Letters to the Editor

IgA rheumatoid factor in patients with chronic HCV infection: Prevalence and clinical correlations

Sirs,

The significance of various rheumatoid factor (RF) isotypes such as IgM, IgG and IgA has been previously assessed in both rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) (1, 2). Many studies reported that IgA RF was found in association with heightened RA and SLE disease activity when detected in co-existence with IgM RF (3, 4). Polyarthritis, in association with positive IgM RF, is frequently described in patients with chronic HCV infection (5), thus making the differential diagnosis between HCV-related arthritis and "true"RA difficult in some cases. Since the role of IgA RF in HCV-infected patients has not been investigated, we conducted this study to ascertain whether the presence of IgA,in addition to IgM,RF differs in RA and HCV patients and correlates with extrahepatic signs such as arthritis and/or cryoglobulinemia.

Two groups of patients were studied for the presence of both IgM and IgA isotypes of RF. The first included 39 randomly selected HCV-infected patients, positive for anti-HCV antibody, with detectable HCV RNA and scored for histological activity index. All patients underwent the following laboratory studies: alanine aminotransferases (ALT), cryoglobulines, antinuclear antibodies, antibodies to smooth muscle (aSMA), and cardiolipin (aCL). Disease severity was estimated by taking into consideration the viral load, serum level of ALT and liver histology (6). The second group included 37 patients suffering from rheumatoid arthritis, HCV negative and scored for disease severity using a global score of the patient's clinical state (in particular articular swelling/ deformity, subcutaneous nodules and radiographic erosions) and serological markers such as C-reactive protein (CRP), RF and anti-keratin antibodies (AKA).

Arthritis was noted in 12/39 (31%) of HCV-infected patients (in 2 erosive arthritis) with type II cryoglobulinemia. IgMκ was documented in 14/33 (42%) patients. We found IgA RF in 14/39 (35%) patients with chronic HCV infection (co-existing with IgM in 8 and alone in 6 patients). Whereas the presence of IgA RF was positively associated with cryoglobulinemia ($p = 0.012$, and arthritis,$p = 0.019$) (Fig. 1),its presence did not correlate with liver disease severity or with the HCV load. None of the analyzed autoantibodies were found to correlate with IgA RF positivity.

In RA, IgM RF was present in 29/37 (78%) patients and IgA RF in 10/37 (27%), all of whom were IgM RF positive as well. The co-existence of IgA and IgM RF, as well as the presence of AKA, were found to be in significant association with clinical RA disease severity, compared to that of IgM RF alone, $p = 0.002$.

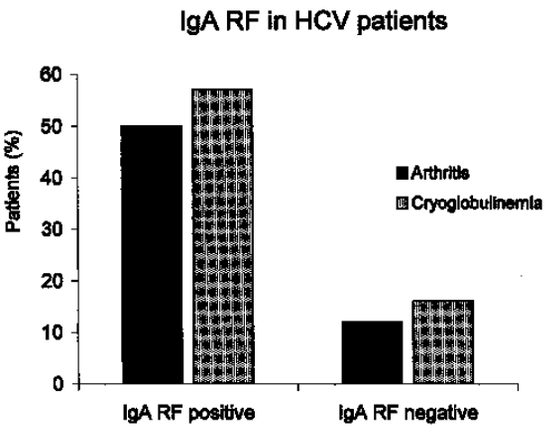

Fig. 1. Association between IgA RF presence, arthritis and cryoglobulinemia in chronic HCV-infected patients.

The frequent finding of RF in patients with chronic HCV infection along with articular complaints and even erosive arthritis in some, creates confusion in differentiating between true RA and HCV-related arthritis. In this regard we previously reported that anti-keratin antibodies are highly specific to RA, while relatively rare in HCV-infected patients (7). In this limited sample, the finding of IgA RF in the absence of IgM RF was only noted in HCV and thus may be additionally useful in distinguishing true RA from HCV-related arthritis. Our finding of an association between the presence of IgA RF and both arthritis and cryoglobulinemia could be the result of a higher extent of polyclonal B cell activation. Therefore, it may be proposed that the polyclonal activation of HCV-infected B cells is important for the initiation of autoimmunity during the early stages of chronic HCV infection, when both IgM and IgA RF are produced.

Additionally, it may be speculated that altered uptake of IgA RF/ HCV immune complexes, different from IgM RF immune complexes by phagocytes, leaves them longer in the circulation, thus further promoting inflammation and the association with arthritis and cryoglobulins. Based on our findings,the presence of IgA along with IgM RF in untreated patients with chronic HCV infection might be used as a marker for predicting the development of arthritis or cryoglobulinemia. We will further study the possibility that antiviral treatment might target IgA RF along with other targets of prognostic value.

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