To the Editor:

I have a number of concerns with the editorial by Dr. Pincus, et al in the February issue of The Journal of Rheumatology. Firstly, Dr. Huizinga and his group have shown in an elegant study that methotrexate (MTX) has little influence on the smaller proportion of patients who may progress to rheumatoid arthritis but who have a negative test for anti-cyclic citrullinated peptide (CCP) antibodies. This is a simple test to do; why not use it, rather than persisting in an approach that is unlikely to work? However, at worst this would result in a few patients getting MTX unnecessarily — not a major issue. My big concern is that they appear to be suggesting a return to the truly “bad old days” when family doctors would routinely prescribe steroids (alone) for their rheumatoid patients, and only refer after calamitous deformities develop — assuming the patients did not die of a heart attack beforehand. There is no evidence that steroids, whatever the dose, if given alone have any remittive qualities. I am not impressed by their impact even when given with disease modifying antirheumatic drugs (DMARD). The title clearly advocates steroids alone as an option for this undifferentiated disease. I think this is wrong, but what is worse is that to many family doctors, less skilled at recognizing joint swelling than Dr. Pincus and his colleagues, almost all rheumatoid is “undifferentiated” — at least without the anti-CCP test — and steroids will effectively remove the need for referral.

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demia\textsuperscript{15-17}, in which many patients may be treated with relatively safe therapies who may not require these treatments. Ironically, 30–90 days of very low-dose prednisone and/or MTX appears to have lower toxicity than almost any medication for hypertension or hyperlipidemia.

6. We also agree that referral of patients with early arthritis to rheumatologists as soon as possible provides the best possible care. However, this ideal procedure is not present in most locales all over the world. A profound shortage of rheumatologists already exists in many areas, and will likely increase substantially over the coming years\textsuperscript{15,18,19}.

The case for low-dose prednisone for patients with RA has been made by others\textsuperscript{6,20-22}, including 2 recently reported clinical trials\textsuperscript{24-25} and 2 eloquent more recent editorials in The Journal\textsuperscript{26,27}, although disagreement remains respectfully recognized\textsuperscript{28-30}. A randomized trial over 5–10 years with particular attention to adverse events, which would be regarded as ethical in view of the absence of consensus, would appear desirable.

None of these comments reduces the importance of further research concerning anti-CCP to increase understanding of pathogenesis and treatment of RA, such as new information concerning the influence of association with HLA class II in its severity, although limitations of anti-CCP in clinical care are recognized by others\textsuperscript{7,31,32}. Rheumatologists might recognize whether some information that is very useful in research settings may not necessarily have value in clinical decisions, and even lead to possibly incorrect conclusions in many patients.

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Antiperinuclear Factor Test Is More Useful than Anti-Sa Assay When Used with Anti-Cyclic Citrullinated Peptide Test in Diagnosis of Rheumatoid Arthritis

To the Editor:

We read with interest the article by Lopez-Longo, et al regarding anti-cyclic citrullinated peptide (anti-CCP) versus anti-Sa antibodies in diagnosis of rheumatoid arthritis (RA). The authors insisted that the sensitivity of the anti-Sa test (43.6%) is lower than that of the anti-CCP test (72.4%), but since 12% of patients with RA showed anti-CCP test negatives with anti-Sa test positives, performing the anti-Sa test in RA patients with anti-CCP-negative results can aid in the diagnosis of patients with RA. Instead of the anti-Sa, we used the antiperinuclear factor (APF) test simultaneously with the anti-CCP test and found interesting results.

We analyzed the results of patients from the outpatient clinic of Hanyang University Hospital for Rheumatic Diseases who underwent both tests. The disease distributions of patients were as follows: 56 patients with RA, 65 with non-RA connective tissue diseases, and 139 with osteoarthritis. APF test was performed by the indirect immunofluorescent method using a commercial kit (IT-APF™; ImmunoThink Co., Seoul, Republic of Korea). The anti-CCP test was referred to a commercial reference laboratory, and a second-generation enzyme immunoassay kit was used (Diastat™ Anti-CCP: Axis-Shield Diagnostics Limited, Dundee, UK). Each test was performed such that the result of the other test is not known. In addition, a comprehensive autoimmune antibody screening test, the “autoimmune target” (AIT) test, was performed using an indirect immunofluorescent test kit (IT-AIT™; ImmunoThink Co.).

Sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratio for each test are shown in Table 1. Although there were no big differences between the 2 tests, the sensitivity was higher in the anti-CCP test, while the specificity and predictive value were similar. The likelihood ratios for positive findings were also similar. If we define positives as cases in which both tests are positive, specificity increases to 98.5% and the likelihood ratio for positive findings increases to 38.86, suggesting significant usefulness in the diagnosis of RA. Cases showing discrepant results between the 2 tests were similar. The concordance rate of the 2 tests was 82.7%, while the specificity and predictive value were similar. The likelihood ratios for positive findings were also similar.

The APF test was essential in the diagnosis of RA for a long time, but since then, various problems regarding commercialization of the test led to only limited use in certain specialized rheumatic disease laboratories. In Korea, however, a commercial APF kit was developed to be readily used in the general laboratory, and it is actively in use with the approval of the Korean Food and Drug Administration for in vitro diagnostic purposes. In addition, the external quality control program is adopted under the supervision of the Korean Society for Laboratory Medicine to standardize the test. The anti-CCP test was developed as an enzyme immunoassay method using the recombinant peptide that is similar with part of the APF target antigen. The early first-generation kit showed a low sensitivity rate, around 50%, but the current second-generation kit shows an improved average sensitivity rate of 70%. As a consequence, use of the anti-CCP test is growing worldwide, and some researchers have insisted that the anti-CCP test can replace the APF test. However, according to the results of this study, these 2 tests are in a complementary relationship, and since 40% of those patients with clinically suspected RA who were negative for the anti-CCP test showed positive APF test results, replacing the APF test by the anti-CCP test would be inappropriate. On the other hand, 33% of those patients with RA who were negative for both tests showed positive results in the AIT test, and we think it would be diagnostically helpful when the AIT test is performed upon those patients who are clinically suspected of RA.

The AIT test is a comprehensive autoimmune antibody screening test, using macrophage cell line (IT-1 cell) as substrate for the antinuclear antibody (ANA) test. The AIT test is more reliable and more easily interpreted than the ANA test performed with the customary HeP-2 cell line. In addition, the AIT test can detect anti-MTOC and anti-GiM, which are the marker antibodies.

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[Table 1. Diagnostic performance of antiperinuclear factor (APF) test and anti-cyclic citrullinated peptide (anti-CCP) test for the diagnosis of RA.]

<table>
<thead>
<tr>
<th></th>
<th>APF</th>
<th>Anti-CCP</th>
<th>APF and Anti-CCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>67.9</td>
<td>73.2</td>
<td>57.1</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>91.2</td>
<td>91.2</td>
<td>98.5</td>
</tr>
<tr>
<td>Positive predictive value (%)</td>
<td>67.9</td>
<td>69.5</td>
<td>91.4</td>
</tr>
<tr>
<td>Negative predictive value (%)</td>
<td>91.2</td>
<td>92.5</td>
<td>89.3</td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>7.69</td>
<td>8.30</td>
<td>38.9</td>
</tr>
<tr>
<td>Negative likelihood ratio</td>
<td>0.35</td>
<td>0.29</td>
<td>0.43</td>
</tr>
</tbody>
</table>

[Table 2. Discrepancy between antiperinuclear factor (APF) test and anti-cyclic citrullinated peptide (anti-CCP) test results in patients with RA.]

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Negative</th>
<th>Total, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive APF, n (%)</td>
<td>32 (57.1)</td>
<td>6 (10.7)</td>
<td>38 (67.8)</td>
</tr>
<tr>
<td>Negative APF, n (%)</td>
<td>9 (16.1)</td>
<td>9 (16.1)</td>
<td>18 (32.2)</td>
</tr>
<tr>
<td>Total, n (%)</td>
<td>41 (73.2)</td>
<td>15 (26.8)</td>
<td>56</td>
</tr>
</tbody>
</table>
Duration of Treatment After Eye Involvement in Giant Cell Arteritis

To the Editor:

Patients and physicians would like to know the duration of treatment required for giant cell arteritis (GCA). It is not always possible to accurately estimate how long treatment will be required. There is some histopathological evidence that the presence of eye manifestations in GCA is associated with more advanced disease. Loss of vision in GCA may be due to ischemic optic neuropathy, central retinal artery occlusion, choroidal ischemia, or stroke. Other ophthalmic complications include double vision with extraocular muscle ischemia, ischemic ocular motor nerve palsy, ocular ischemic syndrome, hypotony, and Horner’s syndrome.

We investigated whether the presence of eye involvement significantly lengthens the duration of steroid therapy. We conducted a retrospective study of 30 patients with biopsy-proven GCA between 1995 and 2004 at Southend University Hospital. We compared the duration of treatment for patients with and without eye involvement. The study was approved by South Essex Research Ethics Committee.

All patients followed the same treatment protocol; however, individual patient regimes were formulated depending on clinical presentation, severity of symptoms, patient response to treatment, and the development of side effects. An initial single daily dose of 40–80 mg prednisolone was given for 2 to 4 weeks, then gradually reduced every 2 to 4 weeks by no more than 10% of the total daily dose. Regular assessment of clinical symptoms, erythrocyte sedimentation rate, and C-reactive protein was used to monitor the patient response. Once patients were taking a lower dose of prednisolone, monitoring was reduced to every 6 to 8 weeks and the prednisolone was tapered toward the lowest required dose or stopped. In addition, all patients received calcium and vitamin D supplements.

Of 30 patients with GCA, 16 patients had serious eye involvement. Of these, 15 had anterior ischemic optic neuropathy and one patient had a fourth cranial nerve palsy. The mean duration of treatment in patients with eye involvement (25.69 mo ± 12.80) was significantly longer than in those without eye involvement (11.2 mo ± 3.25; T test p = 0.0018; Table 1).

It is probable that the presence of eye involvement in GCA determined the need for longer corticosteroid therapy. In practice, a physician can better estimate the length of treatment period required depending on the presence or absence of eye involvement.

Larger studies could better show the exact value of this prediction.

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We describe the first case of interstitial and glomerular granulomatous nephritis in a patient with arginine to glutamine substitution in position 334 (R334Q) of NOD2.

A 4-year-old Caucasian girl presented symmetrical polyarthritis of wrists, hips, knees, and ankles as well as intermittent nonspecific fever. There was thickening of the synovium and prominent tenosynovitis. Over the next 2 years she developed a maculopapular, evanescent, and at times urticarial exanthema in trunk and upper extremities histologically corresponding to a nongranulomatous leukocytoclastic vasculitis. Initial routine laboratory assessments are given in Table 1. Antinuclear antibodies and rheumatoid factor were negative. Knee and hand radiographs showed periarticular osteopenia.

At the age of 8, she developed an asymptomatic nongranulomatous bilateral anterior uveitis with vitreous involvement. Flares associated with red eye led to posterior synechiae, and subsequent visual impairment (OD 9/10, OS 5/10). At age 9 she presented a worsening dermatitis, arthritis, fever, mild pericarditis, and splenomegaly. She received corticosteroids and methotrexate for articular disease, but corticosteroid dependency ensued. Etanercept was introduced, with marginal response.

At age 10 she developed leukocyturia, granular casts, raised serum creatinine 13.9 mg/l (3–7 mg/l), creatinine clearance of 34 ml/min, proteinuria (1 g/24 h), and elevated urinary β2-microglobulin at 5.63 µg/ml (1.01–1.73 µg/ml). The angiotensin-converting enzyme level was normal at 18 IU/l. Her erythrocyte sedimentation rate was elevated to 98 mm/h.

A percutaneous renal biopsy showed central granulomatous lesions constituted by epithelioid cells, multinucleated giant cells, and lymphocytes in 3 of 9 glomeruli. Fibrosis in Bowman’s space was found in 2 glomeruli and fibroepithelial crescents were observed in 2. There were interstitial granulomas with severe fibrosis and infiltrating lymphocytes, histiocytes, neutrophils, and eosinophils. There was no vascular damage. Tubules presented atrophy and dilated morphology with epithelial degeneration and hyaline and white cell casts (Figure 1). Infliximab therapy (3 mg/kg/dose, every 8 wks) was instituted, with excellent response in renal function and arthritis, starting with the fourth infusion (Table 1). Genotyping of NOD2 revealed a R334Q substitution confirming the diagnosis of PGA.

PGA is the name recently proposed to encompass the familial and sporadic forms of early onset arthritis, with uveitis and dermatitis (usually below age 5 yrs), associated with mutations at the NACHT domain of NOD26. Renal involvement has been reported infrequently in this disease, yet at the time of the diagnosis or later during the course of the disease, mainly as interstitial granulomatous nephritis. However, these reports preceded the availability of genetic testing, hence the presence of NOD2 mutations could not be documented.

Ting, et al were the first to document a family with Blau phenotype, in which the mother of the proband developed acute nephritis at age 27 years. The renal biopsy showed interstitial involvement including giant cell granuloma and glomerulosclerosis resulting in significant renal impairment7.

In the French series of Coutant, et al, 11 children with sarcoid nephritis were reported8, but the authors do not differentiate between adult and childhood forms (PGA). It should be noted that 3 patients presented arthritic symptoms, suggesting the possibility of PGA, although the adult form can rarely be associated with arthritis as well. Also 7/11 patients had uveitis.

Between 10% and 50% of patients with PGA phenotype are not associated with identified mutations in the NOD2 gene9,10. Hence the importance of the current report in which we document the first case of a young girl with classical PGA carrying a mutated form of NOD2 (R334Q), who developed a rather significant form of granulomatous nephritis leading to renal impairment. Thus, granulomatous nephritis becomes an established component of disease phenotype. This adds to the growing evidence supporting an expanded phenotype for PGA, a disease for which a mutation in NOD2 has been well documented in the literature, and also alerts the clini-
cian on the need to watch for sudden development of internal organ involvement. Although the term PGA was recently suggested by the authors\(^6\), the expansion of the phenotype suggested by our report may call for the substitution of the word “systemic” to reflect the newly documented clinical manifestations.

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Correction

Mancarella L, Bobbio-Pallavicini F, Ceccarelli F, et al. Good clinical response, remission, and predictors of remission in rheumatoid arthritis patients treated with tumor necrosis factor-\(\alpha\) blockers: The GISEA study. J Rheumatol 2007;34:1670-3. Two authors should be identified as follows: S. Bombardieri, MD, Professor, Rheumatic Disease Unit, University of Pisa; R. Giacomelli, MD, Professor, Rheumatic Disease Unit, University of L’Aquila. We regret the error.