Correspondence

INSTRUCTIONS FOR LETTERS TO THE EDITOR

Editorial comment in the form of a Letter to the Editor is invited; however, it should not exceed 800 words, with a maximum of 10 references and no more than 2 figures (submitted as camera ready hard copy per Journal Guidelines) or tables and no subdivision for an Abstract, Methods, or Results. Letters should have no more than 3 authors. Full name(s) and address of the author(s) should accompany the letter as well as the telephone number, fax number, or E-mail address.

Contact. **The Managing Editor, The Journal of Rheumatology, 920 Yonge Street, Suite 115, Toronto, Ontario M4W 3C7, CANADA. Tel: 416-967-5155; Fax: 416-967-7556; E-mail: jrheum@jrheum.com Financial associations or other possible conflicts of interest should always be disclosed.**

Human Immunodeficiency Virus-1 and Rheumatoid Arthritis: A Puzzling Association

To the Editor:

We read with great interest the article by Wegrzyn, *et al*, who described a patient who developed rheumatoid arthritis (RA) after long-lasting human immunodeficiency virus-1 (HIV-1) infection[1]. This male patient developed early virus-related arthralgias followed by lamivudine-related arthritis and, finally, typical RA. The critical point of this clinical history was when combined tritherapy improved HIV-1 disease; as well, CD4 T cell count increased to normal levels. By that time joint symptoms began and defined RA developed. The authors speculated on Th1/Th2 cell imbalance occurring in both HIV-1 infection and RA. In HIV-1 infection, reduction of CD4 T cells and increased Th2-related cytokines interleukin 4 (IL-4) and IL-10 suppress tumor necrosis factor-α (TNF-α) and IL-1 production and may prevent RA. Improvement of HIV-1 disease and restoring of CD4 T cells and Th2 cytokine levels may allow onset of RA in genetically susceptible individuals in which a defect of Th2 cytokines has been reported[2].

The role of CD4 T cells in RA pathogenesis is a matter of debate, with obvious therapeutic implications. We reported an intriguing case of HIV and RA association in which HIV-1 infection occurred after RA[3]. This female patient had long-standing erosive symmetric polyarthritis with positive rheumatoid factor (RF). HIV-1 disease developed and 3 months later, although she refused any drug treatment, RA ameliorated and RF became undetectable. Afterwards, due to cerebral toxoplasmosis, spastic left hemiplegia occurred, and one year later arthritis fully recovered only in paralytic limbs with healing of bone erosions, but mild synovitis persisted in the non-paralytic side. Phenotypic and functional T cell assessment was performed in this patient and also in a small group of healthy donors, RA patients, and subjects with clinically overt acquired immunodeficiency syndrome (AIDS). Lymphomonocyte proliferation to phytohemagglutinin (PHA) and bound-phase OKT3 "*in vitro*" was strongly depressed in the AIDS patients and in our HIV-RA patient; also CD4 T cells, CD4-CD45 memory T cells, and CD4-CD26 T cells were decreased.

In our case, HIV-1-related improvement seemed to affect only those components of the rheumatoid process mediated by the immune system. This suggests that other pathologic events of RA are not controlled by the immune system and are therefore not influenced by immunosuppression. The observation that RA completely recovered only in the hemiplegic limbs suggests that the mild joint inflammation seen in the non-paralytic side was related to "activity" of the nervous system. A large body of evidence has shown that the autonomic nervous system plays a key role in modulating the inflammatory process, and substance P seems to be the critical peptide in this setting[4].

RA has a multifactorial etiopathogenesis in which CD4 T cells, and more generally the immune system, may be important in initiating the inflammatory process, but do not seem to be crucial in maintaining it. HIV-1 infection is a natural model of severe global immunosuppression, and persistence of RA during AIDS raises the question whether RA is an immune-driven disease or a more complex inflammatory disease in which extra-immunologic mechanisms also play an important role.

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Drs. Wegrzyn and Miossec reply

To the Editor:

We thank Drs. Iannone and Lapadula for their comments; we are happy our report can stimulate additional discussion. Obviously only limited numbers of cases associating human immunodeficiency virus (HIV) infection and arthritis are available. Their case is to some extent the opposite of ours[1,2]. We described a patient with long-standing HIV with acquired immunodeficiency syndrome (AIDS), who developed RA that improved when its virus-related immune defects improved with tritherapy[2]. In their case, the joint manifestations of a patient with long-standing RA improved when she developed HIV infection[1]. At the same time, rheumatoid factor became negative. At such an early stage immune defects remained limited and were clearly not as impaired as in our patient. However, functional defects can still be observed, although at this stage circulating levels of CD4 T cells remain in the normal limits.

Their case is far more complex when taking into account the improvement of joint manifestations including healing of joint erosions, following hemiplegia. This has already been observed in classic RA, but the mechanisms remain to be clarified.

Together, these observations underline the complexity of the pathogenesis of these diseases. At the same time, they suggest a large number of therapeutic modalities ranging from cytokine and chemokine inhibition and neuropeptide induction to sustained switch in the Th1/Th2 balance[3].

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Antibody Response to Influenza Immunization in Patients with Systemic Lupus Erythematosus

To the Editor:

I read with interest the report by Abu-Shakra, *et al*[1]. Many clinicians have been reluctant to immunize patients with systemic lupus erythematosus (SLE) because of the concern that it may induce or exacerbate underlying rheumatic disease. Patients with SLE are prone to infections due to the immune effects of the disease itself or to the frequent use of immunosuppressive agents. Thus vaccination might be useful in this infection-prone population, provided the vaccine produces protective antibodies (> 4-fold rise in titer) without inducing autoimmune phenomena or exacerbating the primary rheumatic disease.

Vaccination remains the best defense against influenza virus, and patients with SLE are at high risk for influenza infection, particularly if they are taking immunosuppressive drugs. Because influenza vaccines are poor at boosting T cell responses they function primarily by inducing a specific antigen-antibody response. The best protection is afforded by hemagglutination-inhibition (HAI) antibodies, which block the function of hemagglutinin. Generation of antihemagglutinin antibodies by B lymphocytes is under the control of helper T cells.

Patients with SLE have multiple immunological abnormalities including hyperactivity of B cells that produce a great number of self/reactive antibodies. It has been hypothesized that hyperactivity of B cells is dependent on T cells, and the persistence in serum of self/reactive T cells and B cells causes autoantibodies in SLE patients. Thus, the administration of exogenous antigens in SLE patients might be worse. However, controlled and uncontrolled studies[2-5] have shown that influenza vaccination in patients with SLE is also safe and immunogenic. It has also been reported[6] that the simultaneous administration of 3 vaccines (pneumococcal polysaccharide, Hemophilus influenza type B (HIB), tetanus toxoid) to SLE patients is safe and immunogenic. We recently observed the antibody responses to simultaneous administration of pneumococcal polysaccharide and HIB vaccines in SLE patients[7]. All were receiving oral prednisone (mean 18.1 mg/day, range 5–50) and 2 were taking pulse cyclophosphamide at the time of vaccination. After vaccination the geometric mean titer (GMT) of antibodies to both vaccines, capsular serotypes, and tetanus protein conjugate to HIB increased significantly. The antibody responses were to the specific antigen and caused no significant changes in anti-dsDNA levels or flares of the primary disease.

Recently we determined the safety, immunogenicity, and generation or increase of preexisting autoantibodies in 18 women with SLE following influenza vaccination recommended for the season 2001-2002 (unpublished data). The GMT of HAI antibodies in 18 healthy female blood donors was also measured. Sixteen of 18 patients were receiving oral prednisone (mean 14.02 mg/day, range 2.5–50), and 2 of them were receiving pulse cyclophosphamide at the time of vaccination. Before vaccination, the percentage of patients with HAI antibody titer ≥ 1:40 to influenza A/Moskow, influenza A/New Caledonia, and B/Sichuan was lower in patients with SLE than in healthy donors (28%, 22%, and 17% vs 77%, 94%, and 94%). At 4 weeks, the percentage of SLE patients with protective antibodies (≥ 1:40) increased to 67%, 72%, and 61%, respectively. Eight patients developed HAI titers ≥ 1:40 to all 3 influenza antigens, 5 to 2 antigens, and 2 to 2 antigens. Three patients achieved ≥ 2-fold rise in titer. Post-vaccination GMT of HAI antibodies to the 3 strains increased significantly.

While disease activity decreased significantly, anti-dsDNA levels showed no changes.

We did not find a significant correlation between antibody response to influenza antigens and age, prednisone dosages, disease activity, or immunoglobulin concentrations (Pearson correlation). Finally, only one of the antinuclear antibodies (anti-Sm) increased in transient form after vaccination, but had no clinical significance.

As pointed out by Abu-Shakra, *et al*[1] the influenza vaccination is safe and immunogenic. After 25 years of studies on antibody response to influenza vaccination in patients with SLE, the response on whether we should vaccinate these patients must be yes.

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Dr. Abu-Shakra replies

To the Editor:

The results of Dr. Mercado's work support our published data. However, we identify few differences between our study and his. We have shown in a controlled study that influenza virus vaccine is safe for patients with SLE. Six and 12 weeks after vaccination, SLE Disease Activity Index scores of cases and controls were not statistically different[1]. In addition, no flare of renal disease was observed.

Dr. Mercado reports that at time of vaccination, the percentage of SLE patients with protective titers of antiinfluenza antibodies was lower than for healthy controls[2].

We have shown that SLE patients had lower titers only against influenza A (H1N1) compared with healthy controls. We have also shown that post-timmunization only 33% of our patients had protective antibodies against H1N1[4]. This discrepancy might be related to type and immunogenicity of the vaccine (we used A/Beijing/262/95 compared with A/New Caledonia/20/99), prevalence of influenza in the general population, and history of previous vaccination.

We have also shown a trend toward a lower immune response in patients with age > 50 years, prednisone dosage > 10 mg, and use of azathioprine. This observation was not reported by Dr. Mercado.

Finally, we have found that 6 weeks after vaccination 3, 4, 3, and 3

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patients generated autoantibodies reacting with Sm, RNP, Ro, and La autoantigens, respectively. This autoactivity was short-term and was not associated with clinical significance[3]. Only one patient in Dr. Mercado's series developed anti-Sm antibody.

Since Dr. Mercado's study was based on only 18 patients and ours was also based on only 24 patients, the differences between both studies might be the result of sample size and their clinical significance is not clear. As suggested previously, we agree that patients with SLE should be encouraged to receive influenza vaccine.

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Autonomic Involvement in Sjögren's Syndrome

To the Editor:

Niemelä, *et al*[1] report no significant difference in cardiovascular autonomic testing between patients with primary Sjögren's syndrome (SS) and healthy controls. However, we disagree with their broad conclusion that autonomic dysfunction is not increased in patients with primary SS. The tests used in their study are measures of cardiac sympathetic-parasympathetic interaction and do not measure overall autonomic function. As such, their study does not represent a comprehensive assessment of sympathetic, parasympathetic, or enteric function in primary SS. Their conclusion would be strengthened by additional sensitive tests such as the quantitative sudomotor axon reflex test and pupillometry, together with a validated instrument to assess autonomic symptoms. Further, their study neglects the gastrointestinal and genitourinary systems, whose functions are controlled by the autonomic nervous system. We have shown that IgG from patients with SS inhibits cholinergic neurotransmission in smooth muscle of both gut and bladder by blocking M3-muscarinic receptors[2,3]. Impaired esophageal motor function is frequently observed in SS patients[4] and these patients have a significantly increased severity of lower urinary tract symptoms[5]. Since the heart expresses M2- and not M3-muscarinic receptors, the cardiovascular autonomic testing used by Niemelä, *et al* will miss potential autoantibody-mediated effects on other organs such as bowel and bladder, which express M3-muscarinic receptors. The question of autonomic dysfunction in SS is far from settled and awaits more comprehensive evaluation, including objective testing of the gastrointestinal and genitourinary tracts. It is important for investigators to be aware that cardiovascular autonomic testing tests only a subset of autonomic nerve fibers and is not necessarily representative of the autonomic innervation in other organ systems.

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Dr. Niemelä, *et al* reply

To the Editor:

We thank Dr. Smith and co-workers for their comments on our report. While we agree that cardiovascular autonomic tests, even comprehensive ones, do not definitively rule out possible local dysfunction in other sections of the autonomic system, we think that they represent systemic autonomic function. Cardiovascular autonomic tests are widely used and accepted as an indicator of autonomic neuropathy[1]. Signs and symptoms of cardiovascular autonomic dysfunction are also usually found together with signs and symptoms of other sections of the autonomic system, especially with pupillary and sudomotor systems, in Sjögren's syndrome (SS) and in other rheumatic diseases, in diabetes, and in several other diseases[2-5]. This co-existence is shown in most case reports and also in controlled studies, although the correlation between the individual test results may be poor[3,6].

Investigation of the autonomic nervous system is complicated. Results of autonomic studies in SS as well as in other diseases have frequently been contradictory, reflecting the many difficulties in the standardization and interpretation of these tests. Also, selection bias and wide interindividual variation in test results are likely to lead to different conclusions in various studies. Further, tests of gastrointestinal and genitourinary functions do not satisfactorily discriminate autonomic regulation from other functions, such as end-organ disorders[7].

Since the first controlled studies of the autonomic function in primary SS were performed with conventional cardiovascular reflex tests, with conflicting results[8,9], we evaluated the autonomic function of patients with a well validated and standardized package of autonomic tests and investigated the possible methodological reasons for the discrepancy in previous studies[8-10].

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