Therapy options in pulmonary alveolar proteinosis

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Maurizio Luisetti, Zamir Kadija, Francesca Mariani, Giuseppe Rodi, Ilaria Campo and Bruce C. Trapnell

***Abstract*:** Pulmonary alveolar proteinosis is a rare condition characterized by the accumulation of lipoproteinaceous material within the airspaces, resulting in impaired gas transfer, and clinical manifestations ranging from asymptomatic to severe respiratory failure. To the best of the authors' knowledge, there are only a few conditions whose natural history has been so dramatically changed by the influence of advances in basic science, clinical medicine, and translational research in therapeutic approaches. Whole-lung lavage is the current standard of care and it plays a critical role as a modifier factor of the natural history of proteinosis. That notwithstanding, the identification of autoantibodies neutralizing granulocyte-macrophage colony-stimulating factor in serum and lung of patients affected by the form of proteinosis previously referred to as idiopathic, has opened the way to novel therapeutic options, such as supplementation of exogenous granulocyte-macrophage colony-stimulating factor, or strategies aimed at reducing the levels of the autoantibodies. The aim of this paper is to provide an updated review of the current therapeutic approach to proteinosis.

***Keywords*:** anti-GM-CSF, autoantibodies, granulocyte-macrophage colony-stimulating factor, plasmapheresis, pulmonary surfactant, whole-lung lavage

Introduction

Pulmonary alveolar proteinosis (PAP) is a rare condition characterized by the accumulation of lipoproteinaceous material within the airspaces, resulting in impaired gas transfer of various degrees of severity, and clinical manifestations ranging from asymptomatic to severe respiratory failure [Trapnell *et al.* 2003]. The condition was first described in 1958 by Rosen and associates, who reported on 27 cases studied over 4 years, starting in 1953 [Rosen *et al.* 1958]. In retrospect, at least two other cases were reported earlier, the first in 1953, although the term *pulmonary alveolar proteinosis*, coined by Rosen and colleagues, was not used [Seymour and Presneill, 2002]. To the best of the authors' knowledge, there are only a few conditions whose natural history has been so dramatically changed by the influence of advances in basic science, clinical medicine, and translational research in therapeutic approaches. For a better understanding of the progress made in the classification of PAP forms and consequently on its tailored therapy, it is necessary to review briefly the milestones that marked the last four decades of PAP history.

PAP milestones

The first important achievement in our understanding of PAP was the identification of the material accumulating in the airspaces. Actually, at the time of the original description [Rosen *et al.* 1958], a high lipid content, together with proteins and carbohydrates, was already recognized. However, it took 7 years to identify the material as *surfactant* [Larson and Gordinier, 1965]. A perturbation of the surfactant metabolism was then suspected, and at that time it was only possible to hypothesize that it could be due to increased secretion, impaired clearance (or both), or abnormal composition.

Irrespective of the nature of the accumulated material, in the early 1960s Dr Ramirez-Rivera proposed the concept of the mechanical removal of accumulated material by washing the lung. The technique evolved from first attempts at performing 'segmental lung lavage' [Ramirez *et al.* 1963] to 'whole-lung lavage' (WLL) [Ramirez *et al.* 1965], to bilateral sequential WLL in the same treatment session [Shah *et al.* 2000], which is now the current standard WLL regimen in most centers.

Correspondence to:
Maurizio Luisetti, MD
SC Pneumologia,
Fondazione IRCCS,
Policlinico San Matteo,
Piazza Golgi 1, 27100
Pavia, Italy
m.luisetti@smatteo.pv.it

Zamir Kadija, MD
Francesca Mariani, MD
SC Pneumologia,
Fondazione IRCCS,
Policlinico San Matteo,
Università di Pavia, Italy

Giuseppe Rodi
Rianimazione 1,
Fondazione IRCCS
Policlinico San Matteo,
Università di Pavia, Italy

Ilaria Campo, PhD
SC Pneumologia,
Fondazione IRCCS
Policlinico San Matteo,
Università di Pavia, Italy

Bruce C. Trapnell, MD
Division of Pulmonary Biology, Pulmonary, Critical Care, and Sleep Medicine, Cincinnati Children's Hospital Medical Center, OH, USA

A major advance in the current concepts of PAP pathogenesis was provided by evidence that knockout mice for the granulocyte-macrophage colony-stimulating factor (GM-CSF) gene (GM-CSF$^{-/-}$ mice) develop pulmonary changes resembling human PAP [Dranoff *et al.* 1994; Stanley *et al.* 1994]. The critical role of macrophages in the slow turnover of surfactant in the alveolar spaces, and the regulatory activity of GM-CSF in mice macrophage terminal differentiation, indicated that myeloid cells are the cellular site of the effects of GM-CSF deficiency in the PAP animal model [Nishinakamura *et al.* 1996].

There is no evidence for an inherited GM-CSF deficiency in humans affected by PAP, so the link between GM-CSF and development of PAP was not clear. Interestingly, the findings that in the airspaces of PAP patients in the first hours following WLL, the rapid turnover of surfactant protein A (SP-A) was intact, led to the hypothesis that WLL is able to remove factor(s) interfering with surfactant clearance [Alberti *et al.* 1996]. The interfering factor was subsequently identified by the Japanese group led by Koh Nakata: most patients with PAP display in their serum and bronchoalveolar lavage (BAL) fluid a polyclonal, IgG autoantibody neutralizing GM-CSF [Kitamura *et al.* 1999; Tanaka *et al.* 1999]. These findings were then corroborated by a number of reports, and now the PAP form previously referred to as 'idiopathic' or 'acquired' PAP, is identified as 'autoimmune' PAP (see the following section).

For many years the role of autoantibodies neutralizing GM-CSF (here after designated as Abs) was considered pathogenic. This was not proven, until it was possible to demonstrate that the passive transfer of Abs to the experimental animal induced many features of human PAP [Sakagami *et al.* 2009].

PAP classification

An important output of the evolving concepts in the pathogenesis of PAP is the revolution of PAP classification (Table 1). It is quite important to review the classification before discussing the therapeutic approach to PAP, because the various forms of PAP may require different therapeutic options. Nevertheless, WLL is the current standard of care for PAP as it can be prescribed for the various forms of the disease, irrespective of the pathophysiological mechanisms involved. Autoimmune PAP (accounting for more than 90% of all forms of PAP), in which the loss of GM-CSF signaling is due to the presence of Abs, may be treated by exogenous GM-CSF supplementation. This treatment is not likely to be useful in the other two forms of primary PAP, in which the loss of GM-CSF signaling is due to mutations in the α or β chain of the GM-CSF receptor, although a signal transduction triggering by high-dose GM-CSF supplementation cannot be excluded. Consistently, secondary forms of PAP benefit from treatment of the underlying condition. Clinical presentation of PAP-like conditions, due to dysfunction of surfactant metabolism, varies from acute respiratory distress to more or less fibrotic interstitial lung disease; this category, with a few similarities with classic PAP, and its treatment options are not discussed in this paper.

Treatment of PAP in the pre-WLL era (or before its widespread use)

A hallmark characteristic of the natural history of PAP is its marked variability: long-term stability of pulmonary abnormalities; from spontaneous improvement to complete remission; or progressive deterioration and death due to respiratory failure or infection [Seymour and Presneill, 2002]. There is also variability in the above-mentioned ranges: the most relevant figure is the 20–25% death rate which progressively decreases to disease resolution in the most recently reported series of PAP patients [Inoue *et al.* 2008; Beccaria *et al.* 2004]. These dramatic changes paralleled the implementation of WLL, thus emphasizing that early empiric attempts at administering drugs with the aim of removing the accumulated material were unable to change the clinical course of the disorder. In particular this was the case with c*orticosteroid* or *antibiotic* treatments [Davidson and Macleod, 1969]. However, there are anecdotal reports of positive effects after treatment with *potassium iodide* [McDowell *et al.* 1959] and aerosolized *heparin* [Nicholas, 1965]. Several case studies have reported on inhaled *trypsin* or *chymotrypsin* [Jay, 1979; Riker, 1973; Arora, 1968; Brodsky, 1961]: transient improvement was described, but also significant allergic reactions. More recently, the long-term efficacy of *ambroxol* in a case of PAP patients refractory to segmental lavage has been reported [Hashizume, 2002]. It is very important to emphasize that single case reports should have little, if any, weight in the review of therapeutic approaches for any given disorder, and this also holds true

Table 1. Classification and nomenclature of pulmonary alveolar proteinosis syndromes.

Clinical type	Disease	Pathogenesis
Primary PAP	*Autoimmune PAP*	GM-CSF autoantibody
	GM-CSF receptor β chain mutations	Loss of GM-CSF signaling
	GM-CSF receptor α chain mutations	Loss of GM-CSF signaling
Secondary PAP	*Dust inhalation*	Aluminum
		Cement
		Insulation
		Silica
		Titanium
	Hematologic disorders	Myelodysplastic syndrome
		Acute lymphatic leukemia
		Acute myeloid leukemia
		Chronic myeloid leukemia
		Hairy cell leukemia
		Hodgkin's disease
		Non-Hodgkin's lymphoma
		Multiple myeloma
		Melanoma
		Essential thrombocythemia
		Polycythemia vera
		Amyloidosis
		Fanconi's anemia
	Immunologic diseases	Monoclonal gammopathy
		Selective IgA deficiency
		Severe combined immunodeficiency
	Miscellaneous	Dermatomyositis
		Lung transplantation
	Lysinuric protein intolerance	Unknown
PAP-like diseases	*SP-B mutations*	SP-B deficiency
	SP-C mutations	Abnormal surfactant
	ABCA3 mutations	Abnormal surfactant

PAP, pulmonary alveolar proteinosis; GM-CSF, granulocyte-macrophage colony-stimulating factor; SP, surfactant protein.

for PAP, especially when taking into account the above-mentioned variability of the clinical course. Nevertheless, we believe that the extreme rarity of PAP warrants the inclusion of single case reports, although they must understandably be considered with great caution.

Whole-lung lavage

Technical issues

As already mentioned, bilateral sequential WLL during the same treatment session, is the current standard of care for PAP (Figure 1). This modality has slowly evolved since the first attempts in 1960 where segmental flooding was performed by using a percutaneous transtracheal endobronchial catheter [Ramirez *et al.* 1965]. WLL has been adopted in a limited number of specialized clinical centers as an institutional procedure [Beccaria *et al.* 2004], and is performed on an occasional basis to treat single PAP patients, in smaller centers. However, WLL is not standardized and no perspective clinical trials have been performed. As a result, the procedure has been modified by each center [Luisetti and Trapnell, 2010], and a number of published papers deal step by step with the WLL technique [Michaud *et al.* 2009; Ben-Abraham *et al.* 2002; Rodi *et al.* 1995]. Only a few procedures have been tested in a comparative study. For example, manual chest percussion has proven superior to mechanical percussion to clear the material in the airspaces [Hammon *et al.* 1993]. On the other hand, chest percussion associated with positional changes during WLL seems to enhance material recovery [Perez and Rogers, 2004]. Another modification of WLL is the so-called 'Bingisser modification' [Bingisser *et al.* 1998], consisting of several cycles of manual ventilation after recovering half of the amount of instilled water, to improve the removal of the accumulated material. Severe hypoxemia is considered the major limitation to WLL: in such instances, oxygen enrichment, under hyperbaric conditions

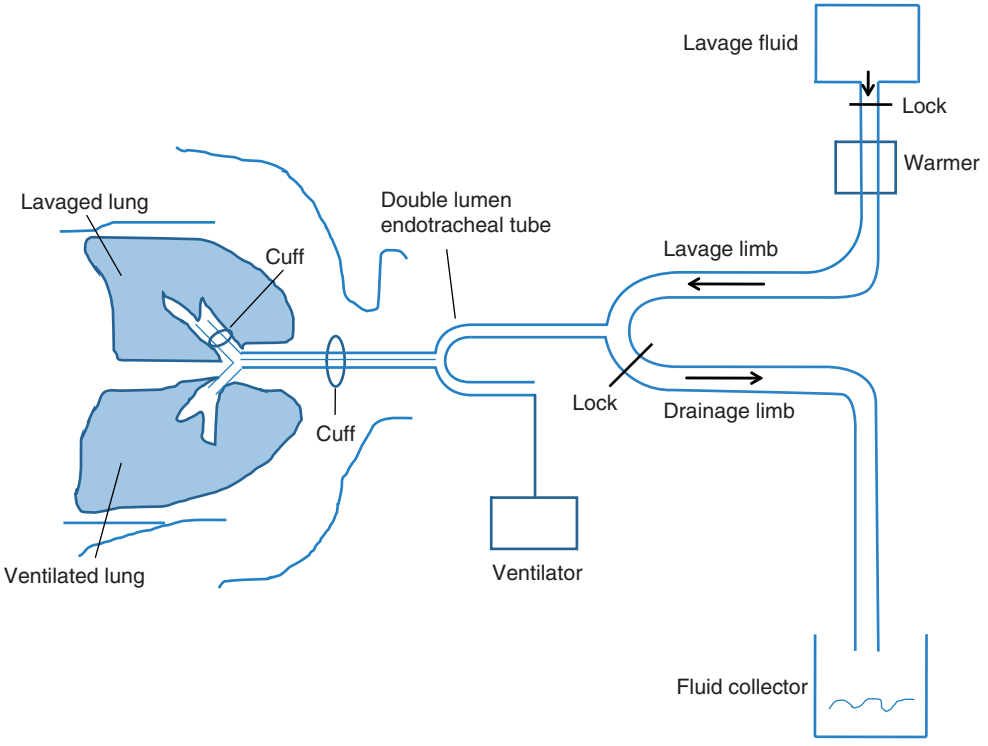

Figure 1. Scheme of the WLL technique used at the Pavia center, according to technique developed by Giorgio Iotti and coworkers [Rodi *et al.* 1995] (the figure has been modified from Michaud *et al.* [2009]). Aliquots (usually at the tidal volume) of saline warmed to body temperature, are infused in the nondependent, lavaged lung; the dependent lung is ventilated. At the end of the aliquot infusion, the drainage limb is clamped, and maneuvers are performed (manual clapping). Advantages of the nondependent lung lavage include: (i) the lung is exposed to a more efficacious manual clapping; and (ii) the perfusion is deviated towards the ventilated lung, thus reducing the V/P mismatch and avoiding the consequent hypoxemia. Details are reported in Alberti *et al.* [1996] and Rodi *et al.* [1995].

[Jansen *et al.* 1987] or infusion with hyperoxygenated solution [Zhou *et al.* 2009] have been suggested, while extracorporeal membrane oxygenation (ECMO) should be reserved for extreme situations [Sihoe *et al.* 2008; Sivitanidis *et al.* 1999]. WLL complications are rare, consisting mostly of hypoxemia, hydropneumothorax, ARDS, and post-procedure infections (pneumonia, sepsis).

Clinical issues

As with many other aspects of WLL, recommendations on when to treat are not standardized. However, a review of available reports indicates that PAP patients should be submitted to WLL as follows: (1) presence of persistent or progressive respiratory failure; (2) absence of respiratory difficulty at rest, but presence of exercise desaturation (≥5% points); (3) in selected cases, WLL may be discussed with the patient even in the absence of the above two situations, if a PAP patient, in particular a young adult, reports a significant limitation in daily or sport activities.

A very careful evaluation of the efficacy of WLL has been performed by Seymour and Presneill in their review which covers all of the available data in the literature [Seymour and Presneill, 2002], ranging from relatively large series of PAP patients [Goldstein *et al.* 1998; Wasserman and Mason, 1994; Prakash *et al.* 1987; Du Bois *et al.* 1983; Selecky *et al.* 1977] to single case reports. The authors have collected data on 231 PAP patients with long-term follow ups. There was a significantly ($p = 0.04$) greater survival rate in the 146 PAP patients who underwent WLL than in the 85 who did not ($94 \pm 2\%$ *versus* $85 \pm 5\%$, respectively). The median number of lavages was two, with a median interval of 15 months between the two procedures. As far as outcome was concerned, disease recurrence was observed in 80% of PAP patients within 3 years of the procedure.

Two considerations must be kept in mind in the evaluation of the above-reported data. First, as

already discussed, WLL is not a standardized technique and data thus derive from PAP patients lavaged under very different modalities. Second, the reports span several decades, and it is likely that PAP patients lavaged in more recent years have benefited more from the advanced WLL techniques. Therefore, it is possible that the data reported by Seymour and Presneill are actually biased, at least in part, by these factors. For these reasons, we examined in detail the data from our large series of PAP patients collected in Pavia over the last 20 years. This series of PAP patients has been collected relatively recently, with the first WLL was performed in 1990, and the WLL technique used, originally developed by Giorgio Iotti and coworkers [Rodi *et al.* 1995], and described in detail in Figure 1, has not been modified over time; thus, this is an ideal series for comparison with the pooled outcome data described by Seymour and Presneill [2002].

The first marked difference is that in our experience, 33% of lavaged PAP patients (14/42) required more than one WLL (Figure 2), whereas in the review of the literature this fraction rose to 66%. However, our group of 14 patients included also three patients in which two consecutive WLLs were performed within 3 months. We consider these three patients as refractory to the first WLL, and the two consecutive WLLs, which were not followed by additional WLLs during the follow up, could be considered as a single, intensive WLL. In this case, the percentage of PAP patients requiring more than one WLL drops to 26%. As a consequence, the median number of WLLs performed in our cohort is one, but the median interval between the two procedures is 13 months, shorter than that reported by Seymour and Presneill [2002].

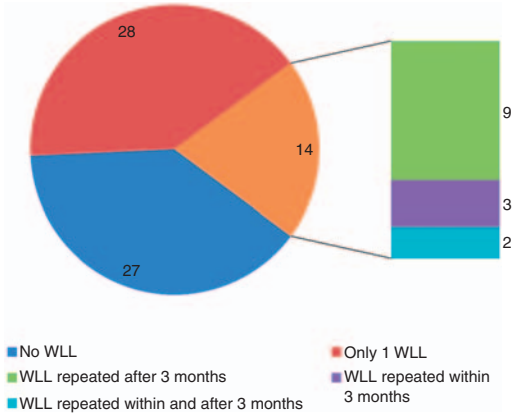

Figure 2. Treatment decision in 69 PAP patients seen in Pavia. In 42 PAP patients lavaged, 28 underwent a single whole-lung lavage (WLL). In 14 patients, more than one WLL was performed, but three patients received only two WLLs over 3 months, and no other WLL during the following years. Twenty seven PAP patients were not submitted to WLL, for different reasons (spontaneous resolution or improvement, minimal functional impairment not requiring treatment, consent refusal).

The impact of WLL on the long-term evaluation of lung function in 16 PAP patients from our cohort was examined [Beccaria *et al.* 2004]. We found that in PAP patients undergoing WLL, there is a significant increase in forced vital capacity (FVC), partial pressure of oxygen in arterial blood (PaO_2), and alveolar-arterial oxygen gradient (A-aDO_2) within the first week, whereas the respiratory parameters diffusing capacity (Dl_{co}) and treadmill distance walked significantly improved over time, reaching a plateau at 6–12 months. The only parameter that was not significantly influenced by WLL even in the long term was total lung capacity (TLC). Interestingly, at a median of 5 years follow up, the Dl_{co}, A-aDO_2, and distance walked did not totally recover, even in the presence of complete radiological resolution of PAP infiltrates. Another notable difference was the recurrence rate of PAP after WLL. In contrast with the 80% rate reported by Seymour and Presneill [2002], in our series [Beccaria *et al.* 2004] the recurrence rate was 28% in prolonged follow up. However, in a more recent analysis of our data (unpublished data), including 38 lavaged PAP patients, the recurrence rate rose to 45%.

Bronchoscopic segmental/lobar lavage

Partial lung lavage, performed with a bronchofiberscope, is considered a possibility when WLL is potentially harmful as in the case of severe hypoxemia and when extracorporeal membrane oxygenation is not feasible [Cheng *et al.* 2002]. This option is also indicated for children: since there is no pediatric-size double-lumen endotracheal tube available, unilateral lung lavage by bronchofiberscope and selective ventilation, with a cuffed endotracheal tube [Dogru *et al.* 2009], is another alternative. Paquet and Karsli also utilized a two-cuffed endotracheal tube for the treatment of a pediatric patient [Paquet and Karsli, 2009].

Granulocyte-macrophage colony-stimulating factor (GM-CSF)

As mentioned previously, the occurrence of PAP in GM-CSF knockout mice [Dranoff *et al.* 1994; Stanley *et al.* 1994] promptly led to the use of GM-CSF in humans with autoimmune PAP. The first PAP patient who was administered with subcutaneous (s.c.), i.e. the usual route of administration for GM-CSF, recombinant GM-CSF (rGM-CSF) at the dose of 6 μg/kg/day, exhibited a transient improvement in exercise tolerance and A-aDO_2 [Seymour *et al.* 1996]. Subcutaneous GM-CSF has been administered over the years to a relatively small number of autoimmune PAP patients. Data on these patients have been published as: (i) single case reports [Rahaman *et al.* 2004; Barraclough and Gillies, 2001]; (ii) one preliminary report [Kavuru *et al.* 2000]; (iii) two side publications, one suggesting that PAP patients with low Abs titer have less active disease and respond to s.c. rGM-CSF with a further decline in Abs [Bonfield *et al.* 2002], and the second reporting that serum Abs were not correlated with PAP severity, and that LDH was the only biochemical parameter predicting response to therapy [Seymour *et al.* 2003]; (iv) two studies with the characteristics of a clinical trial, although with an open-label design. In the first of these two papers, Seymour and colleagues treated 14 PAP patients over a three-month period with an increasing GM-CSF dose (5–20 μg/kg/day subcutaneously), with a response rate of 43% [Seymour *et al.* 2001]. In a subsequent study, 21 patients with autoimmune PAP were treated over a period of 6–12 months with increasing doses of s.c. rGM-CSF [Venkateshish *et al.* 2006]. Twelve out the 21 patients (48%) showed improvement in A-aDO_2 and other clinical parameters. Taken together, these data suggest that less than 50% of autoimmune PAP patients are responsive to s.c. GM-CSF. These results are affected by the fact that, at least in the series reported by Venkateshish and colleagues, the trial enrolled only moderately impaired patients; in other words, the impact of s.c. rGM-CSF in severe forms of PAP remains to be determined.

Evidence that, in rGM-CSF knockout mice, s.c. GM-CSF was unable to ameliorate PAP, whereas aerosolized rGM-CSF did [Reed *et al.* 1999], strongly supports the rationale to deliver the drug by this route. Again, only two papers have covered this issue in a relatively large cohort of patients. The first was a retrospective study including 12 autoimmune PAP patients, treated with a rGM-CSF dosage of 250 μg/day every other week (one patient required dose escalation at 500 μg/day and different treatment length) [Wylam *et al.* 2006]. Six out of 12 were responders in this series (50% positive response rate). In a very recent paper, the first open-label trial with inhaled rGM-CSF is described [Tazawa *et al.* 2010]. This study was preceded by a case report [Arai *et al.* 2004] and a pilot study in three patients which analyzed the biological efficacy of the treatment [Tazawa *et al.* 2005] by the same group of investigators. The trial dealt with 35 stable PAP patients treated with an induction dose (rGM-CSF 250 μg/day b.i.d. every other week for 6 weeks) and then a maintenance dose (125 μg/day b.i.d. for 4 days every 2 weeks for six cycles). The positive response rate, in terms of decrease in A-aDO_2 and DI_{co}, was 62%, and no adverse events were recorded. This study, as well as that of Wylam and colleagues, utilized a PARI LC plus nebulizer (PARI, GmbH, Starnberg, Germany) [Wylam *et al.* 2006].

Plasmapheresis

The rationale for plasmapheresis is based on the concept that Abs play a pathogenic role in PAP [Sakagami *et al.* 2009], thus plasmapheresis should reduce Ab levels sufficiently to restore surfactant catabolism in alveolar macrophages. In one case report by Bonfield and colleagues, a PAP patient, refractory to three WLLs and one course of s.c. rGM-CSF, underwent low-intensity plasmapheresis, which resulted in a reduction of plasma Abs levels, and improvement in symptoms, blood oxygen saturation, and radiographic appearance of the lungs [Bonfield *et al.* 2002]. The clinical course was complicated by a Gram-negative sepsis; however, the patient subsequently recovered, thus the plasmapheresis schedule was terminated [Kavuru *et al.* 2003]. No long-term follow-up data on this patient are available.

B-lymphocyte depletion

Reduction in Abs serum levels is an interesting goal in autoimmune PAP. Rituximab (humanized monoclonal Abs that by binding CD20 selectively abrogates the B-cell pool) was administered in one PAP patient who refused WLL [Borie *et al.* 2009]. Rituximab (1 g iv on days 1 and 15) was well tolerated and induced long-lasting B-lymphocyte depletion, as well as a marked

decrease in titer and activity of neutralizing Abs. This was paralleled by an improvement in CT scan findings, A-aDO_2, DI_{co}, and six-minute walking test (6MWT).

Lung transplantation

Although it is likely that some PAP patients underwent lung transplantation, there is only one specific report on this option [Parker and Novotny, 1997]. The transplantation was successfully performed in the PAP patient, but the clinical course was characterized by disease recurrence 3 years later.

Combination therapy

As for other medical conditions, adoption of two or more therapeutic tools, proven to be effective alone, can be considered for the management of difficult PAP cases.

WLL-inhaled GM-CSF

A young Japanese girl, aged 9, affected by autoimmune PAP and refractory to inhaled GM-CSF, was treated with three single-lung whole lavage sessions, resulting in partial remission. She then continued GM-CSF inhalation therapy for 9 months, with progressive improvement of gas exchange and CT scan appearance [Yamamoto *et al.* 2008]. This represents a promising approach, requiring, however, a controlled trial to correctly assess the efficacy (see the following).

Plasmapheresis–WLL

Another combination reported is WLL followed by plasmapheresis and then WLL(s) again [Luisetti *et al.* 2009]. One patient refractory to three WLLs performed in less than 12 months was submitted to 10 sessions of low-intensity plasmapheresis followed by another WLL. This approach resulted in: (1) marked and sustained decrease in plasma Abs levels; and (2) increased length of symptom-free intervals between following WLLs.

Treatment of other forms of PAP

Primary PAP associated with GM-CSF receptor mutations

To date, 15 cases of this form of primary PAP have been reported worldwide [Suzuki *et al.* 2010, 2008; Dirksen *et al.* 1997]. In spite of this low figure, we have found that the response of WLL in primary PAP associated with GM-CSF receptor α chain is good, with relative sustained improvement. Bone marrow transplantation was attempted in one case, but the patient died shortly after due to an opportunistic infection [Martinez-Moczygemba *et al.* 2008]. GM-CSF receptor gene transfer has been hypothesized [Suzuki *et al.* 2010]. Interestingly, the prognosis in primary PAP associated with GM-CSF receptor β chain is much worse [Dirksen *et al.* 1997], possibly because it occurs at an earlier age than those with GM-CSF receptor α chain.

Secondary PAP

PAP associated with hematologic malignancy, especially *myelodysplastic syndrome*, represents the vast majority of secondary PAP. In such a setting, as in other forms of secondary PAP, the prognosis is generally worse than in autoimmune PAP, and WLL, although feasible, usually provides only transient benefit. The prognosis is clearly linked to the underlying disease, but, following chemotherapy-induced remission of the hematologic disorder, a remission of the associated PAP is possible [Dirksen *et al.* 1998]. The most frequent form of secondary PAP associated with exposure, i.e. the *silicoproteinosis*, is now quite rare in western countries, whereas for one series reported no information on therapeutic treatment was available [Marchiori *et al.* 2007].

PAP associated with lysinuric protein intolerance (LPI)

PAP is a complication occurring in about 15% of cases of lysinuric protein intolerance (LPI), a rare inherited condition due to mutations in the cationic amino acid transporter gene SLC7A7. Prognosis in these cases is usually poor: WLL offers only transient benefit, rGM-CSF administered subcutaneously has induced serious side effects, whereas when administered by inhalation it was ineffective, and heart–lung transplantation was followed by PAP recurrence [Douda *et al.* 2009; Santamaria *et al.* 2004]. However, there is at least one case of long-lasting remission following WLL [Ceruti *et al.* 2007]; interestingly, this patient became subsequently refractory to WLL, but he responded well to a short course of inhaled GM-CSF (manuscript in preparation). Bone marrow transplantation has been discussed, but never tested.

Ongoing trials

Currently, three trials are listed on the US NIH Clinical Trials website (http://clinicaltrials.gov/) associated with the word search 'alveolar proteinosis'.

One is a prospective, nonrandomized, open-label trial of rituximab planned in 10 patients with primary PAP. The second study is a randomized, placebo-controlled study with s.c. rGM-CSF (but the study seems to have last been updated in 2005). The third study is a randomized, open-label, active control, parallel assignment of WLL followed by inhaled rGM-CSF: the first patient in this trial was randomized in July 2009, and the enrolment of 18 patients is expected to be completed in 36 months.

Conclusions

It is indubitable that WLL is the main determinant in the improved outcome and long-term survival in PAP, which is no longer considered a potentially lethal disorder. Nevertheless, emerging concepts in the pathophysiology of PAP open the way to innovative treatment options, which could be considered as alternatives in PAP patients refractory to WLL or with physical impairment, a contraindication to the prolonged general anesthesia necessary during WLL. It is also likely that as our knowledge in this field progresses, the picture of treatment options will become more defined, with the ultimate goal of providing optimal therapy for subjects with this rare, yet fascinating disease.

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Conflict of interest statement

The authors have declared that there is no conflict of interest.

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