LETTERS

Exacerbation of systemic lupus erythematosus after hepatitis B vaccination: comment on the article by Battafarano et al and the letter by Senécal et al

To the Editor:

We read with interest the article by Battafarano et al. on immunization in patients with systemic lupus erythematosus (SLE) (1), and the comments by Senécal et al (2). Battafarano et al. concluded that immunization is safe in SLE. Senécal et al. agreed that pneumococcal vaccination is safe and useful in SLE, but reported a case of exacerbation of SLE following hepatitis B vaccination. We would like to report our experience with hepatitis B vaccination in SLE.

In 1997, a questionnaire about rheumatic symptoms following hepatitis B vaccination was sent to rheumatology departments in 9 French hospitals. Criteria for entry were any rheumatic symptoms of 1-week duration or more, occurrence of the symptoms during the 2 months following hepatitis B vaccination, no previously diagnosed rheumatic disease, and no other explanation for the occurrence of symptoms. The clinical and laboratory data of all patients were analyzed. The results of this study were published recently (3). Twenty-two patients, including 2 women, developed exacerbation of previously undiagnosed SLE. We can add another patient who developed exacerbation of SLE following hepatitis B vaccination. This patient was not included in the study, since SLE was diagnosed at the time of vaccination.

The 3 patients (2 women and 1 man, ages 19, 23, and 22, respectively) developed exacerbation of SLE 1 week, 1 month, and a few days, respectively, after vaccine injection. One of the patients received an additional hepatitis vaccine injection 1 month later, which resulted in worsening of the symptoms. The clinical manifestations were arthritis of the right ankle in 1 patient, thrombocytopenic purpura in another patient, and polyarthritis, fever, pleuritis, and pericarditis in the third patient. Corticosteroids were started for 2 of the patients and increased for the third, resulting in regression of the disease flare.

These additional cases suggest that, in SLE patients, hepatitis B vaccine may be followed by disease exacerbation. The case of 1 patient, in whom a further hepatitis vaccine injection resulted in worsening of the symptoms, was very suggestive. However, we agree with Battafarano that the relationship between immunization and SLE flare may be coincidental. There are currently no epidemiologic data that support the hypothesis that hepatitis B vaccination may induce the onset or exacerbation of autoimmune disorders, especially SLE. In our opinion, since the benefits of hepatitis B vaccine outweigh the possible adverse events, universal immunization has to go on. However, questions arise for some subjects such as SLE patients. Gartner and Emlen did not observe disease flares (4), but their series was too small to allow conclusions to be drawn. However, cases of flare, sometimes very suggestive, have been reported. Additional studies are needed.

Jean Francis Maillefert, MD
Christian Tavernier, MD
Dijon University Hospital
Dijon, France

Jean Sibilia, MD
Strasbourg University Hospital
Strasbourg, France

Eric Vignon, MD
Centre Hospitalier Lyon-Sud
Lyon, France

Reply

To the Editor:

We thank Dr. Maillefert and colleagues for their interest in our recent study of immunizations in SLE and our response to the letter of Senécal et al (1). The majority (n = 19) of the patients reported on by Maillefert et al developed rheumatic symptoms other than those of SLE after hepatitis B vaccination. The authors further comment on 2 patients who developed SLE after hepatitis B vaccination, and also on another previously diagnosed patient with SLE who had an exacerbation of SLE following hepatitis B vaccination.

The development of connective tissue disease following immunization has rarely been reported in the medical literature (2). The onset of SLE following hepatitis B vaccination is also unusual (3,4), and hepatitis B vaccination has mostly been reported to be associated with rheumatoid arthritis (2). Individual vaccines and a combination of vaccines have been associated with the onset of SLE within 1–3 weeks of vaccination and typically after secondary or booster immunization (2). Our observations and literature review support the patient descriptions by Maillefert et al. However, hepatitis B vaccination has been extremely safe and well tolerated in the normal population and even in SLE patients (5).

Hepatitis B vaccine is only one of many vaccines that have been temporally related to the development of SLE. The vaccine type and class (live or killed) are not predictively correlated with a specific connective tissue disease (2). The etiopathogenesis of clinical SLE has been related to both
genetic factors and environmental triggers such as ultraviolet radiation, food, infection, and drugs. We propose that immunizations be added to the list of possible triggers for SLE when symptoms develop within 3 weeks of booster immunization.

To the Editor:

Recently, Han et al (1) reported that at least 2 mutants with a codon change at positions 213 and 239, respectively, in exon 6 of the p53 gene, which were identified in the joints of rheumatoid arthritis (RA) patients, are dominant-negative and suppress endogenous wild-type p53 function. Firestein et al reported a high percentage of mutant p53 transcripts in cultured RA fibroblast-like synoviocytes by using a mismatch detection system (2). In addition, Réme et al detected mutations of the p53 suppressor gene in rheumatoid arthritis synovium. Proc Natl Acad Sci USA 1997;94:10895–900.

Based on these results, we investigated the relationship between the genomic alterations of p53 and the clinical phenotype in Japanese RA patients. The purpose of the study was explained to all of the patients, who gave their written consent to the use of their samples for this research. Synovial tissues were obtained from the RA patients (n = 22; 2 male, 20 female) at the time of total knee replacement. All patients met the revised American College of Rheumatology (formerly, the American Rheumatism Association) criteria for RA (4). High molecular weight DNA extracted from frozen samples was subjected to polymerase chain reaction (PCR) using a primer kit for the p53 exon 6, covering codons 187–224 (Nippongene, Toyama, Japan). The PCR products were cloned into the pBlueScript vector (Stratagene, La Jolla, CA), and at least 3 clones obtained with the primer set from each sample were subjected to sequencing using an ALF-Red DNA sequencer (Amersham-Pharmacia Biotech, Uppsala, Sweden).

We could not find any mutations in exon 6 derived from the 22 synovial tissue samples from RA patients. In some cases, we found an apparent mutation in 1 of 3 or more clones, but we confirmed by repeated examination that these were PCR errors. The contrast between our findings and those of the 3 cited studies (1–3) might have been due to racial differences. It is also possible that the PCR method itself performs differently in certain conditions to identify mutated DNA, especially using Taq polymerase (5).

Hidero Kitasato, PhD
Kitasato University School of Medicine
Kanagawa, Japan
Renzo Okamoto, MD, PhD
Yokohama City University School of Medicine
Kanagawa, Japan
Shinichi Kawai, MD, PhD
St. Marianna University School of Medicine
Kanagawa, Japan


Reply

To the Editor:

We appreciate the comments of Kitasato et al and recognize the wide variability that can occur in studies of this nature. A number of factors might contribute to disparate results, including duration of disease, extent of joint destruction, and criteria for surgical interventions as well as the use of insensitive methods for detecting low-abundance mutations (1). In addition, Imamura and colleagues note that the location within the rheumatoid joint that serves as the source of material can also lead to variable results (2). For instance, they recently observed oligoclonality in synovioyte populations derived directly from invasive pannus, but polyclonality in the rest of the sample. This suggests that significant bias can occur.
depending on whether one evaluates p53 mutations at the invasive front of synovial tissue or from other sites. A certain degree of caution must also be exercised when considering the limited number of clones and the narrow region (exon 6) of the p53 gene evaluated by Kitasato et al. We have now sequenced nearly 50 mutations from RA synovial samples; <30% of these were detected in exon 6 (3). Since a minority of subclones actually contain mutations, the percentage of the total p53 complementary DNA pool that contains mutations in exon 6 is rather small (~20%). This level is consistent with the findings of a study by Rème et al, in which p53 mutations in exon 6 were identified in 17% of the patients in a French cohort (4).

Although the mutations could be less prevalent in some ethnic or racial populations as suggested by Kitasato et al, alterations in the p53 gene have recently been confirmed in a population of Japanese patients with RA (5). In that study, 44% of RA patients requiring total joint replacement had documented synovial p53 mutations in exons 4–11. Only 5% of the p53 subclones contained mutations in codons 245–393, which was somewhat less than that observed by us. However, as in our original study, the majority of mutations identified in the Japanese population were transitions (presumably, from oxidative damage) and had been previously isolated from various neoplastic diseases.

The issue of PCR artifact is naturally of considerable importance, although we and others have expended great effort to minimize this problem. Subclones demonstrating mutations were rare in non-RA and non-synovial samples. Furthermore, studies using pfu instead of Taq to minimize transcription errors gave similar results. The clustering of mutations in “hot spots,” the abundance of transition mutations, the existence of identical mutations in tumors, and the demonstration of dominant-negative function of some RA mutants (6) support the veracity of our findings.

The ultimate functional importance of somatic mutations in RA and other inflammatory diseases is still uncertain. However, it is clear from independent studies from 3 continents that p53 mutations can and do occur in RA synovial tissue samples. In this way, RA bears a striking resemblance to other chronic inflammatory diseases such as ulcerative colitis in which DNA damage occurs (for review, see ref. 7). Other somatic mutations also exist in the rheumatoid joint, including HPRT in synovial T cells (8). Although this gene has less functional significance than p53, it serves as a useful marker for oxidative damage to DNA in the intensely inflamed synovium. What is less certain is when in the course of RA the p53 mutations occur, how many and which cells harbor the mutations, and whether they alter the natural history of the disease.

Gary S. Firestein, MD
Nathan J. Zvaifler, MD
Douglas R. Green, PhD

University of California, San Diego School of Medicine and La Jolla Institute for Allergy and Immunology
La Jolla, CA


Severity of rheumatoid arthritis in Portuguese patients: comment on the article by Drosos et al and on the letter by Ronda et al

To the Editor:

We read with great interest the article by Drosos et al (1) and the comment on this article made by Ronda et al (2) in which they stated that rheumatoid arthritis (RA) is less severe in Greek (1) and Spanish (2) patients than in British patients. In 1998, we carried out a review of 964 Portuguese RA patients in which the results were similar to those in the Greek and Spanish studies. This review included all patients satisfying the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) criteria for RA (3) who were seen at the Rheumatology Unit of Santa Maria Hospital (Lisbon) during a 20-year period (1977–1997).

All RA cases were evaluated according to a protocol that included the assessment of extraarticular involvement, presence of Sjögren’s syndrome, rheumatoid factor detection, presence of erosive disease, disease duration, and patient functional class as defined by the ACR (4). The patients were considered to have extrarticular manifestations if at least 1 of the following clinical features could be detected: subcutaneous nodules, pulmonary fibrosis confirmed by chest roentgenograms and lung function tests, echocardiographic evidence of pericardial effusion or pleural effusion shown by chest roentgenograms, Felty’s syndrome (<2 x 10^9/liter granulocytes, and splenomegaly), cutaneous vasculitis (leukocytoclastic vasculitis histologically proven), or noncompressive neuropathy confirmed by electromyography. The diagnosis of Sjögren’s syndrome was based on the clinical symptoms of dry eyes and dry mouth, confirmed by a positive result on the Schirmer’s test and/or keratoconjunctivitis sicca, with involvement of salivary glands documented by positive findings on lip biopsy and/or salivary scintigraphy. Patients were considered seropositive if the Rose-Waaler test yielded a titer >1:64 on 2 or more occasions.

Gary S. Firestein, MD
Nathan J. Zvaifler, MD
Douglas R. Green, PhD

University of California, San Diego School of Medicine and La Jolla Institute for Allergy and Immunology
La Jolla, CA
The characteristics of this group of patients were generally similar to those in the Spanish and Greek studies. The mean (± SD) age was 56.9 ± 14 years, 80% were female, the mean disease duration was 10.9 ± 9.6 years, and the age at disease onset was 45 ± 10 years. Of interest was the occurrence of extra-articular manifestations in only 18% of the patients (subcutaneous nodules 6.9%, amyloidosis 3.4%, pulmonary fibrosis 3%, vasculitis 1.9%, eye disease other than sicca syndrome 1.1%, serositis 0.6%, Felty’s syndrome 0.6%, Caplan syndrome 0.2%, large granular lymphocytosis 0.1%), a prevalence that was similar to that in the Greek (20.4%) and Spanish (17.5%) patients, but much lower than the prevalence in British patients (66.4% in the Drosos et al study [1] and 41.3% in the Ronda et al study [2]). Moreover, only 51.2% of our patients had erosive disease, suggesting that Portuguese patients might have less destructive arthritis than the British patients (61% of the British patients were found to have Steinbrocker radiologic grade III or IV disease [5] in the Drosos et al study [1]). In accordance with these results was the finding that 92.4% of the Portuguese RA patients were in Steinbrocker functional class I or II, 4.2% in functional class III, and 3.4% in functional class IV (4). In addition, only 28% of the 68 patients with more than 30 years of disease were in functional class III (20.6%) or IV (7.4%). Sjögren’s syndrome was present in 13.3% of our patients, which is comparable with that in the British and Spanish patients, but less than the 39.8% prevalence depicted in Greek RA patients (1).

Our observations support the idea that RA in southern Europe is less aggressive than in other geographic areas. This hypothesis needs further investigation, since it may reflect environmental and genetic factors that will need to be identified to contribute to better management of RA.


Reply

To the Editor:

We greatly appreciate the comments of Dr. Fonseca and colleagues and the interesting results of their study, which are similar to ours and those reported by Ronda et al from Spain.

During the last few years, 2 other studies, 1 from Italy (1) and another from southern France (2), have also supported our findings that RA in Mediterranean countries is less severe with less extra-articular manifestations. Recently, in an attempt to clarify these results, we conducted an epidemiologic survey in which a total of 428 cases of RA were identified. The total prevalence of RA was 2.05 and 4.78 cases/1,000 inhabitants for men and women, respectively. The ratio of women to men was 2.33 and the annual incidence rates fluctuated between 0.15 and 0.36/1,000 inhabitants. These results suggest a relatively low prevalence and low incidence of RA in northwest Greece (3) compared with that reported in northern European and North American countries (4).

All of the above differences observed between Mediterraneans and northern Europeans could be attributed to the differences in genetic, environmental, or other factors. In northern Europe and the US, most white patients with RA express HLA–DRB1 alleles. These alleles have in common, in the third hypervariable region, an epitope called the “shared epitope” (SE) (5). The presence and frequency of the SE are reported to be associated with very destructive arthritis and systemic manifestations in patients with RA. In Greece and in other Mediterranean countries, the course of RA is mild and extra-articular manifestations are rare. This may be because in southern Europe, patients with RA do not express with high frequency the HLA–DRB1 allele that contains the SE (6).

In addition, environmental factors, such as climate, nutrition, or microbial agents, may influence RA disease expression and severity. It is well known that the climate is milder and warmer in Mediterranean countries that in northern Europe. It is known that ultraviolet B light is immunosuppressive, and this could be an additional factor influencing the disease expression in southern Europe. Dietary factors are thought to affect the clinical course of RA. Recent evidence has shown that olive oil and fish oil may offer a protective effect against RA development (7). Olive oil and fish are usually consumed by inhabitants of Mediterranean countries.

All of these points may partly explain the differences in the manifestations of RA among southern and northern Europeans. However, further collaborative studies need to be done for better understanding of RA disease expression, severity, and outcome.

Alexandros A. Drosos, MD, FACR
University of Ioannina
Ioannina, Greece

Gabriel S. Panayi, ScD, MD, FRCP
Guy’s Hospital
London, UK

Haralampos M. Moutsopoulos, MD, FACP, FRCP(Ed)
University of Athens
Athens, Greece

Clinical Images: Leg pain and clubbing

The patient, a 45-year-old woman, presented to the rheumatology clinic with a 6-month history of left leg pain, worse at night. During physical examination, clubbing of her fingers was noted (A). When asked about this, the patient replied that the clubbing had been present all of her life. Her daughter pointed out that it had gotten “much worse over the last 2 years.” The patient’s history of pain and the clubbing prompted us to obtain radiographs of her chest and legs. Radiography of the left leg showed marked thickening of the cortex, and a periosteal reaction (B; arrow) with cortical irregularities (B; arrowhead). The suspicious findings on the chest radiograph led us to obtain a computed tomography (CT) scan of the chest (C). A large posterior right lung mass was defined by CT scan. The mass was biopsied, and the results confirmed a diagnosis of adenocarcinoma of the lung. Further evaluation revealed metastatic disease to her brain. She was treated with radiation for 3 months and later lost to followup. Hypertrophic osteoarthropathy is associated with lung cancer in >90% of the cases in the industrialized world. In this patient, who did not have any risk factors for lung cancer, careful physical examination provided the clues to the correct diagnosis.

Yusuf Yazici, MD
Doruk Erkan, MD
Stephen A. Paget, MD
Hospital for Special Surgery
New York, NY