

PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/22818>

Please be advised that this information was generated on 2018-07-07 and may be subject to change.

sensitive and cost-effective markers for most patients with PMR.

M. Tellus, MB, BS
K. Byron, BSc, PhD
S. Sachthep, MB, BS
S. Ratnaike, MB, BS, MSc, FRCPA
*Royal Melbourne Hospital
Victoria, Australia*
I. Wicks, MB, BS, FRACP, PhD
*Walter and Eliza Hall Institute
and Royal Melbourne Hospital
Victoria, Australia*

1. Baumann H, Gauldie J: The acute phase response. *Immunol Today* 15:74–80, 1994
2. Roche NE, Fulbright JW, Wagner AD, Hunder GG, Goronzy JJ, Weyand CM: Correlation of interleukin-6 production and disease activity in polymyalgia rheumatica and giant cell arteritis. *Arthritis Rheum* 36:1286–1294, 1993
3. Riches P, Gooding R, Millar B, Rowbottom AW: Influence of collection and separation of blood samples on plasma IL-1, IL-6 and TNF-alpha concentrations. *J Immunol Methods* 153:125–131, 1992

Reply

To the Editor:

A prompt therapeutic response to corticosteroids is one of the characteristic features of PMR. However, due to the age of the patient population affected, steroid side effects are likely. Minimizing the steroid dose remains an attractive goal in the management of these patients. Cytokine measurements might be suitable for monitoring disease activity and adjusting the steroid therapy appropriately.

Tellus et al have addressed the question of whether IL-6, IL-8, and TNF α concentrations in the blood represent sensitive tools for assessing disease activity in patients with PMR. In their study, 4 patients with established PMR were monitored for different parameters indicative of acute-phase responses. The authors found that despite marked elevations in the ESR and CRP level, serum levels of IL-6, IL-8, or TNF α were not increased. Normal levels of IL-6 were defined as <20 pg/ml. They concluded that both accurate timing of the sample collection and highly sensitive cytokine assays are necessary to reliably monitor these mediators in the blood.

We and others have previously reported that elevated plasma levels of IL-6 is a consistent finding in patients with untreated or partially treated PMR and GCA (1,2). Peripheral blood monocytes are constitutively activated in both diseases and represent the likely source of the circulating IL-6 (3). Our original observation that plasma IL-6 levels correlated explicitly well with symptoms in patients with PMR prompted us to monitor standard clinical and laboratory parameters and plasma IL-6 concentrations in a prospective study.

Thus far, we have enrolled 24 patients with PMR and 14 patients with biopsy-proven GCA. We have used a commercial ELISA that has a sensitivity of <1 pg/ml to determine IL-6 levels (R & D, Minneapolis, MN). Plasma IL-6 levels in normal controls are 1.3 ± 1.6 pg/ml (mean \pm SD). Thirty-eight percent of patients with PMR had IL-6 concentrations above

20 pg/ml at the initial presentation. In 79% of patients, pretreatment IL-6 levels were higher than 5 pg/ml. In general, patients with lower IL-6 levels also had a lower ESR. However, we agree with the observation of Tellus et al that there is not a linear correlation between IL-6 levels and the ESR. In the longitudinal studies, increases in plasma IL-6 levels correlated with flares of PMR and increased requirements for steroids. Interestingly, both IL-6 elevations and steroid dose increases necessary to control clinical disease could be subtle.

One intriguing observation from these studies is that heterogeneity exists for IL-6 induction in the patient population. Some patients have highly elevated plasma concentrations of IL-6, but a small fraction of patients appears not to produce increased amounts of IL-6. In patients with PMR, this heterogeneity could reflect a diversity of disease processes presenting with a PMR-like syndrome. However, we have seen a similar phenomenon in patients with biopsy-proven GCA. We have therefore begun to explore the possibility that genetic heterogeneity is responsible for the differences in IL-6 induction. The distinct geographic distribution of PMR and GCA, with a marked preference for individuals of Northern European origin, is likely a surrogate for genetic risk determinants clustering in some ethnic populations. The regulation of IL-6 production may be related to such a genetic susceptibility factor. Comparison of patients from different geographic regions and of different ethnic origin will be extremely helpful in unraveling genetic components in PMR and GCA.

Cornelia M. Weyand, MD, PhD
Jörg J. Goronzy, MD, PhD
*Mayo Clinic
Rochester, MN*

1. Roche NE, Fulbright JW, Wagner AD, Hunder GG, Goronzy JJ, Weyand CM: Correlation of interleukin-6 production and disease activity in polymyalgia rheumatica and giant cell arteritis. *Arthritis Rheum* 36:1286–1294, 1993
2. Dasgupta B, Panayi GS: Interleukin-6 in serum of patients with polymyalgia rheumatica and giant cell arteritis. *Br J Rheumatol* 29:456–458, 1990
3. Wagner AD, Goronzy JJ, Weyand CM: Functional profile of tissue infiltrating and circulating CD68⁺ cells in giant cell arteritis: evidence for two components of the disease. *J Clin Invest* 94:1134–1140, 1994

Analysis of anti-U1 RNA antibodies in patients with connective tissue diseases: comment on the article by Hoffman et al

To the Editor:

We read with interest the article by Hoffman and coworkers, in which they report a correlation between the presence of anti-U1 RNA antibodies with anti-70K and anti-A polypeptide antibodies, and the immunogenetic distinction between the anti-U1 RNA positive connective tissue disease (CTD) patient group with the anti-U1 RNA negative patient group (1). Furthermore, Hoffman et al found that the anti-U1 RNP positive, anti-U1 RNA negative group consisted of patients with various symptoms of mild mixed connective tissue disease (MCTD) and systemic lupus erythematosus (SLE), while the anti-U1 RNP, anti-U1 RNA positive group com-

prised patients with more typical MCTD features. According to the authors, these findings indicate that the presence of anti-U1 RNA antibodies may be a specific marker for MCTD.

This indication needs to be further examined since the concept of MCTD as a separate disease entity has been challenged (2), and since the majority of patients with MCTD will eventually fulfill well-established classification criteria for SLE, systemic sclerosis (SSc), rheumatoid arthritis (RA), or combinations of these diseases (3). The authors should have shown how many anti-U1 RNA positive patients in their study fulfilled classification criteria for CTDs such as SLE, SSc, RA, Sjögren's syndrome, or polymyositis/dermatomyositis. Moreover, in larger groups of anti-U1 RNP positive patients with a well-established CTD, the presence of anti-U1 RNA antibodies should be examined. Without these analyses, no judgment about the specificity of anti-U1 RNA antibodies can be made.

Frank H. J. van den Hoogen, MD, PhD
 Agnes M. T. Boerbooms, MD, PhD
 Leo B. A. van de Putte, MD, PhD
*University Hospital Nijmegen
 Nijmegen, The Netherlands*

1. Hoffman RW, Sharp GC, Deutscher SL: Analysis of anti-U1 RNA antibodies in patients with connective tissue diseases: association with HLA and clinical manifestations of disease. *Arthritis Rheum* 38:1837-1844, 1995
2. Black C, Isenberg DA: Mixed connective tissue disease—goodbye to all that. *Br J Rheumatol* 31:695-700, 1992
3. Van den Hoogen FHJ, Spronk PE, Boerbooms AMT, Bootsma H, De Rooij DJRAM, Kallenberg CGM, van de Putte LBA: Long-term follow-up of 46 patients with anti-(U1)snRNP antibodies. *Br J Rheumatol* 33:1117-1120, 1994

Reply

To the Editor:

We recognize that disease classification for patients with MCTD is an area of controversy among some investigators who would prefer to classify MCTD as SLE or SSc, or simply rename MCTD as "undifferentiated connective tissue disease." We have recently reviewed this controversy and have discussed the problems that are encountered in all disease classification schemes, wherein the etiology of a disease is unknown and the clinical manifestations are pleomorphic and overlap with other diseases (1). Briefly, it is important to recall that a single clinical syndrome (e.g., polyarthritis) may have many etiologies, and a disease with a single etiology (e.g., Lyme disease) may cause many different clinical syndromes. Until the precise etiology of each of the entities (i.e., MCTD, SLE, and SSc) is known, controversy will remain. Based on its distinctive clinical, serologic, and, more recently, immunogenetic characteristics, we believe that recognition of MCTD does serve a useful purpose for research, as well as for treatment and prognosis (1).

Contrary to the statement of van den Hoogen et al, it is not definite that the MCTD in the majority of patients will progress to fulfill well-established classification criteria for other rheumatic diseases (1-3). Furthermore, only 2 published

reports have examined this question among relatively small numbers of anti-U1 RNA positive patients (4,5), and clearly, more study is needed before any final conclusions can be reached.

A large and expanding body of data support our position that disease classification by specific autoantibodies and HLA genotypes identifies distinct disease groups in patients more precisely than can be accomplished using previous serologic or clinical classification schemes, either alone or in combination (6). We have recently reviewed the relationship between autoantibodies, immunogenetic markers, and disease classification (6).

We disagree with van den Hoogen et al that stratification of patients by clinical disease classification criteria rather than by serologic criteria, such as the presence of anticentromere antibodies, anti-SS-A/Ro and anti-SS-B/La antibodies, anti-double-stranded DNA (dsDNA) antibodies, or anti-RNP antibodies, would have enhanced our study. We intentionally classified patients based solely upon serologic findings in an attempt to avoid ambiguity and inadvertent bias in our selection criteria. We would note for the readers' interest that the patients who were reported (4) to have anticentromere antibodies had SSc, those with anti-SS-A/Ro or anti-SS-B/La had Sjögren's syndrome or SLE, and those with anti-dsDNA antibodies had SLE.

Finally, we agree that collaborative, multicenter, international studies using large numbers of well-characterized patients should be performed, and might provide additional information on the nature of patients possessing anti-U1 RNA antibodies. Only by moving forward in cooperation will these questions be answered.

Robert W. Hoffman, DO
 Gordon C. Sharp, MD
 Susan L. Deutscher, PhD
*University of Missouri-Columbia School of Medicine
 Columbia, MO*

1. Sharp GC, Hoffman RW: Mixed connective tissue disease. In: *Connective Tissue Disease*. Edited by JF Belch, RB Zurier. London, Chapman and Hall, 1995
2. Sullivan WD, Hurst DJ, Harmon CE, Esther JH, Agia GA, Maltby JD, Lillard SB, Held CN, Wolfe JF, Sunderrajan EV, Marieq HR, Sharp GC: A prospective evaluation emphasizing pulmonary involvement in patients with mixed connective tissue disease. *Medicine (Baltimore)* 63:92-107, 1984
3. Lundberg I, Hedfors E: Clinical course of patients with anti-RNP antibodies: a prospective study of 32 patients. *J Rheumatol* 18:1511-1519, 1991
4. Hoffman RW, Sharp GC, Deutscher SL: Analysis of anti-U1 RNA antibodies in patients with connective tissue diseases: association with HLA and clinical manifestations of disease. *Arthritis Rheum* 38:1837-1844, 1995
5. Hoet RM, Koornneef I, de Rooij DJ, van de Putte LB, van Venrooij WJ: Changes in anti-U1 RNA antibody levels correlate with disease activity in patients with systemic lupus erythematosus overlap syndrome. *Arthritis Rheum* 35:1202-1210, 1992
6. Hoffman RW, Sharp GC: Is anti-U1 RNP autoantibody positive connective tissue disease genetically distinct? *J Rheumatol* 22:586-589, 1995