NOVEL TREATMENT OPTIONS FOR AUTOIMMUNE PULMONARY ALVEOLAR PROTEINOSIS

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ABSTRACT

Pulmonary alveolar proteinosis (PAP) is a diffuse pulmonary disease, characterised by the accumulation of lipoproteinaceous material in the distal air spaces, which results in impaired gas transfer. Autoimmune PAP accounts for the vast majority of cases in humans and is caused by autoantibodies directed towards granulocyte-macrophage colony-stimulating factor (GM-CSF), which causes a defect in the function of alveolar macrophages linked to the disruption of surfactant homeostasis. Whole lung lavage (WLL) is the current standard of care for PAP patients and although it is effective in the majority of cases, disease persistence is not an unusual outcome, even if airspace accumulation is well controlled by WLL. Even though WLL remains the current standard therapy for PAP, in this review we focus on novel treatment approaches for autoimmune PAP.

Keywords: PAP, autoantibodies, WLL, GM-CSF.

INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a rare respiratory disease, first described by Rosen et al. in 1958,[1] and characterised by the accumulation of lipoproteinaceous material in the alveoli, which may lead to impaired gas-exchange and progressive respiratory failure. The pathogenesis of the disease has been widely reconsidered over the last 20 years, with the conclusion that the acquired form is an autoimmune disease, in which autoantibodies directed against neutralising granulocyte-macrophage colony-stimulating factor (GM-CSF), lead to defective maturation of alveolar macrophages. The latter contain giant secondary lysosomes filled with the same material that accumulates within the alveoli, and cause defects in chemotaxis, adhesion, phagocytosis, microbicidal activity, and phagolysosome fusion.[2]

Alveolar macrophages and type II pneumocytes are responsible for the re-uptake and clearance of pulmonary surfactant, a lipid-protein complex, which is synthesised, packaged, and secreted by alveolar type II cells. The lipid portion constitutes approximately 90%, whereas the protein portion constitutes approximately 10% by weight.[3] Pulmonary surfactant plays a pivotal role in reducing the surface tension at the air-liquid interface of the alveolar wall, thus preventing alveolar collapse and transudation of fluid into the lumen of the alveolar capillary.[4]

The amount of surfactant is tightly regulated by mechanisms controlling its synthesis, recirculation and catabolism.[5] The results of ultrastructural, biochemical, and functional analyses, together with studies in genetically modified mice, strongly support the hypothesis that the basis for PAP is a defect in the clearance of surfactant rather than due to its overproduction.[6]

Evidence for adult PAP as an autoimmune disease was first presented by Kitamura et al.,[7] who noted that circulating anti-GM-CSF autoantibodies neutralised GM-CSF biological activity, and thus resulted in a virtual GM-CSF deficiency. Subsequent studies in idiopathic adult PAP patients confirmed the existence of anti-GM-CSF antibodies and demonstrated that

autoantibody measurement could be a clinical tool for diagnosis.[8,9]

PAP THERAPY

Different treatment options have been utilised since PAP was first described. As far as the therapeutic aspects of the disease are concerned, in the pre-lavage era the death rate was approximately 30% of cases[10], but the introduction of the whole lung lavage (WLL) in the mid-1960s has changed the natural history of PAP, with a dramatic reduction of the mortality, at least where the WLL is performed, with an immediate positive outcome in >90% of cases, but with a recurrence rate ranging from 30 to 70%, according to different series reported. WLL for idiopathic pulmonary alveolar proteinosis is currently a safe procedure in an experienced setting, and yields durable benefit in the majority of patients.[11] Little is known about the intimate mechanisms of action of WLL. Presumably WLL is able not only to remove the surfactant excess, but also the autoantibodies, interfering with surfactant homeostasis, as it was suggested several years ago.[12] Even though WLL remains the current standard therapy for PAP, in this paper we focus on novel treatment approaches for autoimmune PAP.

RITUXIMAB

Rituximab is a monoclonal antibody directed against the CD20 antigen on B lymphocytes. In B cell lymphoproliferative disorders, the mechanism of action is mediated by eradication of the malignant CD20 positive B cells. Subsequently, rituximab therapy has been applied in the treatment of autoimmune disease with clinical benefit.[13-15]

Based on data indicating autoantibody involvement in PAP, Borie et al.[16] described a 41-year-old non-smoker who refused WLL; the patient exhibited clinical, functional and radiographic improvement after 1,000 mg of rituximab was delivered intravenously on day 1 and day 15. In particular, the treatment resulted in a decrease in anti-GM-CSF concentration. 9 months after treatment, dyspnoea improved; similarly, diffusing capacity of the lung for carbon monoxide (DLCO), CT scan and alveolar–arterial oxygen gradient ($P(A\text{-}a)O_2$) at rest improved. This response was sustained at a 12-month follow-up.

Amital et al.[17] described a 40-year-old female, non-smoker with severe dyspnoea and hypoxaemia. Despite WLL and subcutaneously delivered GM-CSF, a year later the patient's condition deteriorated. Rituximab at 375 mg/m^2 was administered weekly over 4 weeks, with improved DLCO and oxygen saturation at rest and during exercise, as well as chest CT and X-ray.

Recently, the first prospective, open label, proof of concept trial of rituximab has been carried out in 10 PAP adult patients.[18] The intervention consisted of two intravenous infusions of rituximab (1,000 mg), 15 days apart. The primary study end-point was improvement in oxygenation, as assessed by the $P(A\text{-}a)O_2$; in seven out of nine patients (one patient dropped out of the study for unknown reasons) partial pressure of oxygen in arterial blood (PaO_2) and $P(A\text{-}a)O_2$ were significantly improved at 3 and 6 months. Improvements were also noted in total lung capacity (TLC), high-resolution CT (HRCT) scans and transitional dyspnoea index (TDI).

The data also indicated that a single course of rituximab therapy was well tolerated, with no major adverse reactions in this PAP cohort. The major limitation of this study was the absence of a placebo group. Moreover, as the trial was conducted recently, with a 32±6 month post-therapy follow-up, the durability of response and the need for longer-term therapy remains an open question.

Mechanisms responsible for rituximab-mediated improvement in PAP are unclear; this trial demonstrated that rituximab effectively depleted circulating B lymphocytes for a period of 3 months, but the potential role of B cells in PAP, is not well defined. In fact, the majority of antibody-forming B cells are plasma cells, which do not express CD20 and are, therefore, not susceptible to rituximab depletion. Importantly, neither the total serum anti-GM-CSF, nor serum GM-CSF neutralising capacity, were reduced following rituximab therapy. On the contrary, reduction in anti-GM-CSF levels in bronchoalveolar lavage (BAL) fluid from the lung correlated with disease changes, suggesting that disease pathogenesis is related to autoantibody levels in the target organ.

Starting from these results, the same research group demonstrated that the clinical improvement in rituximab-treated PAP patients might be due to restoration of alveolar macrophage lipid homeostasis, associated with reduced GM-CSF autoantibodies in the pulmonary compartment.[19] Utilising BAL samples from the original cohort of PAP patients treated with rituximab, confirmed the positive therapeutic effect of rituximab on

PAP lung, by enhancing alveolar macrophage functional activity and expression of lipid regulatory genes, PPARγ, ABCG1, and LPLA2. Compared to baseline, both PPARγ and ABCG1 were significantly upregulated by rituximab treatment. An unexpected finding was the LPLA2 deficiency in untreated PAP patients, a situation that was significantly reversed by rituximab therapy. In conclusion, these data indicate that rituximab is able to reconstruct lipid homeostasis in PAP alveolar macrophages.

GM-CSF

Based on the role of neutralising anti-GM-CSF autoantibodies in autoimmune PAP, treatment aimed at relieving functional GM-CSF deficiency by administering exogenous GM-CSF has been utilised. Several studies have reported a favourable response with systemic (subcutaneous) or localised (aerosol) GM-CSF. Prompt improvement with resumption of GM-CSF in patients who relapsed suggests that disease resolution was not attributable to spontaneous remission and that GM-CSF does have therapeutic activity.

Subcutaneous GM-CSF

Evaluation of GM-CSF supplementation as a potential therapy in autoimmune PAP was initially prompted by the demonstration that this cytokine exhibits restorative activity on impaired surfactant metabolism and innate immunity in GM-CSF-deficient mice.[20] Seymour et al.[21] were the first to treat 14 autoimmune PAP patients with subcutaneous GM-CSF. Patients not responding to an initial dose of 5 μg/kg/d GM-CSF underwent stepwise dose escalation until a therapeutic response (represented by improvement in oxygenation at the lung level) was obtained. The treatment showed efficiency in 43% of patients with a median treatment time of 39 weeks. Among responders, there was a significant effect on PaO_2, $P(A\text{-}a)O_2$, DLCO, CT scan and the 6-minutes walking test.

In 2000, Kavuru et al.[22] published the preliminary results on four patients treated with subcutaneous GM-CSF for moderate exacerbation of PAP. GM-CSF was self-administered once daily for 12 weeks (dose escalation from 3 to 9 mg/kg/d). In three of the four patients with idiopathic PAP, administration of GM-CSF improved oxygenation and conferred symptomatic benefit.

Subsequently, in an open-label study on 25 patients, using escalating doses of GM-CSF from 5 to 18 mg/kg/day, GM-CSF treatment was associated with improvements in $A\text{-}aDO_2$ and other clinical parameters in 48%, with relapse rates of 25% among responders.[23] Nevertheless, in this PAP series, only subjects with moderate symptomatic disease were enrolled, thus we cannot speculate on the role of this treatment in severe forms of PAP.

Inhaled GM-CSF

Since it is conceivable that the alveolar space is the site of GM-CSF signal disruption, with the impairment of surfactant catabolism in autoimmune PAP, then it is reasonable to propose that local GM-CSF supplementation would result in better treatment outcome. In 2006, Wylam and coworkers[24] reported a retrospective case series of 12 idiopathic PAP patients, elected to receive aerosolised GM-CSF (250 mg b.i.d. every other week). All patients except one showed mean improvements in arterial oxygen tension, $P(A\text{-}a)O_2$, DLCO, and forced vital capacity. Two patients made a complete recovery and were disease-free 1 and 2 years after discontinuing treatment. 4 patients showed complete response to both the initial course or when treated again for recurrence after discontinuation of treatment. One patient required dose escalation (500 mg b.i.d.) and achieved a complete response. Importantly GM-CSF was well-tolerated without late toxicity.[24] Subsequently, Tazawa et al.[25] treated 35 stable PAP patients with an induction dose (recombinant GM-CSF (rGM-CSF) 250 mg/day b.i.d. every other week for 6 weeks) followed by a maintenance dose (125 mg/day b.i.d. for 4 days every 2 weeks for 6 cycles). The positive response rate, in terms of decrease in $P(A\text{-}a)O_2$ and DLCO, was 62%, and no adverse events were recorded. A total of 29 of the 35 remained stable without further therapy during the follow-up period. The Tazawa group also demonstrated that GM-CSF inhalation therapy decreased markers of surfactant accumulation in BALF of high responders.[26]

Combination Therapy

The cumulative response rate of GM-CSF is lower than that described for WLL age; in fact it seems only to limit disease progression.[27] For this reason, it has been proposed as standalone therapy in PAP patients with less severe disease and as a supplementary therapy to WLL in patients with more advanced autoimmune PAP.

Yamamoto et al.[28] described a 9-year-old girl with autoimmune PAP, who was initially refractory to inhalation therapy (250 mg of GM-CSF daily).

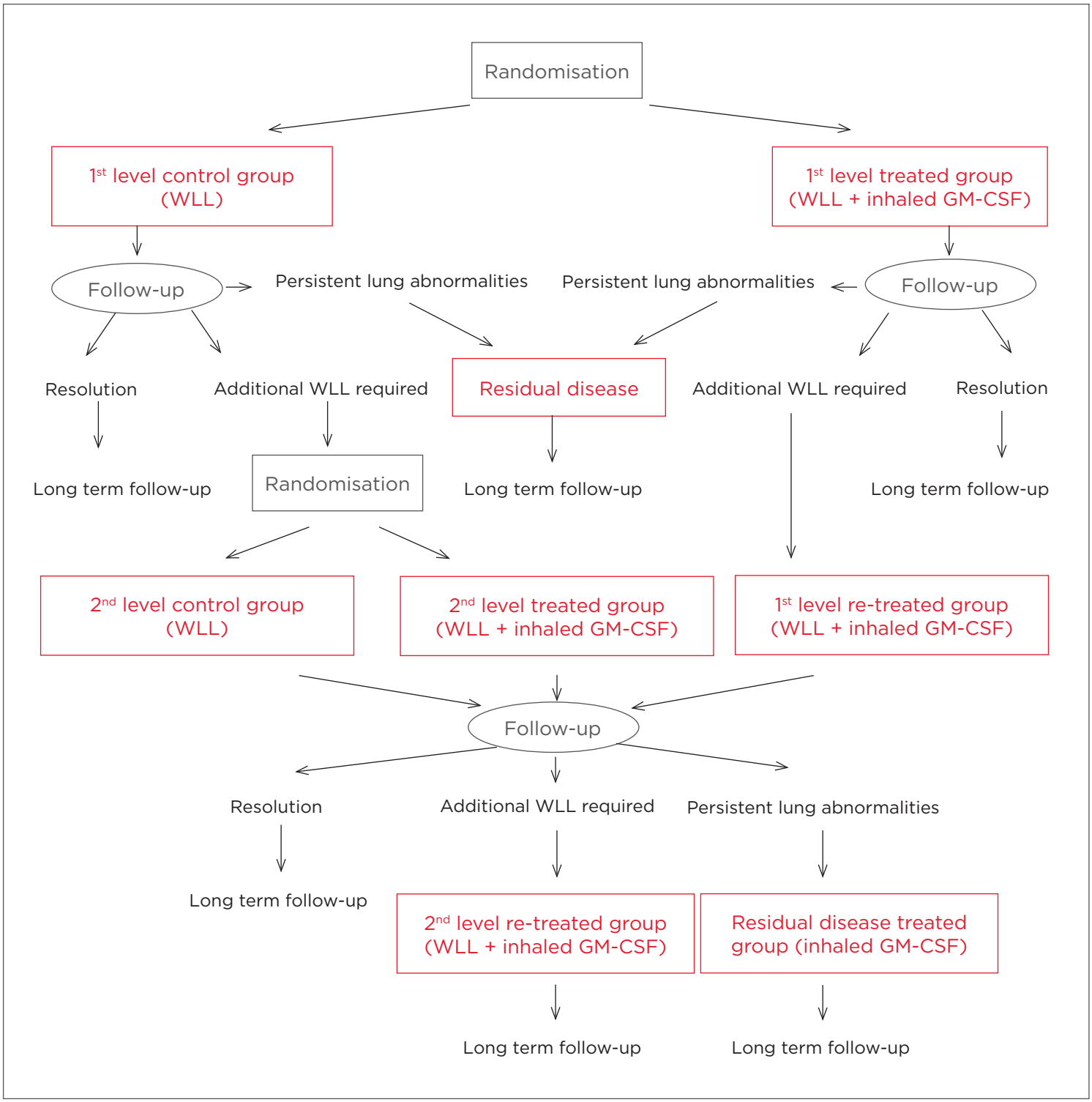

Figure 1. Flow Chart of the Pavia Centre Study.
PAP patients requiring a first WLL will be randomised 1:1 to receive either WLL followed by inhaled GM-CSF (first level treated group) or WLL alone (first level control group). PAP patients requiring a second WLL, if previously treated by WLL alone, are randomised 1:1 to receive either WLL followed by inhaled GM-CSF (second level treated group) or WLL alone (second level control group); if previously treated by WLL followed by inhaled GM-CSF, these subjects will be submitted to WLL followed by another course of inhaled GM-CSF (first level re-treated group). PAP patients requiring a third WLL, irrespective of the previous treatment, will be submitted to WLL followed by inhaled GM-CSF (second level re-treated group). In case of PAP patients not requiring additional WLL, but with persistent lung abnormalities and without severe functional impairment, this group will be submitted to a course of inhaled GM-CSF (residual disease treated group), since the main objective of the study is 100% resolution of PAP lesions.

Initial failure of the GM-CSF inhalation seems to be due to inefficient access of GM-CSF to the alveolar spaces because of densely accumulated surfactant. Unilateral WLL was performed three times and subsequent GM-CSF inhalation therapy yielded marked physiological and radiological improvements.

Recently, a study protocol for the treatment of autoimmune PAP, with WLL followed by inhaled GM-CSF (Sargramostin), has been started by our research group (AIFA FARM7MCPK4). We designed an experimental, phase II, parallel randomised trial with two cohorts. We plan to identify the best treatment schedule for PAP patients, looking at the evaluation of the superiority of the combination WLL/inhaled rGM-CSF versus WLL alone in PAP patients. The working hypothesis is that inhaled GM-CSF might speed recovery after WLL and reduce the frequency of disease recurrence in autoimmune PAP patients.

The study protocol is to be continued over a period of 36 months, with an expected target enrollment of 18 patients. Patients are divided in two groups (Figure 1): the control group, in which patients are treated with standard WLL, and the study group, where WLL is followed by inhaled GM-CSF. The treatment involves an acute phase lasting 12 weeks (250 mcg/day every second week) and a maintenance period of 6 months, 4 weeks after the completion of the acute treatment (250 mcg/day for 2 days every 14 days). The primary objective is to obtain complete and lasting regression of pulmonary infiltrates.

At scheduled visits, the PAP patients are evaluated by questionnaire, respiratory function testing, severity score, quality of life, clinical chemistry serum biomarkers, and CT-assisted lung profusion score. The latter is a method that, although originally developed for scoring interstitial pneumonitis, has been successfully applied to score changes in PAP lung infiltrates. The CT scan is performed at baseline and then 3 and 10 months after WLL (corresponding, in patients of the study group, to the end of the acute treatment and the maintenance treatment, respectively). Physiology and CT scoring data so far collected are encouraging, suggesting that the trial will be helpful in identifying the optimal sequence of treatments, to gain durable resolution of lung infiltrates in PAP patients.

Plasmapheresis

The presence of systemic anti GM-CSF antibodies in idiopathic PAP led to the hypothesis that PAP could be an autoimmune disease and hence the rationale for plasmapheresis as a therapeutic be an option. This should reduce autoantibody levels sufficiently to restore surfactant catabolism in alveolar macrophages. A 41-year-old non-smoking woman, with a 5-year history of non-resolving pulmonary infiltrates, was the first case of PAP treated with plasmapheresis. She was refractory to three WLLs and subcutaneous GM-CSF. She underwent low intensity plasmapheresis on ten separate sessions, resulted in a reduction of the levels of plasma autoantibodies, and improvement in symptoms, blood oxygen saturation, and radiographic appearance of the lungs[29]. The clinical course was complicated by a Gram-negative sepsis; however, the patient subsequently recovered, thus the plasmapheresis schedule was terminated.[30]

Subsequently, a patient with autoimmune PAP refractory to three WLLs, performed in less than 12 months, was submitted to 10 sessions of low-intensity plasmapheresis, which lowered the serum autoantibody level, but did not improve respiratory impairment. Further WLL therapy was required, but it was transiently effective, with increased length of symptom-free periods between subsequent WLLs.[31]

CONCLUSION

WLL is the current standard treatment for PAP patients and, although it is effective in the majority of cases, disease persistence is not an unusual outcome with a substantial portion of patients needing more than one or even repeated WLL. Even if the mechanism leading to the development of autoimmune antibodies towards GM-CSF is poorly understood, in the past two decades efforts made by researchers have contributed to the development of more refined and specific treatment options for PAP. While with rituximab therapy questions remain concerning the durability of response and the need for longer-term therapy,[18] GM-CSF, both systemically and targeted directly to the lungs, seems to be ineffective in about one-third of patients treated.[32] In this context, combination therapy with WLL followed by aerosolised GM-CSF would represent the best strategy.

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