

In addition, these guidelines offer some practical advice for the clinician when delivering an approach to patient care that takes account of multimorbidity:

- Discuss with your patients the purpose of an approach to their care that takes account of their multimorbidity.
• Establish patient (and caregiver) disease burden and treatment burden
• Establish patient goals, values, and priorities
• Conduct comprehensive medical management, along with other treatments, taking into account evidence of likely benefits and harms for the individual patient, and their important goals and outcomes
• Agree on an individualized management plan with the patient

In essence, the guidelines recommend having a conversation with the patient, documenting what their concerns and priorities are, and establishing a set of goals which can be operationalized and consulted. The major domains for which comorbidity becomes multimorbidity in patients with RA are ones with which we are all familiar: cardiovascular risk factors and CVD, infections and vaccinations, osteoporosis, gastrointestinal disease, lymphomas and other cancers, and mental health.

TABLE 3: Recommendations for Improving CVD Care in Patients With RA

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA patients are more likely to have a silent MI, or sudden cardiac death on admission to coronary care, than patients without RA.62</td>
<td>Changes in cholesterol levels and other metabolic markers are to be expected when inflammatory processes are modulated, either due to RA disease activity or through the use of pharmacologic treatments. RA disease activity generally reduces available cholesterol molecules.</td>
</tr>
<tr>
<td>Treat-to-target approaches in RA have demonstrated a 21% reduction in CVD risk with a 10-point reduction in CDAI score.64</td>
<td>CVD risk can be quickly and easily calculated based upon a number of well-investigated parameters.65</td>
</tr>
<tr>
<td>RA pharmacotherapies have shown elevations in low-density lipoprotein cholesterol (LDL-C), a key marker of elevated CVD risk.66</td>
<td>Clinical trials have demonstrated an increased risk of heart failure with TNF inhibitor therapy.</td>
</tr>
</tbody>
</table>
When we look at domains such as cardiovascular disease, serious infectious diseases, and cancer, considering the evidence base and guidelines we have currently, some useful clinical recommendations appear. While this is not truly considering multimorbidity yet, it still works from the perspective of CVD being comorbid to RA. This is likely the most reasonable current starting point as we have no clinical trials specifically addressing multimorbid patient groups. As we move forward, more effectiveness studies, real-world experience, and open-label trials may help to provide us with more practical strategies not only regarding management of RA, but for the whole patient who is more reflective of the people visiting our practices.

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