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The Holy Grail and systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a clinical condition that fascinates physicians, scientists and laymen, possibly due to some characteristics, such as unpredictability, multifaceted phenotype, potential morbidity and its etiopathogenesis mystery. These features permeate several aspects of SLE, making it one of the most difficult diseases to manage clinically. Among several others, two challenges have a special place in scientific and clinical SLE forums: definition of type and degree of renal activity, and definition of activity status and quiescence of this disease. Despite researchers' efforts, these are two problems in clinical practice for which there is no easy and generic solution, but relative and specific solutions for each case. This edition of *Brazilian Journal of Rheumatology* brings two relevant studies on these topics.

Melo *et al*.[1] made an interesting approach on clinical and histological correlation in diagnosis and therapeutic analysis of lupus nephritis. In this study, the authors carried out a retrospective analysis of 100 consecutive SLE cases followed by lupus nephritis at Department of Rheumatology of Santa Casa de Misericórdia de São Paulo. The goal was to compare therapeutic response at 12 and 24 months related to several variables at the beginning of treatment and according to the nephritis class alternately established based on histological analysis or clinical judgment. Although it was not a prospective and controlled study, the authors have benefited from the fact that the therapeutic regimen recommended in the service is standardized and regularly used, so there was an acceptable homogeneity in this item. To forms considered milder (class II), corticosteroid was used at 1mg/kg/day doses; and to more severe forms (classes III, IV and V), classical regime was used, based on induction with intravenous cyclophosphamide and methylprednisolone and maintenance with azathioprine or mycophenolate mofetil.

During observation period, there was a favorable response in most patients, with 72.7% of patients reaching total remission at 12 months and 85.7% at 24 months. Partial remission was observed in 27.3% of patients at 12 months and in 14.3% of patients at 24 months. Although follow-up had been relatively short, these cases are encouraging, especially when considering conditions not always ideal for support, due to poor medical assistance in public health service. As expected, a significant portion of patients presented relapse, most during maintenance phase, but there was favorable response after adjusting corticosteroid and immunosuppressant doses.

Considering the influence of several variables on therapeutic response, authors found some interesting findings. As expected, men presented a lower rate of total remission (45.5%) compared with women. This confirms the notion already established of a worse prognosis of lupus nephritis in men. Clinical and laboratory variables assigned in the beginning of treatment could not distinguish patients who presented total remission from those with partial remission at 12 months. However, it is noteworthy mentioning that serum creatinine levels and leucocyturia levels presented trends to higher values in patients who presented only partial remission.

The most relevant contribution of this study was the ingenious comparative analysis between the clinical and laboratory judgment and the histopathological examination to define glomerulonephritis class related to therapeutic result. It is interesting to say that parameters referring to disease activity, urinary changes and serum Complement consumption did not differ among patients defined as class IV by histological criterion or clinical and laboratory judgment. This finding seems to suggest a reasonable equivalence between both criteria. However, therapeutic response was clearly more favorable in patients defined as class IV by the clinical and laboratory trial than in group defined by histological criterion. These findings may be interpreted in various ways. A reasonable interpretation is that in the group selected according to the clinical and laboratory judgment there could be patients whose histological classification did not correspond to class IV, although clinic and laboratory manifestations had suggested. As possible representatives of histological classes II and III, these patients may have diverted this group to a higher index of total remission. This rationale is consistent with the concept that histological criterion is more accurate in predicting clinical evolution. This interpretation may suggest that renal biopsy can be assigned more liberally. However, it may also reinforce the idea that, for most of the cases, the clinical and laboratory judgment may be sufficient for initial decision made by an expert physician, and that therapeutic response may represent

an additional parameter to conduct these cases. Thus, the work of Melo *et al*. reaffirms this issue complexity and confronts the possibility of two different and complementary ways of approaching lupus nephritis.

Another intriguing aspect in SLE research is the search of authentic parameters to monitor inflammatory activity. Several parameters have been proposed such as serum levels of some autoantibodies, Complement components determination, acute phase reactants, evaluation of urinary sediment and hematimetric index, and others.

Among autoantibodies, the following antibody levels are highlighted: native anti-DNA, anti-nucleosome, anti-C1q and ribosomal anti-P. Several studies have shown that these autoantibodies tend to elevate their levels during periods of increased disease activity and tend to decline or even disappear during periods of remission. Although antibodies against extractable nuclear antigen (SS-A/Ro, SS-B/La, Sm and U1-RNP) also present fluctuation during the illness, there is no evidence of correlation with inflammatory activity[2] also there is no evidence that antinuclear antibody (ANA or antibodies against cell constituents) has association with disease activity. This association with serum levels of antibodies against native DNA, nucleosome, C1q and ribosomal P protein seems to suggest that such autoantibodies have a real physiopathologic role in some SLE patients. However, such association is far from being absolute, since many patients do not comply. Additionally, a great part of patients does not show these autoantibodies in any moment of the disease. Thus, certain autoantibody levels in SLE have a true role, but restrict, in monitoring SLE activity.

Because one of SLE physiopathologic pathways is based on deposition of immune complexes and Complement system activation, it is natural that monitoring this system component is useful in SLE activity follow-up. During many decades, total hemolytic activity of Complement has been measured, as well as serum levels of some components in this system, as support to monitor disease activity in SLE. Although there is association between Complement consumption and disease activity, especially in lupus nephritis, there are several cases of disagreement, mainly in non renal manifestation. Part of this disagreement possibly comes from the fact that component levels of Complement suffer influence from external variables, such as pool replacement rate variability, increment of synthesis as an effect of acute phase response and wide variation of normality values. More recently, some authors have proposed to measure degradation product of Complement, such as C4a, C3a and Bb, that would not suffer such influences.[3] The performance of these parameters in monitoring disease activity remains under trial.

Theoretically, acute phase proteins would be rational parameters to monitor the activity of inflammatory diseases, such as SLE. Curiously, however, this is not seen systematically in practice. Normally, patients are seen with no evident signal of disease activity and presenting consistently high levels of C-reactive protein (CRP) and elevated erythrocyte sedimentation rate. Reciprocally, it is not uncommon to see patients in full activity and with normal or minimally changed values. This paradox probably hides some uncommon aspect and possibly of great interest for understanding SLE physiopathology.

As a consequence of laboratory parameter limits available to monitor SLE activity, several researchers continue searching more efficient alternatives. In this edition of *Brazilian Journal of Rheumatology*, Carvalho *et al*. documented a new and interesting parameter with potential association with SLE disease activity.[4] Lipoprotein lipase (LPL) antibodies were recently described in SLE and in other autoimmune diseases.[5-7] These autoantibodies present correlation with triglyceride serum levels. Carvalho *et al*. had previously demonstrated that anti-LPL antibodies have correlation with some parameters of disease activity, such as hypocomplementemia, ultrasensitive CRP and SLEDAI.[6] In this edition, these authors suggest an interesting dual behavior of these autoantibodies based on case report of 5 patients. In patients with consistently quiescent disease, anti-LPL antibodies were kept stable and in high levels. On the other hand, anti-LPL levels oscillate in patients with unstable disease, with periods of activity alternating with periods of quiescence. This is an intrigant finding and it will certainly stimulate additional studies to establish possible differences in subpopulations of anti-LPL antibodies in such contexts, as well as define their use in monitoring SLE disease activity.

The search for excellence is a human characteristic in all areas in which this restless being works; sometimes this search aims an utopian solution, of absolute simplicity and solvability. The Holy Grail, Philosopher's Stone and *Moto Continuum* are archetypal representations of this feature of our species. However, real progress along our history has been achieved by concrete and infinitesimal efforts; brick by brick, mortar, dream and sweat. So has been the conquest of systemic lupus erythematosus. There is no magic, no absolute parameter. The Holy Grail is a mixture of cumulative knowledge from studies, such as those mentioned before, mature clinical experience, technical excellence, commitment to help the patient and ability to have a humble judgment in front of each case.

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