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Mini Review

Therapeutic Apheresis, Immunosuppression, and Human Monoclonal Antibodies in Respiratory Diseases

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Introduction

Therapeutic Apheresis (TA) is an essential supportive treatment for severe and refractory diseases with or without immunologic origin [1]. The clinical manifestation of allergic diseases of the lung of atopic individuals, such as asthma bronchial, are caused by obstruction of the large and small airways of the lower respiratory tract, Obstruction is caused by immune mediated bronchospasm, edema, thick secretion, and hyperplasia of smooth muscle and mucous glands. This can lead to ventilatory insufficiency, and in severe episodes may require ventilatory support. Medical therapy is aimed at relaxing smooth muscle, relieving bronchospasms and suppressing the immune response [2,3].

Therapeutic Plasma Exchange (TPE) or adsorptions methods would seem advisable in patients with severe therapy-resistant allergic asthma bronchial, particularly in status asthmaticus when medicinal therapy is inadequate. One could also consider intermittent TA in the chronic steroid dependent asthmatic to decrease steroid requirements when indicated. The Human Monoclonal Antibody (HMA) omalizumab inhibits IgE effector functions by blocking IgE binding to high-affinity receptors on IgE cells, and in patients with atopic asthma omalizumab decreases serum IgE levels and allergen-induced bronchoconstriction [4].

Churg-Strauss syndrome is a small-vessel necrotizing vasculitis typically characterized by asthma, lung infiltrate, extravascular necrotizing granulomatosis and hyper eosinophilia, and is a rare disorder which is described as a small vessel vasculitis and is commonly associated with Anti-Neutrophil Cytoplasmatic Antibodies (ANCA) [5]. Besides renal involvement, there are affected the peripheral nervous system and other organ systems. The therapy is a immunosuppression, intravenous immunoglobulin (IVIG), and in severe cases or therapy resistant cases TPE. With the therapy of methylprednisolone and cyclophosphamide and or HMAs, such as mepolizumab or omalizumab, severe cases of Churg-Strauss-syndrome could be improved, too [6]. However, further multicenter studies are necessary.

Wegener´s Granulomatosis (WG) is characterized primarily by granuloma in the upper respiratory tract, necrotic vasculitis, and accompanying glomerulonephritis [7]. The clinical spectrum ranges from initial stages partly with long periods of minimal symptoms to a fulminant, life-threatening generalized stage. Acute process are marked by pulmonal hemorrhaging with respiratory insufficiency and rapidly progressive glomerulonephritis with quick development of terminal renal insufficiency. The etiology is not clear. An autoimmune cause of WG is seen by the frequent presence of immunoglobulins and complement deposits in the vascular changed vessels, indications of T cell activation, and response to immunosuppressive therapy. Histologically, WG is defined of small vessel necrotizing vasculitis, “geographic” necrosis and granulomatous inflammation. Characteristically, organ involvement includes the upper and lower respiratory tracts and kidney, however, virtually any organs can be involved.

The average survival time for untreated patients with WG in a generalized stage is five months. Besides cyclophosphamide and steroids, chlorambucil, azathioprine, and cyclosporin A were also been administered [8]. Therapeutic plasma exchange and synchronized TPE and pulse cyclophosphamide has been implemented with great success in combination with immunosuppression.

Further investigations have focused on other immunomodulatory agents, such as tumor necrosis factor-α-inhibitors, infliximab and etanercept, and anti CD20 antibodies rituximab, etc. for the treatment of patients with WG [9,10]. However, further studies are needed to clarify the long-term safety and effectivity of TA with or without immunomodulatory agents.

Lung Transplantation (LuTx) is an accepted and definitive therapy for patients with end-stage lung disease. With LuTx perioperative mortality and morbidity are essentially due to primary graft dysfunction (10-12%), pulmonary vein obstruction, and fulminant graft rejection during the first hours through day three after transplantation. Over 55 percent of all transplant recipients are treated for episodes of graft rejection during the year [11]. Acute lung allograft rejection occurs in 50-70 % of lung transplant recipients and typically occurs in the first 6-12 months after LuTx [3]. Chronic rejection of the lung allograft remains the most common cause of death in lung transplant recipients after the first year of transplant. Bronchiolitis Obliterans Syndrome (BOS) is a pathophysiological process that effects small airways of the lung and is recognized as a significant etiology of chronic dysfunction in the lung allograft, and represents chronic allograft rejection, and it occurs in approximately 60-80 % of lung transplant survivors 5 -10 year after the transplantation. The major factor is BOS limiting long-term survival after LuTx. There are multiple reasons for the increased incidence of acute rejection after LuTx. The HLA matching is or can be performed and the lung graft is in permanent contact with external environment and is thus exposed to various inhaled agents. The lung graft contains abundant donor antigen-presenting cells constantly processing and presenting HLA alloantigen's to recipient lymphocytes that initiate a process of immune recognition [3].

The immunosuppressive therapy after LuTx consists of a three-drug regimen with cyclosporine or tacrolimus, azathioprine or mycophenolate mofetil, and steroids. The therapy of BOS consists of high dose methylprednisolone, or for patients with unresponsive BOS an alter native immunosuppression including tacrolimus, methotrexate, ATG and OKT3. To remove effective performed non-HLA and HLA-abs, TPE or Immunoadsorption (IA) is indicated. Extracorporeal Photopheresis (ECP) can induce antigen specific immune tolerance via induction of the apoptosis of T cells [12]. Antibody-Mediated Rejection (AMR) in LuTx can be treated successfully with HMAs such as rituximab, daratumumab, etc. These HMAs are effective in AMR refractory to standard therapies in lung transplant, and the subcutaneous administration is well tolerated without side effects [13,14].

Besides conservative therapy, immunosuppression, and /or HMAs, some respiratory diseases can be treated very successfully with TA. All TA methods mentioned here are all very effective and safe in removing of antibodies as a immunomodulatory therapy. With daily or every other day treatments a rapid improvement could be reached. In the mentioned respiratory diseases the treatments with TPE, IA, or ECP must be combined with immunosuppression, IVIG, and/or HMAs, etc.

Acknowledgement

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Conflict of Interest

None.

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