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References


Authors’ reply to Rozin and Quinn et al

We read with interest the comments by Rozin and by Quinn and colleagues about our recent publication on low dose methotrexate (MTX) osteopathy in a patient with polyarticular juvenile idiopathic arthritis. Our report was not intended to suggest that MTX osteopathy may be more common than expected, and we agree that reported cases of low dose MTX osteopathy are exceedingly rare compared with the number of patients treated with MTX. Certainly, at a first glance it might not be very surprising that this patient developed serial insufficiency bone fractures after 25 years of prednisone treatment. However, the temporal association with the introduction of MTX and the multiplicity of fractures was striking.

We acknowledge that we did not provide further information about other possible factors that might have influenced the risk fracture in this patient. This 35 year old woman was not menopausal, did not smoke, and had a normal diet, and her physical activity was markedly restricted as her polyarticular joint involvement was severe. Unfortunately, family history of osteoporosis and bone mineral density were not assessed. We disagree with Rozin about his interpretation of the technetium-99m diphosphonate scintigraphy bone survey. The multiple areas of increased uptake were asymmetric, which would be unlikely for a flare of polyarticular juvenile idiopathic arthritis. Moreover, the enhanced uptake which was localised to the femoral condyles and right calcaneum is not compatible with joint involvement. The increased uptake is certainly too marked and too different to be related to multiple enthesopathies, which would also be very unusual clinical features in this type of inflammatory rheumatism. In a scintigraphic study of the cruciate deficiency model of knee arthritis in dog, the uptake ratio (unstable cruciate(lateral knee) did not exceed 3.0 (controls value: 1.0 to 1.0). Conversely, in a semiquantitative (“scintimetric”) technetium diphosphonate scintigraphic follow up study of patients with peripheral fractures, the uptake ratio(fracture/normal reference site) was much higher (5.0 to 8.0). In our patient the uptake ratio was 5.5 and 3.7 for the left knee/right knee and right calcaneum/left calcaneum, respectively, which is further evidence for the diagnosis of multiple fractures.

Data for the in vivo effect of MTX on osteoblasts are conflicting, but we agree with Rozin and Quinn and colleagues that the in vivo effect assessed on bone mineral density is reassuring in most studies. Moreover, better control of the inflammatory arthropathies should allow an increase of physical activity, which in turn may improve osteoporosis. The hypothesis of bone hypersensitivity or idiosyncrasy to MTX that is discussed by Rozin is only speculative, but appealing. Finally, we obviously concur with both comments and agree that such an exceptional observation of MTX osteopathy should certainly fractures.0 from the use of MTX in idiopathic juvenile arthritis or other inflammatory arthropathies when it is indicated.

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t references


Clinical comparisons of RA between different populations: are they feasible?

Rheumatoid arthritis (RA) is the most common chronic inflammatory disease,
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RA. genetic differences even among populations Colombians, emphasising the importance of DRB1*1001 was related to RA severity. population. DRB1*0401 and RA in the Latin American development of these trials, but they all not available for such analyses, but our comments of the authors that genetic factors, ideally, should have been examined in both populations. However, blood samples were more commonly used azathioprine, sulfasalazine, and antimalarial drugs, whereas Oslo patients had used methotrexate, gold salts, cyclosporin, and t-pecillicilamine. Surgery was more common in the Oslo patients. That study was developed to compare the evolution and outcomes of two different populations with RA and was the first to include health related quality of life. The authors evaluated the differences between these groups to differences in economic status, medical care, drugs used and, to a lesser extent, genetic differences. During the past years the HLA system has been gaining an increasingly important role in the pathogenesis of autoimmune diseases. HLA polymorphism has multiple effects on the immune system. HLA-DRB1 alleles have been associated with RA in a number of populations. In the third hypervariable region of their DRβ1 chain, they share a sequence of amino acids named “the shared epitope” (SE). In a mestizo Colombian population we found that the SE 78QKRRA74 in DRB1*04 alleles had the strongest association with RA. However, we did not find any significant association between HLA and RA in African Colombians, emphasising the importance of genetic differences even among populations living within the same country. There have been different findings from one area to another. In Latin America, the differences are important. In Chilean patients the HLA-DRB1*1001 alleles were DRB1*0404 and *0408 and the SE influenced the radiographic evolution of hands erosions. In the Argentinian population the DRB1*0404 was also important but only DRB1*1501 was related to RA severity. In the Peruvian population an association between RA and the SE was not found. There was a lack of uniformity in the development of these trials, but they all showed a lack of association between DRB1*0401 and RA in the Latin American population. These findings suggest that SE inheritance and genetic influence may vary depending on the genetic background of the studied populations even in apparently closely located countries. The previous study comparing the Norwegian and Lithuanian populations without inclusion of genetic typing may be misleading. Furthermore, not only may the HLA system play a part in the disease outcome and disease progression of these patients but pharmacogenetics may also be at least as important. The efficacy of methotrexate, cyclosporine, and other DMARDs in reducing the radiological progression of RA erosions has been proved; however, their efficacy and tolerability may be influenced by mutations in their metabolic pathways or in their cellular targets. Epidemiology of autoimmune diseases is becoming more complex as our knowledge of HLA and genetics becomes more complete. The time is coming when diseases will be defined not only by their symptomatology but also by the genetic background of their hosts.

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References


Authors’ reply

We thank Drs Cadena and Anaya for their important and interesting comments on our paper reporting differences in disease activity and health status between matched patients in Norway and Lithuania.

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References


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