Journal Scan

Rheumatology

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The following four articles on the topic of anti-cyclic citrullinated peptide antibodies and the timely diagnosis of rheumatoid arthritis are presented as a group.

Context: The progression of rheumatoid arthritis can be slowed by disease modifying antirheumatic drugs (DMARDs). Accordingly, it is important to identify cases of early synovitis syndromes (< 1 year duration) which have the potential to progress to erosive rheumatoid arthritis. Traditional approaches to diagnosis, including the American College of Rheumatology 1987 classification criteria for RA and measurement of rheumatoid factor, do not perform well in evaluating undifferentiated early synovitis syndromes. The discovery of antibodies to citrullinated peptides has provided a new serologic tool for identification of patients who should be referred early to a rheumatologist for treatment.

Citrullination refers to the process in which a terminal nitrogen atom in an arginine molecule on a protein chain is replaced by oxygen, thereby creating the amino acid

citrulline. Citrullination occurs in the normal apoptosis of cells, but environmental factors, such as cigarette smoking, may stimulate it. The process is controlled by an enzyme peptidylarginine deiminase (PAD), of which specific haplotypes have been associated with rheumatoid arthritis. The development of an immune response to citrulline, namely anti-cyclic citrullinated peptide (anti-CCP) antibodies, is thought to be a critical step in the pathogenesis of rheumatoid arthritis. Anti-CCP antibodies are detectable months to years before the onset of clinical disease, and their detection provides an opportunity to identify rheumatoid arthritis at a stage where treatment will have the greatest impact.

A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)—restricted immune reactions to autoantigens modified by citrullination. Klareskog L, Stolt, P, Lundberg K, Källberg H, Bengtsson C, Grunewald J, Rönnelid J, Harris HE, Ulfgren AK, Rantapää-Dahlqvist S, Eklund A, Padyukov L, Alfredsson L. *Arthritis Rheum.* 2006;54: 38–46.

Study Design and Results: This was a case control study of patients with recent-onset rheumatoid arthritis (disease duration < 12 months), with control subjects taken from the same geographic areas in Sweden. Investigators evaluated the hypothesis that the environmental risk factor of cigarette smoking influences the production of anti-CCP antibodies and interacts with the genetic risk factor of the HLA-DR “shared epitope” (SE). In addition, patients had bronchoscopic evaluation for citrullinated proteins in bronchoalveolar lavage cells. Results showed that there is a dose-dependent association of smoking and the presence of anti-CCP antibodies in patients with rheumatoid arthritis. In addition there is an interaction

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between smoking and double copies of the HLA-DR SE genes leading to a 21-fold increased risk for RA compared with nonsmokers without SE genes. In CCP negative RA, these risk factors were not present. The BAL results revealed citrullinated proteins staining cells in smokers but not in nonsmokers.

Conclusions: This is an important study revealing the interaction of an environmental risk factor, namely smoking exposure, with the underlying genetic substrate for rheumatoid arthritis leading to the production of anti-CCP antibodies. Furthermore, the results show that the clinical illness of rheumatoid arthritis is likely a spectrum of diseases with differing environmental and genetic risk factors.

Interaction between smoking, the shared epitope, and anti-cyclic citrullinated peptide. Lee HS, Irigoyen P, Kern M, Lee A, Batliwalla F, Khalili H, Wolfe F, Lum RF, Massarotti E, Weisman M, Bombardier C, Karlson EW, Criswell LA, Vlietinck R, Gregersen PK. *Arthritis Rheum.* 2007;56:1745–1753.

Study Design and Results: This is a case analysis of 2476 North American patients with RA from three research cohorts evaluating the association of smoking, anti-CCP antibodies, and HLA-DR shared epitope alleles. Although an association between the presence of anti-CCP antibodies and the shared epitope alleles was confirmed, only weak evidence between smoking and CCP antibody formation was found in one cohort.

Conclusions: The authors hypothesize that other environmental factors such as air pollution may have a greater influence in North American patients, masking a measurable impact of tobacco.

The role of anti-cyclic citrullinated peptide antibodies in predicting progression of palindromic rheumatism to rheumatoid arthritis. Russell AS, Devani AL, Maksymowych WP. *J Rheumatol.* 2006;33:1240–1242.

Study Design and Results: This is a retrospective cohort design evaluating the presence of anti-CCP antibodies in patients followed at one Canadian center with palindromic rheumatism. (A palindrome is a word or phrase that reads the same in both directions: “Madam, I’m Adam” and “mom” are examples. So-called “palindromic rheumatism” follows a symmetric course of flare up and recession—episodic attacks of synovitis last 1 to 3 days, ending as rapidly as they began.) Testing was performed on serum stored at the first evaluation or within 1 year of initial presentation. After a mean followup of 5.4 years, 83% of the patients who were CCP positive had persistent rheumatoid arthritis. The positive predictive value of the CCP antibody was 71 compared with 60 for a positive rheumatoid factor. The presence of both antibodies increased the PPV to 81.

The performance of anti-cyclic citrullinated peptide antibodies in predicting the severity of radiographic damage in inflammatory polyarthritis. Bukhari M, Thomson W, Naseem H, Bunn D, Silman A, Symmons D, Barton A. *Arthritis Rheum.* 2007;56:2929–2935.

Study Design and Results: Valuable observations regarding the natural history of early inflammatory arthritis syndromes (two or more swollen joints present for at least 4 weeks) have come from the Norfolk Arthritis Register population of community-based primary care patients in the UK. Previous studies from this group confirmed the utility of rheumatoid factor in predicting the risk of progressive erosive arthritis in patients with early arthritis. Now the group presents comparative longitudinal observations over 5 years comparing the value of the rheumatoid factor versus CCP antibody detection. The CCP antibody was found to be a better predictor of erosive disease at presentation and at 5 years followup than the rheumatoid factor. The group of patients in whom CCP antibody detection had the greatest value was in those with rheumatoid factor negative arthritis. The authors emphasize the CCP antibody status by itself should not determine treatment decisions, as some patients with a negative assay do have erosive disease develop with time.

Conclusions: These studies of very early inflammatory arthritis reveal that the anti-cyclic citrullinated peptide antibody is a highly useful serologic marker for the risk of progression in patients with rheumatoid arthritis.

Comments: The discovery and the diagnostic evaluation of anti-CCP antibodies have provided a serologic tool for identifying very early stages of the clinical illness. Moreover, the study if these antibodies offer clues regarding potential environmental and genetic risk factors in the etiology of RA. Although these studies illustrate a risk of disease progression in patients who lack the CCP antibody, the identification of the antibody in a patient with either relapsing or early persistent limited synovitis should lead to early rheumatology referral.

Pearls: DMARDs are powerful drugs which offer great clinical benefits, but because of their power (and potential side effects) they cannot be used indiscriminately. Assessing patients for the presence of the anti-CCP antibody may be a useful step in evaluating early synovitis syndromes where the standard rheumatoid factor is negative.

Treatment of Early Rheumatoid Arthritis and Identifying the Best Approach

Infliximab and methotrexate as induction therapy in patients with early rheumatoid arthritis. van der Bijl AE, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Ten Wolde S, Han KH, van Krugten MV, Allaart CF, Breedveld FC, Dijkmans BA. *Arthritis Rheum.* 2007;56:2129–2134.

Context: Several landmark controlled clinical trials of treatment in early rheumatoid arthritis published during the past 5 years have shown that early treatment is the most effective strategy for reduction of disease activity and radiographic progression. But which approach is likely to provide the greatest benefit? A multicenter trial conducted in the Netherlands, the BeST trial, published initial findings in 2005 and attempted to answer this important question. Patients with RA less than 2 years were randomized to one of four treatment strategies, including sequential DMARD monotherapies, stepwise addition DMARD combination therapy, initial combination therapy with tapered high-dose prednisone or an initial combination of methotrexate and TNF inhibitor therapy with infliximab (Remicade). The latter approach led to the greatest improvements and percentage of patients who achieved remission. However the costs of TNF inhibitor therapies and their risks of infection and potential malignancy raises concerns regarding using these agents early in patients with a chronic disease. A secondary analysis of this cohort provides insight into the potential appropriate strategy for using TNF therapy in patients with early RA.

Study Design and Results: This is a 2-year observational cohort study of the infliximab and methotrexate arm of the BeST trial. Adjustment of the infliximab therapy was based on defined levels of disease activity using a standard instrument for RA—the DAS (disease activity score). Fifty-six percent of these patients were able to completely stop infliximab infusions after a median of 9 months of treatment and maintain a low level of disease activity with only methotrexate as maintenance therapy.

Conclusions: TNF inhibitor therapy in patients with early rheumatoid arthritis may be stopped, and patients who maintain a low level of disease activity may be treated with methotrexate therapy alone.

Comments: This key study and its subsequent longitudinal analysis have provided a foundation for realistic discussion of staged remission induction and remission maintenance therapies in patients with a disease which previously had a slow unrelenting progression. Significant pharmacoeconomic decisions need to be made regarding investing in very expensive therapies early in a chronic disease. An induction phase using costly biologics followed by a remission maintenance phase with less expensive and safer drugs such as methotrexate is the most attractive strategy currently.

Pearls: Aggressive treatment of early rheumatoid arthritis can induce clinical remission and delay progressive joint damage. Management of rheumatoid arthritis must be proactive, not simply palliative, and may be best deferred to a rheumatologist.

TNF Inhibitor Therapy and the Risk of Infections in Rheumatoid Arthritis Patients

The following three articles are discussed as a group.

Context: TNF inhibitor therapies (such as Remicade, Enbrel, or Humira) offer a novel and effective therapeutic option for patients with rheumatoid arthritis. Because these medications broadly and powerfully inhibit inflammation, the risk of serious microbial infections while a patient is exposed to these agents must be considered. Unusual infections such as reactivation of latent tuberculosis and fungal infections such as histoplasmosis have been reported. A larger concern has been the risk of common bacterial infections in patients with rheumatoid arthritis who have an underlying increased risk of infection, especially with *Staphylococcus aureus*. This obviously is of great concern in the elective orthopaedic surgical patient population. Accurate measurement of the true risk requires evaluation of large administrative databases, as infections can occur without these medicines, of course; and patients may be exposed to other medications which also influence the risk of infection.

Risk factors for surgical site infections and other complications in elective surgery in patients with rheumatoid arthritis with special attention for anti-tumor necrosis factor: a large retrospective study. den Broeder AA, Creemers MC, Franssen J, de Jong E, de Rooij DJ, Wymenga A, de Waal-Malefijt M, van den Hoogen FH. *J Rheumatol.* 2007;34:689–695.

Study Design and Results: This is a single-center study in the Netherlands evaluating the risk of surgical site infections in patients with rheumatoid arthritis undergoing elective orthopaedic surgery. Two retrospective cohorts were compared, those exposed to anti-TNF therapies and those who were not exposed to anti-TNF therapies. The former group was subdivided into patients stopping therapy (at least four times the half life of the agent) before surgery and patients continuing anti-TNF therapy perioperatively. The primary end point was a surgical-site infection, but several secondary end points including wound dehiscence also were evaluated. One thousand two hundred nineteen patients having orthopaedic surgery were included.

Conclusions: Increased risk of surgical-site infection was observed in patients undergoing ankle, foot, or elbow surgery. The highest risk for infection was in patients with a prior history of a surgical-site infection or other skin infections. The investigators could not detect a risk of continuing perioperative anti-TNF therapy, however this group contained only 92 patients and it is possible that a small increased risk could not be detected. However they did observe an increased risk of wound dehiscence in patients in the group that continued anti-TNF therapy.

Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor α antagonists. Curtis JR, Patkar N, Xie A, Martin C, Allison JJ, Saag M, Shatin D, Saag KG. *Arthritis Rheum.* 2007;56:1125–1133.

Study Design and Results: This is a retrospective cohort design of 2393 patients with RA in a US healthcare plan. Investigators used multivariable-adjusted risk evaluation of groups receiving anti-TNF therapy versus only methotrexate for hospitalizations for bacterial infections within 6 months of exposure to either a TNF inhibitor or methotrexate. They detected a twofold increased risk of infection in the anti-TNF group; but more important—the adjusted risk of infection was highest during the first 6 months of therapy, increasing to 4.2 (95% CI, 2.0–8.8).

Serious infections following anti-tumor necrosis factor α therapy in patients with rheumatoid arthritis. Dixon WG, Symmons DP, Lunt M, Watson KD, Hyrich KL; British Society for Rheumatology Biologics Register Control Centre Consortium, Silman AJ; British Society for Rheumatology Biologics Register. *Arthritis Rheum.* 2007; 56:2896–2904.

Study Design and Results: This is a retrospective cohort design evaluating infection outcomes in persons receiving anti-TNF therapies. The investigators used the British Society of Rheumatology Biologics Register of 8659 patients given anti-TNF therapy compared with 2170 patients not receiving biologic therapies. The overall adjusted incidence risk ratio for patients with infections requiring hospitalization and intravenous antibiotics was not increased in the patients in TNF inhibitor group; However, like the above US study, they did observe a significant increase in risk of infection early during the course of anti-TNF therapy with an incidence risk ratio of 4.6 (95%CI, 1.8–11.9) during the first 90 days of treatment. The authors discuss the extremely difficult methodologic design issues in answering what would seem to be a simple clinical question.

Conclusions: All of these large cohort studies revealed that TNF inhibitor therapies overall did not increase the risk of infections in patients with rheumatoid arthritis. However, both showed an increase in infection risk during the initial phases of treatment, suggesting that there is a duration of therapy factor in modifying risk from these therapies.

Comments: Anti-TNF inhibitor treatment has significant bearing on orthopaedic management of patients with RA. Although the overall results of these studies is reassuring, the similar observation of an increased risk of serious bacterial infections during the first 3 to 6 months of treatment should be strongly considered when planning elective procedures.

Pearls: It is important to coordinate care with the patient's rheumatologist in planning surgery for the patient with RA receiving anti-TNF therapy. An argument can be made that initiating anti-TNF inhibitor treatment should be delayed until after perioperative recovery and likewise elective surgery should be deferred if the patient is already receiving anti-TNF therapies.

Mismanagement of Gout

The following two articles will be discussed as a group.

Context: The incidence of gout is increasing. Multiple factors are involved including the epidemic of obesity, metabolic syndrome, and aging of our population with associated azotemia. For rheumatologists, gout represents one of the few conditions seen in practice where appropriate management essentially will lead to clinical resolution of the illness. Yet despite the expected benefits of treatment, there have been an increasing number of outcome studies in the US and Europe showing that management is far from optimal. There is a lack of understanding of the principles of treatment and the underlying physiology of hyperuricemia and urate crystallization in the joint. These two recent articles highlight some of these issues.

Time required for disappearance of urate crystals from synovial fluid after successful hypouricemic treatment relates to the duration of gout. Pascual E, Sivera F. *Ann Rheum Dis.* 2007;66:1056–1058.

Study Design and Results: This is an observational cohort study of 18 patients with documented gout who consented to arthrocentesis every 3 months of either the knee or 1st MTP joint, after initiating urate lowering therapy. Synovial fluid analysis was performed to identify monosodium urate crystals (MSU) and perform a crystal count/400x field. The investigators showed that the time required to achieve a state of MSU crystal-free synovial fluid was related to the duration of previously untreated gout (palindromic gout?). In patients with a history of less than 10 years of episodic gout, 90% were free of crystals after just 1 year of uric acid-lowering therapy. By contrast, in patients with chronic gout of greater duration, it took as much as 3 years to achieve crystal-free joint fluid.

Conclusions: It is possible to clear synovial fluid of urate crystals but to achieve this goal requires time. Untreated gout present for more than 10 years may require a long period of urate-lowering therapy to eliminate crystals from the joint.

Concordance of the management of chronic gout in a UK population primary-care population with the EULAR gout recommendations. Roddy E, Zhang W, Doherty M. *Ann Rheum Dis.* 2007;66:1311–1315.

Study Design and Results: Participants were identified by a postal questionnaire of two primary care practices. One hundred sixty-four clinically confirmed persons with gout were identified. These participants were evaluated directly by the investigators and the European League Against Rheumatism (the academic European rheumatology society) in turn evaluated their management in light of recently published guidelines for management of chronic gout. Overall, a low compliance with recommendations for gout management was identified. This included educating the patient regarding lifestyle modifications and instruction for taking allopurinol for progressive episodic gout or tophaceous gout. Only 20% of patients with clinical tophi were taking allopurinol and close to a quarter of those taking allopurinol were not on a sufficient dose to lower the serum uric acid to a level sufficient to promote crystal dissolution. There were many patients who had discontinued allopurinol in the past, but

only a few had discontinued treatment for a hypersensitivity reaction.

Conclusions: Even though chronic gout is a curable form of arthritis, whereas untreated gout leads to permanent joint damage—precisely the setting in which high compliance with treatment should be maintained—patients are not properly educated and the serum uric acid level is not lowered sufficiently in many to accomplish the goal of therapy.

Pearls: Although gout should be curable, most patients do not receive appropriate treatment. Patients need to be treated with allopurinol or probenecid to lower their serum uric acid to $< 6 \text{ mg\%}$ on a long-term basis to successfully reverse the disease; and they need to take their medication for an adequate duration to attain that goal. Gout may be a disease best managed by physicians whose practice is oriented toward long-term longitudinal care, ie, rheumatologists or primary care physicians.