When It Comes to RA, Hit It Hard and Early

Drug combinations should be used, since the 'data show we undertreat' RA.

BY SALLY KOCH KUBETIN

SANTA MONICA, CALIF. — The treatment of rheumatoid arthritis has undergone a sea change, word of which has not reached beyond rheumatology in many cases.

Primary among the new rules of RA care is the admonition to use the best drug first and that "overtreatment" is good. Physicians should move more quickly to using combinations of agents, because the "data show we undertreat," said Dr. John J. Cush, director of clinical rheumatology for the Baylor Research Institute and professor of medicine and rheumatology at Baylor University Medical Center at Dallas.

In addition to the aggressive use of disease-modifying antirheumatic drugs (DMARDs), optimal treatment of RA requires that physicians seize the opportunity to diagnose and manage cases of early disease. Many measures can be adopted to help achieve this goal, but Dr. Cush advocates the "promotion of practice policies to facilitate referral and [ensure] that every patient seeking an appointment for joint pain should be seen within 2 weeks or sooner."

The integration of disease activity metrics can enhance outcomes by guiding treatment changes to achieve a specific goal. "Use of metrics yields a fourfold increase in remission rates," Dr. Cush said at a meeting sponsored by RHEUMATOLOGY NEWS and Skin Disease Education Foundation.

There continues to be room for improvement in rheumatoid arthritis therapy. Remission is not common.

DR. CUSH

Word of the negative impact of comorbidities in RA has not spread far beyond rheumatology to primary care specialties. Given the cardiovascular disease (CVD) risks alone, physicians need to treat comorbidities in this population, he said.

RA patients develop CVD 10 years earlier than their unaffected peers, they have twice the malignancy rate of the general population, their rate of serious infection is six to nine times that of the general population, and their risk for both pulmonary disease and gastrointestinal bleeding is elevated. As a result, the life expectancy of RA patients is shorter than that of their age-matched peers (10 years shorter for women and 4 years shorter for men).

Data from the Mayo Clinic in Rochester, Minn., show that survival has improved significantly over the past decade. Research presented at the 2009 annual meeting of the American College of Rheumatology, but not yet published, indicated that survival was 70.7% among 147 RA patients who were followed in 1955-1994. In 1995-2007, survival increased to 79.5% in a group of 463 RA patients. Both patient groups were from the Olmsted County, Minn., cohort.

Earlier diagnosis and the use of methotrexate and biologic DMARDs may have contributed to this finding, Dr. Cush said.

Although many rheumatologists are enamored with the potential benefits of new biologics, they should remain resolute in their use of methotrexate, according to Dr. Cush. Findings from a recent meta-analysis suggest that the optimal methotrexate dosage may be achieved by starting at 15 mg/week orally, then escalating by 5 mg/month to a maximum dosage of 25-30 mg/week or the highest tolerable dose. In cases of insufficient response, the route of administration can be switched from oral to subcutaneous administration (Ann. Rheum. Dis. 2009;68:1094-9).

Several studies have compared methotrexate vs. tumor necrosis factor inhibitors with regard to efficacy and x-ray–protective effects. Methotrexate appears to be as potent as TNF inhibitors in terms of clinical outcomes. When x-ray outcomes are analyzed, however, the biologic has a margin of benefit over methotrexate that becomes more pronounced when the TNF inhibitor is combined with methotrexate.

Other data have documented the cost-effectiveness of therapy in early RA. Very early DMARD therapy is cost effective in reducing RA progression, but the cost-effectiveness of early biologics remains uncertain (Ann. Intern. Med. 2009;151:612-21).

If methotrexate monotherapy does not produce enough benefit, the recommended course is to add a biologic DMARD, usually a TNF inhibitor. The top five indications for the use of a TNF blocker in rheumatology are failure of methotrexate monotherapy, failure of multiple DMARDs, physician assessment of activity, presence of erosions on x-rays, and functional disability.

There is room for improvement in the treatment of RA. Remission is not common, Dr. Cush noted. ■

__Disclosures:__ Dr. Cush reported being a clinical adviser, investigator, or consultant for numerous pharmaceutical companies. SDEF, Rheumatology News, and this newspaper are owned by Elsevier.

RA Progression Hinges on Genetics, Lifestyle, Sex, Severity

BY SALLY KOCH KUBETIN

SANTA MONICA, CALIF. — Progression of early rheumatoid arthritis is likely in any woman who smokes, has active disease at the time of presentation, and is positive for both rheumatoid factor and anti–cyclic citrullinated peptide antibodies.

Gender and clinical disease activity are the most common risk factors for progression of rheumatoid arthritis (RA), and rheumatoid factor and anti–cyclic citrullinated peptide (anti-CCP) antibodies are the tests used most frequently to assess the likelihood of such progression. Other genetic tests that offer information about progression risk, such as that for HLA-DRB1, are not widely used. And yet other tests for genetic determinants of treatment response and the likelihood of treatment-related adverse events show promise but remain largely in the realm of research, said Dr. Daniel E. Furst, who is the Carl M. Pearson Professor of Rheumatology at the University of California, Los Angeles.

No single marker can absolutely predict disease progression, at least in part because RA is probably more than one disease, dependent on the presence or absence of anti-CCP antibodies. Anti-CCP antibodies are the result of a genetic predisposition and a systemic stress, such as smoking. However, Dr. Furst pointed out that even among all anti-CCP antibody–positive people, the course of RA may vary because of the effects of environmental stimuli, immune events, and interventions (Annu. Rev. Immunol. 2008;26:651-75).

Citrullination is present in a wide range of inflammatory tissues, suggesting that this process is a nonspecific response to inflammation, rather than a disease-specific response, Dr. Furst noted at a meeting sponsored by RHEUMATOLOGY NEWS and Skin Disease Education Foundation. It is present in inflamed tonsil tissue and can be found in tissue of patients with inflammatory bowel disease, he added. Anti-CCP antibodies are more likely to be elevated in patients who both have the susceptibility epitope and smoke.

Subset analyses of data from the PROMPT (Probable Rheumatoid Arthritis: Methotrexate vs. Placebo Treatment) study, presented by Dr. Henrike Van Dongen of Leiden (the Netherlands) University Medical Center at the 2006 congress of the European League Against Rheumatism (EULAR), demonstrated that the presence of anti-CCP determined response to methotrexate. Responses at 15 months after diagnosis in a group of 27 anti-CCP antibody–positive patients were below 10% in those on placebo, but were close to 50% in those on methotrexate. There was no treatment effect in a group of 83 anti-CCP–negative patients (Arthritis Rheum. 2007;56:1424).

The HLA-DRB1 gene is associated with extra-articular manifestations of RA and the development of Felty's syndrome. That syndrome occurs in fewer than 1% of RA patients and is considered to be a complication of long-standing disease. It involves a triad of conditions: RA, splenomegaly, and an abnormally low white blood count. Findings from an unpublished study show that Felty's syndrome was associated with HLA-DRB1.0401. Other extra-articular manifestations of RA (such as pericarditis, vasculitis, interstitial lung disease, and neurologic involvement) were seen not with individual alleles, but with DRB1.04SE double-dose genotypes.

Findings from many other studies show that multiple single nucleotide polymorphisms (SNPs) of the PTPN22 gene have a significant association with RA, as does TRAF1-C5 (on chromosome 9).

Smoking and anti-CCP antibody status seem to be associated in RA, but PTPN22 is an independent risk factor for developing RA, according to Dr. Furst. Although not yet directly applicable to clinical care, attempts are being made to predict response to RA medications using genetic signatures or gene SNPs.

For example, 37 RA patients with the G/G polymorphism of the TNF promoter gene has been shown to have good response as measured by changes in DAS-28 to TNF antagonists. The same response was not seen in 3 RA patients with the A/A polymorphism or 14 RA patients with the A/G polymorphism. The same benefit of the G/A polymorphism on treatment response has been shown in patients with ankylosing spondylitis and psoriatic arthritis, according to Dr. Furst (Rheumatology 2007;46:93-96).

"We can't send off to [a commercial testing laboratory] to do this test at the moment. But I believe it is coming down the pike," he noted.

For now, other factors are more practical predictors of good response. For example, low disease activity and few bony erosions at the beginning of TNF inhibitor therapy imply that early TNF use may be appropriate. When to change TNF inhibitors and whether to try another TNF blocker are practical questions that have been tested. It appears that if a patient has no response to two TNF blockers, a third TNF blocker is unlikely to be helpful and it is time to try a drug with a different mechanism of action.

Dr. Furst reported financial relationships with numerous pharmaceutical companies and the National Institutes of Health.

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