Pulmonary alveolar proteinosis (PAP) is a rare entity, characterized by the excessive accumulation of surfactant proteins and phospholipids in the alveolar spaces and terminal bronchioles, that can typically cause a serious deterioration in gas exchange, with the onset of progressive respiratory failure, or else present without clinical symptoms. First described in 1958, PAP is considered a rare disease, with an estimated incidence of 0.2–0.4 cases per million individuals/year and a prevalence of 3.7–6.2 cases per million individuals/year. It is a heterogeneous entity, divided into 2 categories: congenital PAP and acquired PAP, which in turn is divided into 2 distinct clinical forms, idiopathic PAP (iPAP) and secondary PAP.

In all of its forms, the underlying physiopathological feature is the accumulation of surfactant in the alveolar spaces, caused by macrophages failing to process these compounds, or by acquired neutralization, due to congenital dysfunction of the granulocyte-macrophage colony-stimulating factor (GM-CSF), by gene mutations in cell-surface receptors, and in some cases, by changes in proteins in the surfactant itself.

The mechanisms that lead to macrophage dysfunction differ in each clinical form. Congenital PAP, for example, has been associated with recessive anomalies of the gene that encodes GM-CSF-binding α and β chains, and with mutations in the genes encoding B and C surfactant proteins. Secondary forms are associated with blood disorders, infections, or exposure to diverse environmental substances. The idiopathic variant (iPAP) is the most common form of presentation, accounting for up to 90% of cases of PAP. This clinical form, also known as autoimmune PAP, is characterized by the presence of anti-GM-CSF antibodies that block GM-CSF bioactivity in vivo, affecting the terminal differentiation of macrophages, and consequently their capacity to process lung surfactant.

The detection of high levels of anti-GM-CSF antibodies in peripheral blood and bronchoalveolar lavage (BAL) using ELISA techniques is now accepted as a useful tool in the diagnosis of iPAP, with a sensitivity of 100% and a specificity of 98%, even in asymptomatic phases. This has also guided the development of new treatment strategies for iPAP, such as the exogenous administration of GM-CSF as an alternative or therapeutic complement to whole lung lavage (WLL).

The applicability of anti-GM-CSF antibodies in follow-up and as a marker of therapeutic response is still under discussion. Another line of research involves the possible correlation between anti-GM-CSF antibody titers and the degree of disease extension, but results from studies performed to date have been contradictory. Unlike other serological markers, no association has been observed between anti-GM-CSF antibody levels and iPAP severity, quantified by symptoms and decline in partial pressure of oxygen. Nor has any concordance been demonstrated with lung function decline, or with variations in other serum biomarkers (carcinoembryonic antigen, Krebs von den Lungen-6, surfactant protein A, surfactant protein D, and lactate dehydrogenase). However, antibody levels in BAL samples and the ratio of anti-GM-CSF kappa and lambda light chains in serum have shown some association with the degree of hypoxemia and with Krebs von den Lungen-6 and surfactant protein D levels, previously reported as markers of severity.

The response of anti-GM-CSF antibodies in serum after WWL, the therapeutic technique of choice for PAP, is controversial. Although there are few references in the literature, Sugimoto et al., in a study of 8 patients with iPAP who underwent WWL, showed a decrease in serum levels of Krebs von den Lungen-6, surfactant protein A, surfactant protein D and carcinoembryonic antigen after the WWL. However, anti-GM-CSF antibody levels fell only temporarily in 7 cases. On the other hand, an association between anti-GM-CSF antibodies in BAL and the need to perform WWL as a therapeutic strategy has been observed in some patients.

The response of anti-GM-CSF antibodies in serum after the administration of inhaled and/or subcutaneous GM-CSF has also shown mixed results. Ohashi et al. determined anti-GM-CSF antibody levels in the serum and BAL of patients with iPAP before and after the administration of inhaled therapy with GM-CSF, and found a decrease in antibody levels in BAL, but not in serum, after administration of the drug. They also observed a greater decline of these levels in patients who responded to treatment; these
same patients also had higher antibody titers at the outset. To date, no studies have been performed to monitor anti-GM-CSF antibody levels after treatment with rituximab, or after lung transplantation, which could be interesting in order to assess early disease recurrence in the graft.

Given the available scientific evidence, we believe that while the determination of anti-GM-CSF antibodies has proven to be a useful tool in the diagnosis of iPAP, the implications of these proteins in the follow-up or response to treatment have yet to be defined. The long-term monitoring of anti-GM-CSF serum levels could clarify their usefulness as an early detector of recurrence and would let us determine, individually for each patient, the baseline values and cut-off points that precede the onset of clinical symptoms. Other studies, such as those addressing the standardization of methodology with the international distribution of reference standards, or the possible natural immunomodulator role of cytokine autoantibodies, could open up new lines of research which will help us better understand and manage this disease.

References