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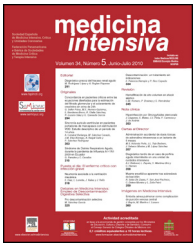

REVIEW

Role of biomarkers in the differential diagnosis of acute respiratory failure in the immediate postoperative period of lung transplantation☆

L. Ruano[a,b,*], J. Sacanell[a,c], A. Roman[a,b,d], J. Rello[a,b,c]

[a] *Vall d'Hebron Institute of Research, Universitat Autónoma de Barcelona, Barcelona, Spain*
[b] *Centro de Investigaciones Biomédicas en Red (CIBERES), Mallorca, Spain*
[c] *Servicio de Medicina Intensiva, Hospital Universitario Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain*
[d] *Servicio de Neumología, Hospital Universitario Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain*

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Abstract Lung transplant recipients are at high risk of suffering many complications during the immediate postoperative period, such as primary graft dysfunction, acute graft rejection or infection. The most common symptom is the presence of acute respiratory failure, and the use of biomarkers could be useful for establishing an early diagnosis of these conditions.

Different biomarkers have been studied, but none have proven to be the gold standard in the differential diagnosis of acute respiratory failure.

This paper offers a review of the different biomarkers that have been studied in this field.

PALABRAS CLAVE
Biomarcadores;
Trasplante pulmonar;
Insuficiencia respiratoria aguda

Papel de los biomarcadores en el diagnóstico diferencial de la insuficiencia respiratoria aguda en el postoperatorio inmediato del trasplante pulmonar

Resumen Los receptores de un trasplante pulmonar tienen un alto riesgo de presentar numerosas complicaciones durante el postoperatorio inmediato, como la disfunción primaria del injerto, el rechazo agudo del injerto o las infecciones. El síntoma más común será la presencia de insuficiencia respiratoria aguda, y el uso de biomarcadores podría ser de gran utilidad para establecer un diagnóstico precoz de estas entidades.

Hasta la fecha, se han estudiado diferentes biomarcadores, pero ninguno ha demostrado ser el gold estándar en el diagnóstico diferencial de la insuficiencia respiratoria aguda.

En este artículo se expone una revisión de los diversos biomarcadores que han sido estudiados en este campo.

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* Corresponding author.
E-mail address: laura.ruano@vhir.org (L. Ruano).

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Introduction

In the last 20 years, lung transplantation has become an established practise for prolonging survival among patients with advanced-stage lung disease. According to the registry of the International Society for Heart and Lung Transplantation,[1] a total of 3272 transplants were carried out in the year 2009, and during the first month mortality was fundamentally attributable to primary graft dysfunction (PGD) (27.1%), followed by infections (20.1%). In turn, almost 4% suffered acute rejection.

Thus, lung transplant recipients are at a high risk of developing many complications during the immediate postoperative period, including PGD, acute graft rejection of the development of infections, as commented above. The most frequent manifestation in all these clinical conditions is acute respiratory failure (ARF). For this reason, the differential diagnosis of these conditions can be very difficult to establish, and may have important consequences, since the treatment required in each case differs in certain aspects. Thus, in the presence of acute rejection, we need to increase the level of immunosuppression; in the case of PGD, immunosuppression must be lowered; and in patients with infections we must prescribe antibiotic treatment. In this context, although the diagnosis of PGD is fundamentally clinical, distinction between rejection and infection often requires histological evaluation of the samples obtained by fibrobronchoscopy with transbronchial biopsy. The use of this technique is limited, however, since it is invasive and has potential complications that can prove serious – particularly in patients with severe ARF.

Despite the existence of preventive measures against PGD,[2] such as the optimization of lung preservation, the minimization of ischemia time, and the avoidance of barotrauma during lung donor maintenance, once the damage has been established, the treatment is similar to that applied in patients with respiratory distress syndrome. In any case, a survival rate of 80% in the first year after transplantation, and of 50% after 5 years of follow-up, is considered acceptable.

The fact that the lungs are in direct contact with the exterior, among other factors, contribute to the need for high levels of immunosuppression; despite such immunosuppression, however, the acute rejection rates remain high.[3]

Different biomarkers have been investigated with the aim of improving and anticipating the diagnosis of these disorders. A biomarker is defined as a parameter or characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathological conditions, or responses to drug treatment.[4] An ideal biomarker is a parameter that can be recorded quickly from a sample obtained in a minimally invasive manner, and which is simple to preserve and handle. In addition, an ideal biomarker should be sensitive, reproducible, predictive and cost-effective. The lack of biological markers capable of predicting the early onset, progression and severity of disease has had a negative impact upon the identification and development of effective drug treatments for improving morbidity and mortality among critical patients.

Many biomarkers potentially useful for the differential diagnosis of post-transplantation ARF have been studied. However, their use in daily clinical practise is very limited, since the available supporting evidence is scarce. The present study offers a clinical review of the available evidence referred to the usefulness of the different biomarkers in application to the differential diagnosis of ARF in the immediate postoperative period of lung transplantation.

Primary graft dysfunction

Primary graft dysfunction (PGD) is a form of acute lung injury occurring in the immediate post-transplantation period, and which has been defined by the consensus document of the International Society for Heart and Lung Transplantation as hypoxemia manifesting in the first 72 h after lung transplantation, with pulmonary infiltrates evidenced on the chest X-rays.[5] The prevalence of PGD ranges widely from 10–40%,[6,7] and its appearance has prognostic implications, since it is associated with increased morbidity-mortality in the Intensive Care Unit (ICU).[6,8,9] At clinical level, PGD has been almost exclusively associated with ischemic damage occurring during lung preservation and posterior reperfusion–though factors related to donor maintenance may also play an important role.[10] The physiopathology of PGD is characterized by an increase in the concentration of inflammatory and endothelial and epithelial dysfunction biomarkers.[11,12] For this reason, an analysis has been made of the usefulness of different biomarkers in the diagnosis of primary graft dysfunction, taking into account the degree of PGD (Table 1).

Cytokines

Cytokines are low molecular weight proteins secreted by different immune cells. They play a key role in inflammation and in regulation of the immune response. Different studies have examined the usefulness of cytokine determination in the diagnosis of PGD. In this sense, it has been shown that elevated interleukin 8 (IL-8) levels in the immediate post-transplantation period are significantly correlated to the subsequent development of PGD.[13] On the other hand, studies of changes in the expression of different cytokines and chemokines during the immediate post-transplantation period[14] have revealed an increase in the plasma levels of monocyte chemotactic protein-1 (MCP-1) and IP-10, a protein induced by gamma-interferon (IFN-γ), implicated in the recruitment of monocytes and lymphocytes, in those patients that develop PGD. These results suggest that macrophage activation induced by IFN-γ, and the attraction of monocytes and effector T cells, could play an important role in the pathogenesis of PGD. In fact, there are data indicating that IP-10 could be an important factor in cardiac and renal post-transplantation injury.[15–19] On the other hand, the concentration of interleukin 6 (IL-6), in both bronchoalveolar lavage (BAL) and in plasma, measured in the first hours after transplantation, is directly related to the development of PGD.[20] Likewise, elevated IL-8 concentrations in donor BAL favor the development of PGD and imply a prolongation of mechanical ventilation in the transplant recipient.[13]