

PERSONALIZED MEDICINE IN RHEUMATOLOGY: TOMORROW'S PROMISE OR TODAY'S REALITY?

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LEARNING OBJECTIVES

- List three reasons driving research into the introduction of personalized medicine for the diagnosis, management, and treatment of rheumatoid arthritis (RA)
- Assess the importance of OMERACT and the applicability of its research initiatives to your current and future practice
- Compare the value of currently-validated biomarkers such as anti-CCP and CRP in the overall diagnostic and treatment process for RA
- Identify at least two biomarkers of treatment response in RA currently under investigation

STATEMENT OF EDUCATIONAL NEED

Rheumatologists have been using biomarkers such as rheumatoid factor and anti-CCP antibodies to help diagnose rheumatoid arthritis (RA) for years. In addition, acute phase reactants (and particularly C-reactive proteins) have been shown to be reliable markers of disease activity and radiographic progression. Yet despite the utility of these markers, new research promises a more refined approach to the current diagnosis, risk assessment, and treatment of patients with RA. Ongoing efforts by the OMERACT soluble biomarker special interest group have been developed to ensure that new biomarkers meet stringent criteria before being adopted for widespread clinical use. With the availability of new biomarkers, rheumatologists may soon be able to select a course of RA treatment based on a patient's clinical and genetic characteristics, and thereby provide treatment options that are most likely to result in good clinical outcomes. It is important that rheumatologists prepare for the future impact of personalized medicine by familiarizing themselves with the type of research being conducted.

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PERSONALIZED MEDICINE IN RHEUMATOID ARTHRITIS

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease consisting of distinct pathologic subsets that each contribute to its common signs and symptoms. Patients with RA show marked variations in natural history and disease severity, as well as highly variable responses to standard therapy. Up to 30% of patients with RA will not respond to disease-modifying antirheumatic drugs (DMARDs), including biologic therapies, or will experience adverse events while on treatment.¹

Personalized medicine aims to refine current RA treatment paradigms, allowing rheumatologists to prescribe the right treatment to the right patient at the right time through the use of simple, noninvasive tests that predict response or non-response to therapy based on genetic, molecular,

or clinical biomarkers.² Through the use of sensitive biomarkers that appear prior to clinical manifestations, personalized medicine intends to allow rheumatologists to target RA at the earliest stages of disease and enable them to more precisely select drug therapies and doses tailored to individual patients based on genetic predictors of drug response. These changes will allow rheumatologists and patients to avoid adverse events and the

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financial burden associated with multiple courses of treatment that are unlikely to adequately control the disease.

Advocates of personalized medicine suggest that major advancements in RA treatment may not just involve the introduction of new agents, but also a dramatic improvement in the efficacy and cost-effectiveness of current regimens.³ The first seedlings of personalized medicine appeared in rheumatology years ago when autoantibody and acute phase reactant assays were introduced; over time, these tests were both widely accepted and are now regularly used to diagnose and assess patients with RA. Personalized medicine's next phase is expected to involve a broad introduction of new biomarkers after they have been consistently validated in RA patients (see OMERACT sidebar on page 5).

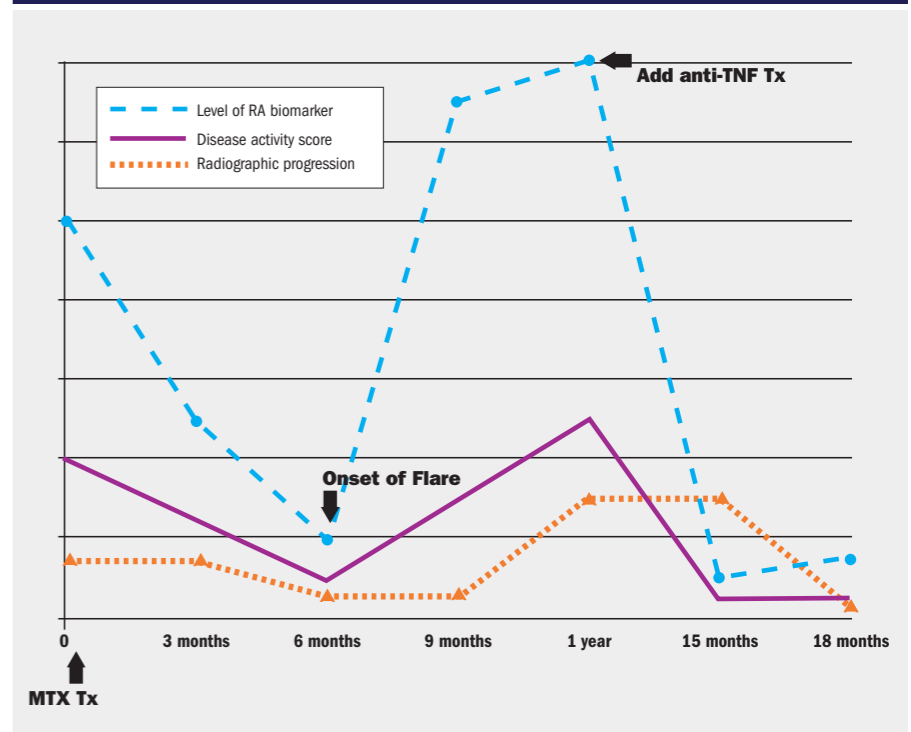
BIOMARKERS IN PERSONALIZED MEDICINE

To be widely adopted in clinical use, biomarker testing must rely on biological samples that are easily obtained from patients and are generally noninvasive, such as blood, urine, and saliva tests. Synovial biopsy, which is used to harvest synovial fluid or small samples of the synovial membrane, is a more elaborate procedure that is unlikely to be an option for most patients.

Biomarkers fall into three categories based upon the information they provide:

- 1 Diagnostic biomarkers** distinguish individuals with active disease from healthy individuals.
- 2 Prognostic biomarkers** stratify patients according to prognosis. In RA, they identify patients at risk for rapid disease progression or early radiologic damage. Prognostic biomarkers are present at disease onset and do not change with treatment.
- 3 Biomarkers of treatment response** detect early and subtle changes in disease activity and are modifiable by effective treatment. Biomarker levels should be very sensitive to spontaneous or treatment-induced changes in disease activity, increasing in response to a disease flare and decreasing in response to effective treatment. The magnitude of change should correspond with other outcomes, such as radiographic progression. Biomarker behavior should be applicable on the population level (for utility in clinical trials) and an individual level (for use in routine practice).

FIGURE 1
Characteristics of an ideal biomarker that can be substituted for radiographic damage in RA.⁶



PROPERTIES OF AN IDEAL BIOMARKER IN RA

Figure 1 illustrates the behavior of an ideal biomarker to be used as a measure of treatment response.⁶ At baseline, all three indicators of disease activity—the disease activity score (DAS), biomarker level, and radiographic progression—are high. After three months of methotrexate treatment, the biomarker levels change in two important ways compared to the other two indicators. First, the biomarker level decreases with greater magnitude than the disease activity score (DAS), making the overall level of improvement easier to detect. Second, the biomarker concentration decreases before radiographic change is apparent, providing an earlier indicator of treatment response. Significant radiographic change does not appear in this example until approximately 6 months of treatment.

At the onset of a disease flare at 6 months, the biomarker changes immediately, again both in greater magnitude than the DAS score and before any radiographic change is detectable. This change, reflecting the rapid worsening of symptoms, initiates rapid introduction of an anti-TNF agent at 1 year. After this treatment adjustment, a similar but reverse pattern is seen; improvement in the biomarker level is more marked than the DAS score and is apparent months before any radiographic improvement.

In this example from the OMERACT group, the activity of the biomarker adds prognostic information about radiographic progression that exceeds the combined information of all other known predictors, such as DAS.⁶

WHY ARE BIOMARKERS SO HARD TO IDENTIFY?

Dozens of potential biomarkers have been identified in RA, yet few are ready for clinical use. Why? There are several issues to note:

- RA is a highly heterogeneous disease, and some biomarkers may play a more pathologically-dominant role in certain patients than in others¹⁰
- Biomarker levels in blood and other body fluids may not reflect levels in the microenvironment of the joint.¹¹ The rate at which various molecules (eg, TNF, IL-6) leak from within the joint to systemic body fluids may vary between patients, or even from joint to joint within the same patient.
- Different biomarkers are associated with different pathologic mechanisms (eg, inflammation vs. cartilage degradation) and may be predominant at different stages of disease progression¹⁰
- While many biomarkers are active in joint destruction or other pathological mechanisms, the concentrations of some biomarkers may not reflect the degree of their contribution¹⁰
- Genetic variations may alter the pathogenic activity of certain biomarkers, causing small concentrations to be highly pathogenic in some patients and large concentrations to be relatively benign in others, thereby clouding our ability to interpret them.¹⁰

CURRENT AND EMERGING BIOMARKERS IN RA

Researchers are scanning untold numbers of molecules, strands of DNA, and other biological options in an effort to identify the ideal biomarker for RA. Several promising markers have been identified to date, including a few that have been used to diagnose and manage RA for decades. Examples of biomarkers from different categories, including genetic markers, autoantibodies, markers of inflammation, markers of joint damage/destruction, and markers of treatment response are summarized in Table 1.

CLASSIFICATION	EXAMPLES
Genetic markers	<ul style="list-style-type: none"> • HLA-DRB-1 • Single nucleotide polymorphisms
Autoantibodies	<ul style="list-style-type: none"> • Rheumatoid factor • Anti-cyclic citrullinated protein antibodies
Markers of inflammation	<ul style="list-style-type: none"> • Acute phase reactants <ul style="list-style-type: none"> – Erythrocyte sedimentation rate (ESR) – C-reactive protein (CRP) • Proinflammatory cytokines <ul style="list-style-type: none"> – Interleukin (IL)-1 – IL-6 – Tumor necrosis factor (TNF) • Inflammatory cells <ul style="list-style-type: none"> – Synovial cells
Markers of joint damage/destruction	<ul style="list-style-type: none"> • Matrix metalloproteinase 1 (MMP-1) and MMP-3 • Tissue inhibitor of metalloproteinase 1 (TIMP-1)
Markers of treatment sensitivity and response	<ul style="list-style-type: none"> • Sensitivity to methotrexate <ul style="list-style-type: none"> – Methotrexate polyglutamates (MTXPGs) • Response to anti-TNF therapy <ul style="list-style-type: none"> – -308G A/G polymorphism • Response to anti-IL-6 therapy <ul style="list-style-type: none"> – -174 C/G polymorphism

GENETIC MARKERS

Genetic markers, which are present at disease onset and do not change during treatment, provide important prognostic information about disease severity. The **human leukocyte antigen (HLA)-DRB1 allele** is the genetic marker most frequently associated with RA, particularly in the research setting. RA is observed with increased prevalence in patients with one of several HLA-DRB1 alleles that encode for the shared epitope (SE). Patients with the SE alleles are more likely to develop anti-CCP antibodies and have a more aggressive and severe form of RA.¹³

Single nucleotide polymorphisms (SNPs) are small sections of DNA that differ between individuals by only one base. SNPs account for approximately 80% of all known polymorphisms, and can be associated with susceptibility to RA, disease severity, and response to treatment. As discussed later, SNPs show promise in predicting treatment response to anti-TNF and anti-IL-6 therapy in RA.

AUTOANTIBODIES

Autoantibodies are a signature feature of autoimmune rheumatic diseases, including RA. Although they do not appear to play a pathogenic role in RA, autoantibodies have become important diagnostic tools and predictors of increased disease severity.

Rheumatoid factor (RF) is a non-specific marker of RA that is present in up to 80% of RA patients and also appears in other rheumatic and chronic inflammatory diseases. The value of RF as a prognostic marker depends on disease stage. The presence of RF is associated with increased levels of disease activity and bone erosion early in the course of RA, but becomes less predictive in later disease stages.¹³

Compared with RF, **anti-cyclic citrullinated peptide (anti-CCP)** antibodies are both more sensitive and more specific for RA, showing better utility as a diagnostic marker. Anti-CCP antibodies are also valuable prognostic markers, as patients with and without anti-CCP antibodies show different natural histories of RA. The presence of anti-CCP antibodies is associated with greater disease activity and faster radiological progression, even with the

OMERACT

CATEGORIZING THE FUTURE OF BIOMARKER USE

Established in 1992, Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) is an international collaboration of clinical and research scientists interested in improving and standardizing outcome measurements in RA. Working groups within OMERACT proceed through an evidence-based process to determine the core clinical domains that constitute a disease, such as RA, psoriatic arthritis, and ankylosing spondylitis. These working groups also develop and validate outcome measures of these domains to use in clinical trials. Some also focus on specific clinical questions, such as the definition of disease flare,⁴ the use of ultrasound in assessing joint damage,⁵ and the role of soluble biomarkers in disease management.⁶ Although OMERACT continues to retain its original name, the group has expanded its interests beyond RA to most other rheumatic diseases. Therefore, the OMERACT acronym is now more broadly considered to stand for “Outcome Measures in Rheumatology.”

In recent years, OMERACT’s soluble biomarker group has developed criteria to help determine whether specific biomarkers can be considered valid markers of structural damage in RA. To be endorsed by OMERACT, a candidate biomarker must successfully pass through the “OMERACT Filter,” a collection of criteria separated into three categories: truth, discrimination, and feasibility.

These categories are designed to answer fundamental questions about biomarker performance:

TRUTH: Does the biomarker truly measure what it intends to measure? Is it clinically relevant?

DISCRIMINATION: Does the biomarker discriminate between healthy and affected individuals? Does it discriminate different levels of disease severity?

FEASIBILITY: Can the biomarker be measured quickly, easily, inexpensively, and in a way that is easy to interpret? Is it practical for use in everyday clinical practice?

The development of biomarker criteria is an ongoing process that continues to evolve as new clinical data becomes available. OMERACT published its preliminary draft criteria following the OMERACT 8 meeting in 2006.⁷ At its next meeting in 2008, the group refined these criteria and published the updated OMERACT 9 draft criteria.⁶ OMERACT 10 recently convened and additional updates are expected to be published later this year.⁸

OMERACT researchers have field-tested the application of biomarker criteria in two case studies. In the first, researchers used the OMERACT 8 draft criteria to test the strength of clinical evidence supporting the use of C-reactive protein (CRP) as a marker of structural damage endpoints in RA.⁷ CRP scored high in some areas, highlighting the simplicity of the CRP assay and the stability of the biomarker both at room temperature and in frozen specimens. However, CRP was deficient in other areas, with available evidence indicating only a moderate correlation between CRP and radiographic progression. Overall, the OMERACT researchers concluded that the evidence was not yet strong enough to support the use of CRP as a valid biomarker for structural damage in RA.⁷

In another case study, researchers applied the OMERACT 8 criteria to five additional candidate biomarkers of structural damage in RA: RANKL, osteoprotegerin (OPG), matrix metalloproteinase (MMP-3), and urine C-telopeptide of types I and II collagen (U-CTX-I and U-CTX-II).⁹ OMERACT researchers concluded that none of these biomarkers showed sufficient evidence to justify their use as a substitute for radiographic changes in the assessment of RA outcomes.⁹

TWO IMPORTANT LESSONS EMERGED FROM THESE CASE STUDIES.

FIRST, it is critical to understand why a particular biomarker received a low score. For example, CRP received a low score on the question of whether “the biomarker demonstrates an independent association with the structural damage endpoint.” Rather than abandoning CRP’s potential as a clinical biomarker, the study authors attributed the low score to the fact that most evaluable studies failed to measure CRP levels across multiple time points, failed to control for potential confounding factors, or had some other design flaw that limited the interpretation of study results.⁷ In the second case study of the five potential biomarkers, researchers also found a range of problems in study design, including low sample size, failure to measure biomarker levels over time, failure to address known confounders, and use of different radiographic endpoints.⁹ These exercises demonstrate the need for robust clinical trial design that allows researchers to definitively evaluate the performance of biomarkers in RA.

SECOND, testing draft criteria against existing clinical data allows researchers to challenge assumptions about the relevance of certain criteria to RA. For example, one of the OMERACT 8 criteria read, “The biomarker has been immunohistochemically localized to joint tissues.” Yet, when examining CRP studies, the OMERACT researchers realized that this criterion is not relevant for CRP.⁷ They were reminded that pathologic events in the joint tissues have systemic consequences—such as increased production of CRP from non-joint tissues—that can reflect activity within the joint. Although CRP has not been identified in joint tissue using immunohistochemistry, it remains useful as an indicator of disease activity. As a result of this exercise, the word “immunohistochemically” was dropped from the OMERACT 9 criteria.⁶ Likewise, in the second case study, researchers realized that the OMERACT 8 criteria of “biomarker metabolism and half-life” had limited utility in judging the performance of a biomarker as a predictor of clinical activity. In the OMERACT 9 criteria set, these parameters were downgraded to “desired but not essential” criteria.⁶

administration of aggressive therapy.¹³ In patients with RA, the presence of anti-CCP antibodies confirms a poorer prognosis and highlights the need for early therapy with biological DMARDs.

MARKERS OF INFLAMMATION

ACUTE PHASE REACTANTS

Acute phase reactants are early markers of inflammation. **Erythrocyte sedimentation rate (ESR)** correlates with disease activity, even in the very early stages of RA. However, ESR fluctuates in response to other factors such as anemia, and therefore lacks specificity for RA. **C-reactive protein (CRP)**, meanwhile, correlates with disease activity, functional disability, radiologic progression, and response to therapy.¹⁴ In the ASPIRE trial, patients with high baseline joint damage and the highest baseline levels of CRP had better responses to a combination of infliximab and methotrexate compared with methotrexate alone.¹⁵

Assays for measuring CRP and ESR are easy to perform and are routinely available, making acute phase reactants the most widely used biomarkers for assessing disease activity in RA.¹² Moreover, as part of the American College of Rheumatology's 20% improvement criteria (ACR20), acute phase reactants have been identified as the most commonly used biomarkers in the assessment of RA treatment response.¹⁶

PROINFLAMMATORY CYTOKINES

In early RA, a characteristic mix of cells and cytokines work together within the inflamed synovium to degrade cartilage and bone. Over time, this destructive activity typically manifests as RA. Ideally, it would be beneficial for rheumatologists to detect wayward cells and cytokines in patients with subclinical RA prior to symptom onset, or even in those who are only at risk for developing the disease.¹⁰

Proinflammatory cytokines such as **tumor necrosis factor (TNF)**, **interleukin 1 (IL-1)**, and **IL-6** have been studied as surrogate markers for disease activity and inflammation in RA.¹² The challenge is discerning a clinically relevant signal from biological background noise associated with

normal physiological variations in cytokine levels. For example, serum IL-6 levels can vary up to 100-fold between individuals, increase with physical exertion, and change depending upon the time of day.¹⁰ However, cytokine profiling performed in aggregate may amplify small individual signals to profile useful prognostic information. In a study that used a protein biochip to analyze serum levels of 12 cytokines, the combined baseline increase of two factors—CRP and epidermal growth factor (EGF)—was predictive of response to etanercept treatment at 3 months.¹⁷

INFLAMMATORY CELLS

Researchers have studied various **synovial cell populations** harvested from joint biopsies in an effort to detect potential biomarkers of early joint damage. Within the heterogeneous cellular infiltrate, promising biomarkers include macrophages, T cell infiltrates, and lymphoid cells.¹⁸ The most consistent marker of disease activity appears to be a certain type of macrophage—sublining CD68+ macrophages—that decrease in number in response to RA treatment.^{19,20} To date, other potential synovial biomarkers have yet to be validated as biomarkers in RA.²¹ However, even if more reliable markers are identified within the synovium, arthroscopic biopsies are regarded as an invasive technique and are unlikely to be used regularly in clinical practice.¹²

Measures of some **peripheral blood cells** can also be used to track inflammatory activity in RA. In one study of patients who were treated with rituximab, post-infusion B cell concentrations correlated with treatment outcome.²² In another study, signs of T cell dysregulation were found in the peripheral blood of patients who appeared to be in clinical remission. Higher levels of inflammatory cytokine-activated T cells significantly predicted relapse within 18 months.²³

MARKERS OF JOINT DAMAGE OR DESTRUCTION

Although inflammatory markers provide important diagnostic and prognostic information in RA, they are not specific for RA disease activity. Instead, biomarkers that

reflect turnover in the synovium, cartilage, and bone may be more useful for monitoring disease activity in patients with RA. Candidate biomarkers include **matrix metalloproteinases (MMP)**, which are enzymes involved in articular cartilage degradation; **urinary carboxyterminal crosslinking telopeptides of type I (CTX-I) and type II (CTX-II) collagen levels**, which are markers of collagen breakdown; and **receptor activator for nuclear factor B ligand (RANKL)**, a marker of bone degradation.¹²

As part of the recent SPECTRA phase II clinical trial, researchers evaluated a panel of 22 biomarkers as potential indicators of disease activity, treatment response, and radiographic progression.¹¹ Among the markers of joint damage, matrix metalloproteinase 1 (MMP-1), MMP-3, and tissue inhibitor of metalloproteinase 1 (TIMP-1) showed the most promise. Both MMP-1 and TIMP-1 were significantly associated with radiographic progression, and early TIMP-1 activity following treatment onset predicted later therapeutic outcome.¹¹

MARKERS OF TREATMENT SENSITIVITY AND RESPONSE

Treatment of newly-diagnosed RA often begins with methotrexate (MTX), followed by the switch to or addition of another DMARD or biologic agent in those who fail MTX monotherapy. As patients progress through treatment options, many will try multiple agents before finding the right combination that adequately controls their RA. Given the costs and potential safety risks associated with multiple courses of ineffective therapy, it would be highly preferable to be able to refer to a treatment algorithm that uses biomarkers of treatment response to assign patients to the type of therapy most likely to promote early disease control. Unfortunately, research on predictors of treatment response in RA is still young so any major breakthroughs appear to be well down the road.

MARKERS OF SENSITIVITY TO MTX

Approximately 30% of patients with RA who begin MTX treatment discontinue its use within 2 years due to side effects or lack



OMERACT's importance to the future of rheumatology

— Philip J. Mease, MD

I have been involved as a member of multiple OMERACT working groups since 2002, working alongside colleagues from around the world to characterize disease states and develop accurate and reliable methods to assess disease severity and clinical outcomes for use in clinical trials and, potentially, daily practice. Currently, I serve as co-chair of the psoriatic arthritis (PsA), single joint assessment, and fibromyalgia working groups. I also sit as a member on a variety of other working groups, including the soluble biomarker group and a group constituted of patients representing various disease states.

Most OMERACT working groups are composed of between 15 and 50 researchers. These groups follow a systematic process that involves a series of discussions (either in person, via teleconference, or over email), a comprehensive literature search, and the development of a paper summarizing the key research questions. After this initial process is complete, groups drill down to determine a core set of domains that they feel characterize the disease stage or subject area in question. For instance, the PsA group I co-chair determined that arthritis, the skin lesions of psoriasis, patient global assessment, function, pain, and quality of life are the core set of domains that should be measured in all clinical trials. A second set of domains, which should be measured at some point during a drug's clinical development program, were also identified.

For some domains that are not well understood (eg, the use of ultrasound in PsA evaluation), a "research" agenda is proposed that allows individual working groups to perform exercises with patients to help develop and validate outcomes measures, indices of disease severity, and composite responder indices such as ACR or DAS measures. Each group presents their progress during biannual, in-person OMERACT meetings.

One of the keys to OMERACT's success lies in the diversity of its working groups. Because, for example, experts in gout or ankylosing spondylitis (AS), as well as patients, may be involved in the discussion

of criteria for vasculitis, it invites a wider perspective that helps correct the sometimes-too-narrow focus of some research consortiums.

The first biomarker working group, the Soluble Biomarker group, had its first meeting at OMERACT 8 in 2006. Experts in rheumatoid arthritis, PsA, and AS all sit on this working group. At its inception, the group performed a series of Delphi exercises (see footnote below for a detailed explanation) to develop the first set of draft criteria that determined what constitutes a valid, reliable, and feasible biomarker. At the conclusion of these exercises, it was determined that the ideal biomarker should have the following features:

- The ability to accurately and independently associate with the structural damage endpoint (eg, evidence of radiographic damage)
- Reproducibility and reliability, taking into account such variables as age, sex, ethnicity, circadian rhythms, body mass index, renal/hepatic function, and fasting/non-fasting state
- Stability at either room temperature or under standardized conditions of refrigeration or freezing, and for long periods of time
- The ability to distinguish between treated and control patients in various stages of disease.

At both OMERACT 8 and 9, the evidence supporting these and other issues were discussed and debated for biomarkers that have been studied for specific rheumatologic diseases, such as CRP, MMP-3, RANKL, OPG, U-CTX-1, and U-CTX-2. There was extensive input considered from attendees outside of the working group, which helped broaden our group's perspective.

The outcomes of our research and subsequent discussion were published in 2007 and 2009—Walter Maksymowych, PhD, and the group's fellow, Silje W. Syversen, served as the lead authors of these papers.^{1,3} Our group's next phase of activity will involve collecting blood samples and obtaining radiographs on clinically well-characterized RA, PsA, and AS patients observed over time in order to determine the performance characteristics of biomarkers that are either currently available or emerging.

Although OMERACT's methodology may seem tedious and arcane, the Soluble Biomarker working group is setting an important foundation to help advance the field of biomarker science in rheumatology. The group's work sets standards for both academic centers and companies to follow to help assure that biomarkers developed for clinical decision making in the future will be valid, reliable, discriminatory, and feasible. While still uncertain, the hope is that biomarkers prove to be useful predictors of disease severity and prognosis, guiding therapeutic decision-making and monitoring in order to achieve disease remission or a low state of disease.

Biomarkers may also play an important role in personalizing treatment, helping us tailor appropriate therapy for individual patients based upon their genetic profiles, demographic characteristics, disease severity, risk for progression, and risk for developing treatment-related side effects. At a personal level, OMERACT has made me look more critically at how I evaluate patients and make therapeutic decisions, a criticality that hopefully is valued by rheumatologists in general when thinking about patient diagnosis, treatment, and monitoring.

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FOOTNOTE

* A Delphi exercise is one in which experts are given a number of points to distribute between sets of choices, anonymously, and over the course of several rounds that includes group feedback, relative consensus is developed.

of efficacy.²⁴ As a prodrug, MTX requires enzymatic conversion to MTX polyglutamates (MTXPGs) to exert antiinflammatory activity within the joints. However, several SNPs involved in MTX absorption and metabolism have the potential to interfere with the therapeutic effect of MTX.²⁵ One commercially-available assay measures MTXPG metabolites to determine whether partial or nonresponders to MTX might benefit from continued dose escalation or require a change in therapy.²⁶

MARKERS OF RESPONSE TO TNF INHIBITORS

Five anti-TNF agents are currently available for the treatment of RA—infliximab, adalimumab, etanercept, golimumab, and certolizumab pegol. Large-scale studies evaluating treatment response to TNF inhibition are only available for infliximab, adalimumab, and etanercept.

Although the therapeutic utility of TNF blockade is well established, approximately one-third of patients with RA have minimal or no response to anti-TNF therapy.^{27,28}

Potential markers of treatment response may include SNPs in genes known to be involved in RA pathogenesis, genes encoding TNF receptors, or genes implicated in TNF metabolism. The –308G A/G polymorphism has emerged as a significant predictor of response to anti-TNF treatment. In a meta-analysis of 311 patients with RA, those who carried the A allele had a poorer response to anti-TNF therapy than those with the G allele.²⁹ In a study of patients treated with infliximab, those with the GG genotype were twice as likely to respond to treatment as those with the AG or AA genotype.³⁰ The predictive value of the –308G A/G polymorphism has also been validated in trials of etanercept and adalimumab^{31,32}

MARKERS OF RESPONSE TO ANTI-IL-6 THERAPY

Approximately one-third of patients do not respond to treatment with tocilizumab, a humanized anti-IL-6 receptor monoclonal antibody, suggesting the presence of a distinct subset of nonresponders.³³ SNPs for IL-6 influence the amount of IL-6 produced in response to various conditions and may influence the potential for response to anti-IL-6 therapy. For example, the -174 C/G polymorphism of the IL-6 gene significantly influences the amount of IL-6 produced in response to IL-1 and other inflammatory stimuli. The C allele, which is present in approximately 40% of individuals, is associated with significantly lower levels of plasma IL-6.³⁴ In patients with unusually low IL-6 concentrations, an IL-6 inhibitor may have little therapeutic benefit. An assay for the -174 C/G polymorphism may help to identify candidates who are more likely to benefit from anti-IL-6 therapy.³⁵

A number of research studies have focused on identifying markers of MTX efficacy or toxicity. Some data has been published that supports the clinical utility of measuring MTX red blood cell polyglutamates to optimize MTX's treatment effect in RA.^{38,39} However, the data are conflicting regarding the accuracy of this test,⁴⁰ and there are limited longitudinal data and data on different racial/ethnic groups are not yet available.

Was an MRI an appropriate test in this patient? How can you use the information you received as a result of it?

There is little doubt that conventional radiography is not a highly sensitive means of identifying early erosions in RA, which is partially why both ultrasonography and MRIs of small joints have increased in popularity. Bone marrow edema is a common finding in RA, and several studies suggest that bone edema predicts progression of joint damage and decreases in response to anti-tumor necrosis factor therapy.^{41,42} Bone edema may also be seen in patients with osteoarthritis, where it has been associated with joint pain as well as radiographic progression.⁴³ In addition, bone edema may be present in conjunction with a number of other conditions, such as following trauma or after heavy manual labor is performed. It should also be noted that what appear to be erosions may be seen in normal individuals, so these findings must be carefully interpreted in the clinical context.⁴⁴ Because of the high cost of adequate resolution MRIs, additional studies on the cost-effectiveness of screening RA patients with MRIs vs. normal conventional radiographs are needed.

CASE STUDY

Daniel E. Furst, MD, and
S. Louis Bridges Jr., MD, PhD

“Erinn” is a 28-year-old woman who awoke nine months ago with pain in her right knee. A month later, she reports to your office and says that the pain has spread to the other knee, both wrists, and scattered distal IP joints. She also says that she has noticed swelling of her proximal IP joints, as well as in her right knee. She has approximately 45 minutes of daily morning stiffness and becomes fatigued after about eight hours.

SOCIAL HISTORY: Legal secretary and single mother of a 9-year-old girl. Smokes half a pack of cigarettes daily and drinks 1-3 glasses of wine on a weekly basis. She is not physically active.

FAMILY HISTORY: Grandmother had arthritis that was thought to be “rheumatoid arthritis”

REVIEW OF SYSTEMS: Positive for recurrent sinusitis and “upset stomach”

PHYSICAL EXAM: Normal vital signs. Tender joint count of 8 (both knees, both wrists, third right and second left metacarpophalangeal MCPs, and bilateral third PIPs), swollen joint count of 4 (right knee, left wrist, bilateral second MCPs). No nodules or deformities present.

LABORATORY RESULTS: WBC=4.6, normal diff; creatinine=0.6; albumin=3.8; ALT=32; rheumatoid factor IgM=46 (NL<24); ESR=26.

What does the presence of a positive rheumatoid factor (RF) signify in this patient?

The presence of serum RF is consistent with rheumatoid arthritis (RA), although this test is not specific as it may be found in patients with chronic infections such as hepatitis C, tuberculosis, and endocarditis, as well as other rheumatic diseases. It is well established that RA patients with elevated levels of serum RF develop more severe disease radiographically and have more extra-articular manifestations than RA patients without serum RF.³⁶ The presence of anti-CCP antibody would, in this case, increase confidence in the diagnosis of RA, as this antibody is relatively specific for RA. Its absence, however, does not rule out the presence of RA.

The patient was started on ibuprofen 800 mg TID, omeprazole 20 mg QD, and methotrexate, escalating up to 20 mg weekly. Three months later, the patient reports back to your office for additional follow-up. Her tender joint count is 10 and swollen joint count is 6. ESR is 30 and anti-CCP antibody is positive.

You decide to perform hand radiographs – which come back negative for findings associated with RA – as well as an MRI of the second and third MCPs and PIPs on the right hand. Bone marrow edema is seen at the base of second MCP while early erosion is noted in the third PIP.

Based upon these findings, what strategies might you be able to employ to determine whether or not the patient's dose of methotrexate (MTX) should be changed?

Activity Learning Assessment Request for Credit and Evaluation Form

ACTIVITY INSTRUCTIONS & CRITERIA FOR SUCCESS

AMA PRA Category 1 Credit(s)TM are offered to physician activity participants. To successfully complete this activity and obtain a certificate of credits awarded, the learner is required to read the entire newsletter, complete the post-test learning assessment, and complete the activity evaluation form. Learners are required to correctly answer 75% of the post-test questions. Certificates of credit will be forwarded via email within 4 to 6 weeks of your submission. All forms must be received by May 31, 2011, to be eligible for CME credits.

1. Please fax both sides of this evaluation to ICHE at (215) 592-9085, *OR*
2. Please complete the evaluation online by going to www.iche.edu/personalizedmedicine2010

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ACTIVITY POST-TEST QUESTIONS *Please circle the letter that matches the correct response to each question below*

1. Biomarker XYZ is indicated to be used at the onset of diagnosis of rheumatoid arthritis (RA) to help identify those patients who are at highest risk of rapid disease progression. Consequently, biomarker XYZ would be classified as which of the following?
 - a. Diagnostic biomarker
 - b. Prognostic biomarker
 - c. Biomarker of treatment response
 - d. Biomarker of exposure
2. In comparison to current methods to measure RA treatment response, an ideal biomarker in RA possesses which of the following qualities?
 - a. Its levels increase/decrease with a similar magnitude to current, validated methods
 - b. Its activity adds prognostic information on par with information that may be gathered via radiographic change
 - c. Its levels increase/decrease before changes with current methods are apparent
 - d. All of the above
3. To date, how many biomarkers have OMERACT researchers found to be suitable substitutes for radiographic changes to assess RA outcomes?
 - a. None
 - b. One
 - c. Two
 - d. Three
4. Which of the following are common hurdles to the introduction of new biomarkers in RA?
 - a. Biomarker levels in the blood may inappropriately reflect true levels in the microenvironment of the joint
 - b. Genetic variations can alter the pathogenic activity of some biomarkers, thereby clouding the ability to interpret them
 - c. Because RA is a highly heterogeneous disease, some biomarkers are more pathologically-dominant in some patients than others
 - d. All of the above
5. C-reactive protein, IL-6, and TNF are all examples of which class of biomarkers?
 - a. Autoantibodies
 - b. Markers of joint damage/destruction
 - c. Markers of treatment response
 - d. Markers of inflammation
6. In the SPECTRA trial, which of the 22 biomarkers tested showed the most promise as potential indicators of disease activity, treatment response, and radiographic progression?
 - a. VEGF, E-selectin, and TGF β
 - b. MMP-1, MMP-3, and TIMP-1
 - c. IL-1α, IL-1β, and Factor VIII
 - d. CD4, CD8, and CD68
7. Which of the following statements about single nucleotide polymorphisms (SNPs) is **not** true?
 - a. SNPs are small sections of RNA that differ between individuals by at least two bases
 - b. SNPs show promise in predicting treatment response to anti-TNF and anti-IL-6 therapy in RA
 - c. SNPs can be associated with susceptibility to RA, disease severity, and response to treatment
 - d. SNPs account for approximately 80% of all known polymorphisms
8. According to a report from OMERACT's Soluble Biomarker Group, an ideal biomarker in RA should have which of the following characteristics?
 - a. A cost-effective nature that makes it likely to be reimbursed by insurance companies
 - b. Limited stability at room temperature (eg, less than a week), ensuring its quick use upon receipt by a rheumatologist
 - c. The ability to accurately and independently associate with the structural damage endpoint (eg, evidence of radiographic damage)
 - d. Applicability that is specific to the use of only one agent used to treat RA

The learning objectives designed for this activity (listed below) can help me strive toward:	Nothing at this time	Reinforcement of current practices	Moderate Improvement	Significant Improvement
List three reasons driving research into the introduction of personalized medicine for the diagnosis, management, and treatment of rheumatoid arthritis (RA)	1	2	3	4
Assess the importance of OMERACT and the applicability of its research initiatives to your current and future practice	1	2	3	4
Compare the value of currently-validated biomarkers such as anti-CCP and CRP in the overall diagnostic and treatment process for RA	1	2	3	4
Identify at least two biomarkers of treatment response in RA currently under investigation	1	2	3	4

Please indicate the extent of your agreement with the following statements:	Strongly Disagree	Not Sure	Strongly Agree			
1. The information presented in this newsletter was pertinent to my professional needs	1	2	3	4	5	6
2. The content of this newsletter contributes valuable information that will assist me in improving patient outcomes	1	2	3	4	5	6
3. Based on my experience, I would recommend future newsletters to my colleagues	1	2	3	4	5	6
4. Were you able to locate information about faculty disclosure at the beginning of the newsletter?	YES			NO		
5. Did you perceive any bias or commercial influence in the newsletter? If so, your help in identifying it is appreciated: _____	YES			NO		

6. Prior to reading this newsletter, how familiar were you with the work being done by the OMERACT group?

- a. I had never heard of them
- b. I was generally familiar with their work, but I didn't really pay close attention to it
- c. I have closely followed the work the group has been doing

7. Which of the following would you consider to be the most significant barrier to the introduction of biomarker assays and genetic tests into your current practice?

- a. Lack of proven applicability of results
- b. Insufficient knowledge about the tests themselves
- c. Reimbursement issues
- d. Concerns about the confidentiality of test results

8. The following is the primary barrier to implementing change at my facility:

- a. Lack of knowledge regarding evidence-based strategies
- b. Misperceptions of or negative attitudes about research and evidence-based care
- c. Demanding patient workloads
- d. Fears about practicing differently from peers

9. Based upon this activity, what changes, if any, do you intend to make in your clinical practice? _____

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SUMMARY

Rheumatologists have been using biomarkers in their daily clinical practice for years, and have seen RF and anti-CCP antibodies become cornerstones of current diagnostic and prognostic procedures in RA. In addition, acute phase reactants, particularly CRP, have been shown to be reliable markers of disease activity and radiographic progression. Despite the utility of these markers, new research in personalized medicine promises a more refined approach to the current diagnosis, risk assessment, and treatment of patients with RA. Ongoing efforts by the OMERACT soluble biomarker special interest group will ensure that new biomarkers meet stringent criteria before being adopted for widespread clinical use. With the availability of new biomarkers, rheumatologists may soon be able to select a course of RA treatment based on a patient's clinical and genetic characteristics, and thereby provide treatment options that are most likely to result in good clinical outcomes.

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