The Libyan International Medical University

Faculty of Basic Medical Science

Inhaled Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) for Pulmonary Alveolar Proteinosis

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Abstract:

Pulmonary alveolar proteinosis is an uncommon lung disease with an accumulation of pulmonary surfactant within pulmonary alveoli that causes progressive respiratory insufficiency. The majority of the cases of pulmonary alveolar proteinosis are actually autoimmune that is associated with a high level of autoantibodies against granulocyte macrophage colony-stimulating factor (GM-CSF). These preformed autoantibodies, which effects the biologic activity of GM-CSF, impairing the clearance of surfactant and lead to the disease. Pulmonary alveolar proteinosis was previously treated with whole-lung lavage while the patient is under general anaesthesia. In this procedure, each lung is infused with up to 50 liters of saline to clear the surfactant sediment. Although this treatment improves lung function in most patients, but repeated treatments are required most of the time because of the re-accumulation of surfactant. Improvement in pulmonary function has been observed in trials of administrating recombinant human GM-CSF involving patients with pulmonary alveolar proteinosis. In one study involving GM-CSF knockout mice, inhalation of GM-CSF corrected pulmonary alveolar proteinosis. So basically inhalation of aerosolized exogenous GM-CSF could benefit patients with autoimmune pulmonary alveolar proteinosis. However, the efficacy of inhaled GM-CSF in patients with mild to moderate disease remains unknown. A study was conducted the Pulmonary Alveolar Proteinosis GM-CSF Inhalation Efficacy in (PAGE) trial to test the hypothesis that inhaled GM-CSF would improve oxygenation, findings on lung imaging, and levels of serum markers in patients with mild to-moderate pulmonary alveolar proteinosis.

Introduction:

Pulmonary alveolar proteinosis is a disease characterized by abnormal accumulation of surfactant within the lung, Most cases are autoimmune and are associated with an autoantibody against granulocyte-macrophage colony-stimulating factor (GM-CSF) that prevent clearing of pulmonary surfactant by alveolar macrophages. Pulmonary alveolar proteinosis may occur in three clinically distinct forms: congenital, secondary, or acquired. The congenital form comprises a heterogeneous group of disorders caused by mutations in the genes encoding surfactant protein B or C or the receptor for granulocyte–macrophage colony-stimulating factor (GM-CSF). Secondary pulmonary alveolar proteinosis develops in association with conditions involving functional impairment or reduced numbers of alveolar macrophages. Such conditions include some hematologic cancers, pharmacologic immunosuppression, inhalation of inorganic dust (e.g., silica) or toxic fumes, and certain infections. Acquired pulmonary alveolar proteinosis has been an idiopathic disorder since its initial description.(1) The disorder has been treated previously by a procedure called whole lung lavage, while mechanically percussing the chest to physically remove the accumulated sediments. Although the treatment improves the lung function in most patients. Surfactant often accumulates again so repeated treatment is usually required. Nowadays a new treatment using recombinant GM-CSF dissolved in 2ml of sterile saline was inhaled using an LC-PLUS nebulizer. The aim of this report is to fully elucidate the role of GM-CSF in the clearance of the accumulated surfactant and treatment of pulmonary alveolar proteinosis.(2)

Method:

The trial was designed by the investigators of the PAGE Trial Study Group at the Niigata University Medical and Dental Hospital and at 11 other hospitals in Japan. Patients were eligible to participate in the trial if they were between 16 and 80 years of age, had received a diagnosis of autoimmune pulmonary alveolar proteinosis on the basis of findings on high-resolution computed tomography (CT) and biopsy, cytologic findings on broncho-alveolar lavage, or had a positive serum GM-CSF antibody level. Patients who met the eligibility criteria were randomly assigned by computer, to receive either inhaled GM-CSF (at a dose of 125 μg twice daily on days 1 through 7

and none on days 8 through 14 for 12 2-weeks cycles) or matched placebo. The sample size was calculated with the use of a two-tailed t-test. For the primary analysis, From September 2016 through December 2016, a total of 64 patients were assessed for eligibility.[2]

Result:

64 patients with mild to moderate autoimmune pulmonary alveolar proteinosis were deemed to be eligible to participate in the trial and were randomly assigned to either the GM-CSF group (33 patients) or the placebo group (31 patients). One patient assigned to the placebo group withdrew from the trial, and a total of 63 patients completed the 24-week double-blind intervention period. The change in the alveolar–arterial oxygen gradient was significantly greater in the GM-CSF group than in the placebo group. Cytokines that recruit monocytes were greater in patients in the GM-CSF group than in patients in the placebo group. It is notable that the change in the level of autoantibodies against GM-CSF was greater in the GM-CSF group than in the placebo group. No deaths occurred during the trial. Adverse events that occurred during the trial did not differ significantly between the two groups. Serious adverse events occurred in 6 of the 33 patients who received GM-CSF. These events were ileus, congestive heart failure, worsening of autoimmune pulmonary alveolar proteinosis, pneumothorax, lacunar infarction, and breast cancer. One patient had both influenza type A infection and worsening of autoimmune pulmonary alveolar proteinosis. Three of the 31 patients who received placebo also reported serious adverse events during the trial; these events were cataract, worsening of autoimmune pulmonary alveolar proteinosis, and peripheral sensory neuropathy.

Discussion:

Surfactant plays a critical role in the prevention of alveolar wall collapse. This is achieved by reducing the surface tension. The surfactant is predominately lipid (90%) with the remaining part composed of protein (10%) and carbohydrate (1%). Surfactant proteins A,B,C, and D each play a role in the surface active properties and structure of

the intra-alveolar surfactant, play a role its metabolism, help in opsonization of microbes, and stimulate alveolar macrophages to perform their defensive functions. Alveolar type II epithelial cells synthesize and store the surfactant lipids and proteins then secretes them into alveoli. The surfactant is cleared by either reuptake into the type II alveolar cells or by macrophages. This process is highly regulated to maintain a specific surfactant pool size. Granulocyte–macrophage colony-stimulating factor (GM-CSF) has a critical role in surfactant homeostasis in the normal lung. Interruption of GM-CSF signaling in the lung results in pulmonary alveolar proteinosis. After exocytosis into the alveolar surface liquid, the lamellar bodies (are secretor granules found in type II epithelial cells) Assemble into surfactant structures known as tubular myelin as well as into large and small aggregates.[1] Normally, surfactant is inactivated by a mechanical and biologic process in which it is converted into small, surface inactive aggregates. Approximately 70 to 80 percent of the small aggregates are taken up by alveolar type II cells, transported to phagolysosomes, and reused or catabolized. Alveolar macrophages internalize and catabolize the remaining surfactant pool, a process critically dependent on GM-CSF. Although GM-CSF stimulates lung growth and causes alveolar type II epithelial-cell hyperplasia, a potential role for GM-CSF in surfactant recycling by these cells has not been defined. In pulmonary alveolar proteinosis, interruption of GM-CSF signaling in the alveolar macrophage impairs the catabolism of surfactant by alveolar macrophages without impairing its uptake. This can occur by either targeted ablation of the gene encoding GM-CSF and/or its receptor in mice or by neutralizing anti–GM-CSF autoantibodies in humans. This result in the intracellular buildup of membrane-bound concentrically laminated surfactant aggregates. Progressive expansion of the extracellular surfactant pool and accumulation of cellular debris due to the impaired catabolism eventually causes filling of the alveoli, thus reducing the size of the available gas exchange surface and eventually leading to the clinical syndrome.[2]

Autoantibodies against GM-CSF inhibits the ability of GM-CSF to stimulate the proliferation of normal monocytes and a GM-CSF–dependent cell line and competitively inhibited the binding of GM-CSF to cells bearing GM-CSF receptors. This inhibitory activity was due to a neutralizing IgG antibody against GM-CSF. The antibody was present in bronchoalveolar lavage fluid and serum from all patients with

acquired pulmonary alveolar proteinosis not those with the congenital or secondary form of the disorder, those with several other lung disorders, or normal controls. [1]

The specific association between neutralizing anti–GM-CSF autoantibodies and acquired pulmonary alveolar proteinosis strongly supports the idea that in this disorder, a neutralizing autoantibody against GM-CSF causes defects in the functioning of alveolar macrophages, including impairment of the catabolism of surfactant lipids and proteins and disruption of surfactant homeostasis. The finding of this autoantibody has led to the development of a latex-agglutination test with high sensitivity and specificity for diagnosing the acquired disease. [3]

Management

Treatments included high- dose GM-CSF administration (125 mg twice daily on Days 1–8, none on Days 9–14) for the first six 2-week cycles, then low-dose administration (125 mg once daily on Days 1–4, none on Days 5–14) for the second six 2-week cycles. These two treatment periods were intended to serve as induction and maintenance therapy. Recombinant human GM-CSF (sargramostim) was administered to patients included in the treatment group by inhalation. [4]

Conclusion

GM-CSF has revealed critical roles for in the regulation of mature alveolar macrophages in the lung, the regulation of surfactant homeostasis, and the stimulation of multiple mechanisms that protect the lung against microbial invasion, Several prospective trials of GM-CSF therapy for acquired pulmonary alveolar stenosis have been undertaken, evaluated the effectiveness of administrating GM-CSF.

Reference

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