Real-World Anti-TNF Therapy Benefits Seen in AS

BY NANCY WALSH
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LIVERPOOL, ENGLAND — The majority of patients with ankylosing spondylitis being treated with anti-tumor necrosis factor agents in a routine care setting experienced improvements in disease activity after 6 months of treatment, according to Dr. Paul A. Lord of the University of Manchester (England).

Clinical trials have demonstrated the efficacy of these biologic drugs in ankylosing spondylitis (AS), but few data exist regarding the effectiveness in a real world setting.

Accordingly, the British Society for Rheumatology's Biologics Register began recruiting AS patients in 2002, recording baseline demographics, disease duration, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) scores, as well as current and former drug treatments.

A total of 572 patients have been recruited, and data have now been analyzed for 261, with the primary outcome being changes in BASDAI and BASFI scores at 6 months.

The patients were predominantly young, with a median age of 43 years, and 81% were male. The median baseline BASDAI score was 7.6 and the median baseline BASFI score was 7.9. "They had severe disease," Dr. Lord said at the annual meeting of the British Society for Rheumatology.

At 6 months, mean improvements of 3.5 and 2.7 U, respectively, were seen on BASDAI and BASFI. Additionally, 71% had improvements on BASDAI of at least 2 U, and 52% achieved a BASDAI 50 response, which represents a major clinical response, he said.

The first TNF blocker given was etanercept in 57%, infliximab in 36%, and adalimumab in 7%. Conventional disease-modifying antirheumatic drugs (DMARDs) also were being used by 54% and 55% of those on infliximab and adalimumab, respectively, compared with 37% of those on etanercept.

Lesser responses were seen in those with higher baseline BASFI scores, and women had a 1-U greater improvement on BASFI at 6 months compared with men.

Concurrent use of DMARDs was associated with improved functional status, demonstrated by a 0.8-U greater improvement on BASFI compared with those on monotherapy, but was not associated with absolute change in BASDAI.

Patients whose inflammatory markers were elevated at baseline had a 0.9-U greater response than those whose ESR and CRP level were normal at baseline, suggesting that these patients may be more responsive to anti-TNF therapy, Dr. Lord said.

Although the patients with baseline inflammatory markers had a better response to anti-TNF therapy, the benefits were not confined to this group, he noted.

Dr. Lord and his colleagues from the biologics register have reported no conflicts of interest. ■

JOINT VENTURES

The Pathogenesis of Rheumatoid Arthritis: A New Model

Our conceptualization of rheumatoid arthritis assumes the disease develops in the context of a genetic predisposition and in the presence of certain environmental factors, with interactions between genes and environment leading to immune reactivity and clinical disease. RA is heterogeneous both clinically and etiologically, with two distinct subsets defined by the presence or absence of anticitrulline antibodies.

BY LARS KLARESKOG, M.D., PH.D.

From RF to CCP

RA is a criteria-defined, versus etiology-defined, disease, with one criterion being the presence of rheumatoid factor (RF), first recognized nearly seven decades ago. Although RF is present in 80% of patients, it is not specific. It also can be detected in up to 15% of healthy elderly people.

Citrullination is a posttranslational enzymatic process mediated by calcium-dependent peptidyl arginine deiminases in which positively charged protein arginine residues are converted to neutral citrullines, rendering the proteins more subject to degradation by proteolytic enzymes. In RA, increased citrullination is seen in the joints, lungs, and sites of extra-articular involvement as well as in many synovial proteins like fibrinogen, vimentin, and type II collagen. In normal synovial tissue, there is no expression of citrullinated molecules.

Increased citrullination as a manifestation of human disease was first identified in the lining and sublining layers of RA synovial tissue.

It had previously been shown that antibodies to cyclic citrullinated proteins (anti-CCP) are present in about 60% of RA patients, versus 2% of healthy controls and fewer than 10% of patients with other rheumatic diseases.

Citrullination is a common event in many physiologic processes, but antibodies in RA have preferential reactivity to proteins that have undergone posttranslational citrullination.

Further studies have shown anti-CCP antibodies are not only predictive of RA but also have been directly implicated in pathogenesis. Animal data suggest citrullination can alter the immunogenicity of "self" antigens. This is in contrast to RF, which does not seem to be directly proarthritogenic.

Blood repository data from Sweden and the Netherlands found that anti-CCP antibodies can be detected years before symptom onset; they increase in concentration as clinical disease approaches, and thereafter rarely disappear, even with treatment. Patients who are anti-CCP positive typically have a more severe disease course than do anti-CCP–negative patients, with a greater likelihood of erosive disease.

Genetics and Environment

Patients with anti-CCP also are genetically distinct from those who are anti-CCP negative. Their disease is linked to the presence of major histocompatibility complex class II alleles, and in particular the HLA-DRB1 shared epitope—genes that are strongly associated with the adaptive immune system and B- and T-cell activation. A polymorphism in the PTPN22 gene also is associated with anti-CCP–positive disease, while genetic risk factors among anti-CCP–negative patients include variations in the interferon regulating factor 5 and polymorphisms in the C-type lectin complex, genes not tied to B- and T-cell responses.

The primary environmental risk factor for RA is cigarette smoking. This association initially was identified in epidemiologic studies, and formerly was considered to be only a nonspecific risk factor. Research determined that this linkage was exclusively seen in RF-positive patients but found no plausible biologic mechanism for this association. Now, we have demonstrated that smoking directly affects citrulline immunity, and specifically in a limited genetic context of HLA-DRB1 positivity.

In a population-based case-control study that included 930 patients aged 18-70 years with newly diagnosed RA and 1,126 matched controls, we found a dose-dependent relationship between number of smoking pack-years and elevations in anticitrulline antibody levels at diagnosis. We also identified a 21-fold higher relative risk for the development of these autoantibodies among smokers carrying two copies of the HLA-DRB1 shared epitope alleles, compared with nonsmokers lacking these genes. No increased risk was seen for smoking in the development of anti-CCP–negative RA.

Further investigations involved analysis of bronchoalveolar fluid from the lungs of healthy smokers, revealing the presence of citrullinated proteins as well as increased expression of the enzymes responsible for citrullination.

We proposed that long-term exposure to cigarette smoke might be a primary triggering event for RA, inducing the presentation of citrullinated autoantigens in the lungs. This would lead to a pathologic inflammatory response, with an influx of cells like macrophages into the pulmonary compartment, where they are activated by toxins in smoke and undergo apoptosis. In genetically predisposed persons, the presence of citrullinated peptides then can activate autoreactive T and B cells. Further steps could then involve antibodies to citrullinated proteins being produced and recruited from the circulation and the formation of immune complexes, which then bind to complement and Fc receptors. Ultimately, proinflammatory cytokines are recruited to the joint (Annu. Rev. Immunol. 2008;26:651-75).

We concluded, "With these findings taken together, an etiologic hypothesis can thus be formulated that involves genes, environment, and immunity to self molecules made immunogenic (and possibly arthritogenic) through posttranslational modifications induced by the environmental agent" (Arthritis Rheum. 2006;54:38-46).

Key Points

► Two distinct subtypes of RA exist, characterized by the presence or absence of antibodies to citrullinated proteins.
► These antibodies not only are specific markers of RA but also appear to be directly linked to disease pathogenesis.
► Only antibody-positive RA is linked with the major susceptibility genes HLA-DRB1 and PTPN22.
► Cigarette smoking might be a triggering event for the development of anticitrulline immunity in those patients who are genetically predisposed.

Future Research

Because anti-CCP antibodies can be present for many years before disease develops, we postulate that there is a need for a second event such as trauma or viral infection that causes transient inflammation and expression of citrullinated proteins in the joints. This remains to be proven, along with a number of other aspects of the process of citrullination.

For example, we have not yet identified exactly which molecules are the targets of immune events in the lungs, nor do we know whether these immune events can be triggered elsewhere than the lungs or why it is that joints are targeted by these immune reactions. However, the framework we have developed should permit further studies on the role of adaptive immunity and the interaction between genes and environment in this subset of rheumatoid arthritis. ■

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