Editorial

Autoimmune Pulmonary Alveolar Proteinosis: "The Sleeping Beauty and the Kissing Drug"

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Autoimmune pulmonary alveolar proteinosis (aPAP) the most common form of PAP (90%) is related to the abnormal production of high titers of autoantibodies against the hematopoietic cytokine granulocyte macrophage–colony-stimulating factor (GM-CSF)[1]. Autoantibodies act neutralizing GM-CSF bioactivity on alveolar macrophages impeding their ability to catabolize phagocytized surfactant as well as their ability to handle microorganisms[1]. Disease is related to the inappropriate accumulation of surfactant lipoproteins inside alveolar macrophages and diffusely in the airspaces occupying space and exhausting pulmonary functional reserve[2]. Clinically the disease presents with progressive dyspnea on exertion and hypoxemia that may lead to respiratory insufficiency leading to death[2]. Occasionally, the slow deteriorating course of the disease may interrupt abruptly due to the occurrence of severe and deadly opportunistic lung infections[3].

The modern history of PAP begins 20 years ago when two groups of independent investigators working with knock-out mice for the gene of GM-CSF made a serendipitous observation discovering the death of their animals from PAP, and therefore the role of GM-CSF on alveolar macrophages and the turn-over of surfactant[4,5]. A few years later investigators working with PAP patients disclosed autoantibodies against GM-CSF[6] and performing elegant experimental studies proved their pathogenetic role[7]. The era of pharmacologic treatment in PAP begins in 1996 when a group of investigators tested the administration of subcutaneous GM-CSF in one patient with aPAP proving its effectiveness[8] also confirmed by other later studies[9-11]. In the 2000 a group of investigators proved also the effectiveness of aerosolized GM-CSF in aPAP patients[12] clearly confirmed in subsequent and much larger studies[13,14].

From the pharmacologic studies on aPAP treatment[10,11,13,14], it became evident that using medium term protocols from twelve to twenty four weeks and occasionally for longer periods, and various dosage schedules inhaled GM-CSF was safe in all and effective in a proportion of patients. This differential response may be used to divide patients into responders and non-responders and confine non-responders to the whole lung lavage (WLL) approach, the standard of treatment for any form of PAP including congenital[15] and secondary[16]. WLL is an effective treatment modality for PAP but several patients may require frequent and repetitive sessions un-

der general anesthesia. Even more important is the fact that few centers in the world detain skills for safety and effectiveness. In the past Greek patients were obliged to travel abroad and some of them repetitively with significant financial and health burden.

Recently our group of investigators presented the experience of our department with aPAP patients and especially the effectiveness and safety of long-term administration of inhaled GM-CSF[17]. Six patients (5 females) were treated with inhaled GM-CSF the first patient is been treated since 2007 and after having performed 64 WLLs abroad. The treatment protocol consisted on the administration of inhaled GM-CSF 250 mcg once a day "4 days on and 4 days off" till the attainment of disease remission (no time limits) defined clinically as the disappearance of exertional dyspnea and physiologically as exercise oxygen desaturation lower than 4% at the 6 minutes distance walking test, plus the significant radiographic reduction of the infiltrates, or at least two of the above. Upon remission inhaled GM-CSF dose was deescalated. Interestingly all patients achieved remission and even more importantly continued to improve their imaging and physiological parameters at deescalating doses permitting us to further reduce the administered dose on the search of the lowest effective dose. In case of deterioration the patients were repositioned on the previous effective dose. At present all patients are in remission (all responders) and receive the lowest effective dose. Furthermore, regarding the eventual hematopoietic toxicity of inhaled GM-CSF, we performed tests able to detect bone marrow stimulation, such as complete blood cells counts, CD_{34+} cells, granulocyte-macrophage progenitor colony-forming-units and burst forming unit erythroid before and after inhaled GM-CSF administration that disclosed no inappropriate effect.

In conclusion the results of our study have shown: a) that the perseverance in the administration of inhaled GM-CSF obtains remission in all patients avoiding non-responders; b) de-escalation of the administered dose is possible towards the lowest effective dose; c) no stimulating activity on hematopoiesis was detected in any patient. The above protocol minimizes burden and costs in safety and we feel ready to declare that "the sleeping beauty needs no water-bucket challenge (WLL) but just a kiss of her beloved… drug".

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