''Treat-to-target'' in pulmonary arterial hypertension and the use of extracorporeal membrane oxygenation as a bridge to transplantation

To the Editor:

A 30-yr-old female was referred to the Hanover Medical School (Hanover, Germany) in July 2007 following a diagnosis of idiopathic pulmonary arterial hypertension (PAH). She had no other comorbidities. At the time of diagnosis she was in World Health Organization functional class (WHO FC) III with a 6-min walk distance (6MWD) of 402 m. Cardiopulmonary exercise testing (CPET) showed that her peak oxygen uptake (V'_{O_2}) was markedly impaired (11.6 $mL \cdot min^{-1} \cdot kg^{-1}$; target range >15 $mL \cdot min^{-1} \cdot kg^{-1}$) [1]. Echocardiography revealed a tricuspid annular systolic plane excursion (TAPSE) of 1.6 cm (normal value >2 cm) indicating serious impairment of right ventricular function. The results of right heart catheterisation (RHC) are shown in table 1. Haemodynamics were compatible with diagnosis; a low cardiac output and high pulmonary vascular resistance. In accordance with guideline recommendations [1], treatment was initiated with sildenafil 20 mg three times daily. This was well tolerated and 3 months later her functional status had improved to WHO FC II and her 6MWD had increased to 465 m. Although her TAPSE had improved to 1.8 cm, it was still below normal, suggesting her right ventricular (RV) function remained impaired. To further investigate this CPET was repeated, which revealed that her peak V'_{O_2} had only slightly improved from baseline (12.5 $mL \cdot min^{-1} \cdot kg^{-1}$) and that her oxygen pulse (V'_{O_2}/heart rate), an indirect measure of stroke volume, was only approximately half of that predicted. Taken together these data indicated the patient's response to sildenafil was suboptimal, particularly with respect to RV function. The decision was then made to initiate treatment with bosentan in addition to her existing sildenafil regimen. Combination therapy was well tolerated, and there was no evidence of elevated liver transaminases throughout the duration of therapy.

After 3 months of combination therapy, the patient was stable in WHO FC II, her 6MWD had improved to 488 m, her TAPSE had improved to 2.2 cm and her peak V'_{O_2} was 14.6 $mL \cdot min^{-1} \cdot kg^{-1}$. Results of RHC showed marked improvements in haemodynamic parameters (table 1). After discussion with the patient, it was decided not to further escalate treatment at this stage and sildenafil/bosentan combination therapy was continued with regular re-evaluations.

The patient continued to do well on sildenafil/bosentan for 2 yrs. In September 2010, she was admitted to hospital following an episode of syncope experienced after running for a bus. Although she remained in WHO FC II, her 6MWD had declined to 464 m, her TAPSE had fallen to 1.9 cm and her peak V'_{O_2} was 11.6 $mL \cdot min^{-1} \cdot kg^{-1}$. RHC showed her haemodynamic parameters had deteriorated toward baseline levels (table 1). At this time, the patient was listed for bilateral lung transplantation, her sildenafil dose was initially increased to 40 mg and then to 60 mg three times daily and *i.v.* iloprost was added to her treatment regimen. Despite attempts to stabilise her condition using catecholamines, the patient deteriorated rapidly, developing right heart failure with renal failure and lactic acidosis within 48 h of admission.

The patient was maintained on veno-arterial extracorporeal membrane oxygenation (ECMO), conscious and without ventilation, for 42 days until suitable donor organs became available, after which she underwent successful bilateral lung transplantation. While receiving ECMO her renal function recovered fully, and there was no infection, bleeding or other complications.

This case illustrates the application of current European Society of Cardiology (ESC)/European Respiratory Society (ERS) guideline ''treat-to-target'' recommendations in routine clinical practice, and also describes the successful use of ECMO as a bridge to lung transplantation following failure of long-term medical management.

Based on the initial assessment of the patient, the decision was made to initiate treatment with sildenafil monotherapy, in line with guideline recommendations for patients in WHO FC III. As the patient was young and quite badly impaired, it may also have been reasonable to consider first-line (upfront) combination therapy at this time. Although theoretically appealing, there is currently little evidence to support this strategy. Evidence regarding the potential benefit of upfront combination therapy relative to monotherapy should come from the AMBITION study [2], a phase III trial comparing first-line combination therapy with an endothelin receptor antagonist (ambrisentan) and a phosphodiesterase type-5 inhibitor (tadalafil) *versus* first-line monotherapy (ambrisentan or tadalafil) in patients with PAH. This large, multicentre study is estimated to be completed in 2013. However, until such data are available initial monotherapy in WHO FC III patients is the recommendation of the current guidelines.

Following initiation of therapy, close monitoring of the patient is mandatory. In this case we reassessed the patient 3 months after sildenafil was introduced. According to the ESC/ERS guidelines, treatment decisions should be based on parameters that reflect symptoms (*e.g.* WHO FC) and exercise capacity (*e.g.* 6MWD) and that are relevant prognostic indicators (haemodynamic parameters, CPET, TAPSE, evidence of right heart failure, *etc.*) [1]. Based on these parameters, a patient's response to therapy can be classified into one of three categories: stable and satisfactory; stable but not satisfactory; or unstable and deteriorating. When a patient is classified in the latter two categories, guidelines recommend the consideration of sequential combination therapy [1]. At her 3-month assessment, although some of the patient's parameters had improved to levels associated with ''better prognosis'' according to treatment guidelines, other measures, in particular TAPSE, remained in the ''grey area'' in terms of prognosis. We repeated CPET in this

TABLE 1 Right heart catheterisation results

	Referral: July 2007	Sildenafil + bosentan for 3 months: Sept 2008	Sildenafil + bosentan for 2 yrs: Sept 2010
P_{ra} mmHg	7	5	8
$\bar{P}_{pa}$ mmHg	62	55	60
P_{pcw} mmHg	5	6	4
Cardiac output L·min^{-1}	2.9	4.2	3.4
Cardiac index L·min^{-1}·m^{-2}	1.6	2.3	1.9
PVR dyn·s·cm^{-5}	1572	933	1318
S_{v,O_2} %	56	66	61

P_{ra}: right artery pressure; $\bar{P}_{pa}$: mean pulmonary artery pressure; P_{pcw}: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; S_{v,O_2}: mixed venous oxygen saturation.

patient as, in our opinion, this gives a better indication of RV functional capacity and reserve than the 6MWD, particularly in patients in WHO FC II in whom exercise intolerance is not severe. RHC was not repeated at this time as sufficient evidence could be obtained from noninvasive testing to assess the patient's response to therapy. Given the indications of continuing RV impairment, confirmed by CPET, the patient was considered to be in the ''stable but not satisfactory'' category according to guideline recommendations for assessing response, and the decision was made to escalate treatment using combination therapy of sildenafil plus bosentan [1].

After 3 months of combination therapy, the patient was stable in WHO FC II with an increased 6MWD and improvements in RV function as shown by TAPSE. Her peak $V'O_2$ was close to the level recommended in treatment guidelines [1]. Although her haemodynamics were not at normal levels, they showed considerable improvement and her cardiac index was only slightly below recommended levels. The majority of the patient's parameters were, therefore, in the better prognosis category, making her largely stable and satisfactory. In these circumstances, consideration may have been given to the addition of a prostanoid to her treatment regimen. One possibility would be the addition of inhaled iloprost, which has shown a short-term benefit [3]. Furthermore, data for inhaled iloprost in combination with oral therapies are limited, and its use in triple combination with sildenafil and bosentan has not been evaluated. Another possibility would be the introduction of an *i.v.* prostanoid, which would be attractive given the survival benefits demonstrated with epoprostenol [4, 5]. Intravenous prostacyclins have become the treatment of choice for patients with severe (WHO FC IV) PAH, but there is also evidence to suggest that their earlier use may also be of benefit in patients with mild-to-moderate PAH, and some authors have suggested they should be used earlier in the disease course [6, 7]. However, *i.v.* administration is associated with a range of risks and considerable inconvenience, which could make this choice unacceptable to patients who are doing well on oral therapies. In this respect, patient preference is an important aspect of management. After discussion with the patient, it was decided not to further escalate treatment at this stage and her therapy was continued with regular re-evaluations.

Her condition declined 2 yrs later. Repeated RHC showed marked deterioration in her haemodynamics and she was placed on the waiting list for transplantation. In an attempt to stabilise her condition, her dose of sildenafil was increased and an *i.v.* prostanoid was added to her regimen. As *i.v.* epoprostenol was not available in Germany at the time this patient was treated, *i.v.* iloprost was the agent of choice. Compared with epoprostenol, iloprost is more stable in solution and has a longer plasma half-life [8], which makes it more convenient to use and potentially safer since interruption of drug supply does not result in immediate cessation of the drug's action [9]. In relatively small studies, *i.v.* iloprost and epoprostenol have been reported to have comparable short- and long-term efficacy [10, 11], although in contrast to epoprostenol, long-term survival benefits of *i.v.* iloprost have not been proven [4, 5, 9, 12]. However, despite this escalation in treatment and the use of further supportive therapies including catecholamines, the patient's condition deteriorated sharply, and she experienced right heart failure, renal failure and lactic acidosis.

Given the lack of a suitable donor at that time, we decided to place the patient on ECMO as a bridge to transplantation. In the past, although increasingly used for adults with ventilation-refractory acute severe respiratory failure, ECMO has, in general, been considered to be a contraindication to lung transplantation [13, 14]. However, there are an increasing number of reports in the literature on the use of this method as a bridge to lung transplantation in patients with a number of underlying conditions, including acute severe respiratory failure [13], acute respiratory distress syndrome [15], cystic fibrosis [16] and pulmonary hypertension [17–20]. A recent report of outcomes in 16 patients with end-stage pulmonary disease found that, in those who survived to transplantation, 1-yr post-transplant survival was 92% [21]. The duration of ECMO support in this study ranged from 1 to 59 days (mean 17 days). ECMO has been reported to have been used for up to 107 days as a bridge to transplantation [15] and several weeks' use is not uncommon [22]. In general, ECMO is used in conjunction with prolonged sedation and mechanical ventilation, increasing the risks associated with the technique. We recently reported upon a series of patients with cardiopulmonary failure due to pulmonary hypertension treated with veno-arterial ECMO as a bridge to transplantation in our centre (Hanover Medical School), who were awake and breathing spontaneously for the duration of treatment (18–35 days) [19]. These patients were able to eat and

drink, and they received physiotherapy as well as psychological support. The patient presented in this case study also remained conscious and was breathing spontaneously throughout the 42 days she spent on ECMO. An alternative form of extracorporeal life support is the Novalung® interventional lung-assist membrane ventilator device (Novalung GmbH, Lotzenaecker, Germany). This device is driven by the patient's cardiac output and, therefore, does not need an extracorporeal pump, which means that the patient can be mobilised while awaiting transplantation. This device has been used successfully in a variety of settings [23], including as a bridge to transplantation in patients with pulmonary hypertension [24]. It has also been used successfully in our centre [25–27], but currently we prefer to use awake ECMO because of the good clinical experience we have with this strategy.

Although it is a feasible approach, ECMO as a bridge to transplantation is not suitable for all candidates. Irrespective of clinical considerations and the risks associated with the technique, such treatment requires that the patient is highly self-disciplined and motivated to tolerate long periods of time restrained in a hospital bed and connected to cardiopulmonary devices. On-going support from family and friends, as well as physicians, therapists and nurses, is also paramount [19]. The prolonged use of ECMO is associated with a higher risk of peri- and post-operative complications and a much longer recovery time compared with patients who are transplanted in a ''normal'' setting, therefore, it cannot be considered to be a ''standard'' procedure in patients waiting for lung transplantation [22]. However, results in this case study add to the evidence that ECMO is feasible and remarkably well tolerated in this setting, and can act as a successful bridge to transplantation with good outcomes for selected patients who otherwise would not survive.

The use of a ''treat-to-target'' strategy with close monitoring of patients allows for early identification of inadequate response and prompt escalation of therapy, including the use of sequential combination therapy, when attempting to prevent further deterioration in the patient's condition. However, although the use of PAH-specific therapy is associated with increased long-term survival, idiopathic PAH remains a progressive disease in a number of patients [28]. For those patients with severe disease who fail to respond to maximal therapy, transplantation remains the only viable option but is limited by the supply of suitable donor organs. Although often considered a contraindication, this case study demonstrates that ECMO can be used to provide a bridge to successful lung transplantation in idiopathic PAH patients with end-stage cardiopulmonary failure.

M.M. Hoeper
Dept of Respiratory Medicine, Hanover Medical School, Hanover, Germany.

Correspondence: M.M. Hoeper, Dept of Respiratory Medicine, Hanover Medical School, Carl-Neuberg-Str. 1, 30625 Hanover, Germany. E-mail: hoeper.marius@mh-hannover.de

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Drug-induced eosinophilic pleural effusion

To the Editors:

We read with great interest the article by ALAGHA *et al*. [1] in the June issue of the *European Respiratory Review*. Since, in our opinion, eosinophilic pleural effusion (EPE), and drug-induced EPE in particular, is an interesting issue, we would like to add some comments to this article.

It should be realised that our knowledge on drug-induced EPE comes almost exclusively from case reports. Although none of the larger series presenting the aetiology of EPE reported the true incidence of drug-induced EPE, the percentage of patients with drug-induced EPE seems to be low. Nevertheless, as in the majority of these patients drug discontinuation is sufficient for resolution of pleural effusion, pharmacological agents should always be considered as a potential cause of pleural effusion, particularly in EPE.

Although numerous drugs can induce pleuritis and pleural effusion, the list of agents associated with eosinophilic pleuritis is not extensive [2–4]. Some drugs used in psychiatry and neurology are some of the most important, including valproic acid (and its derivatives) and dantrolene [5–8]. EPE was also reported as a complication of treatment with tazinidine, trimipramine and fluoxetine [9–11]. It is interesting that, in a substantial number of reports on drug-induced EPE, two or more drugs that can potentially induce pleural effusion were used. This was the case in the first patient described by ALAGHA *et al*. [1], who was treated with dantrolene and fluoxetine. Similarly, two patients with EPE related to valproic acid and sodium valproate, respectively, were also treated with clozapine [12, 13]. Interestingly, when valproic acid and clozapine are used together, clozapine might be a true cause of pleural effusion as demonstrated by DALY *et al*. [14]. Clozapine-induced pleuritis was reported in one patient who was concomitantly treated with olanzapine [15]. These examples show the crucial role of thorough clinical evaluation, including drug withdrawal and re-challenge in making a causative diagnosis of drug-induced pleural effusion.

In order to list the most important drugs associated with EPE, two other groups should also be presented. The first is quite inhomogeneous and includes drugs mainly used in cardiology and internal medicine, these are: warfarin, diltiazem, simvastatin, imidapril, propylthiouracyl and mesalamine. The second group includes the following chemotherapeutics and antibiotics: nitrofurantoin, daptomycin and tosufloxacin. A comprehensive review on drug-induced pleural effusion was published in 2004 [16].

There is one general statement regarding EPE in the report by ALAGHA *et al*. [1] which, in our opinion, requires correction and comment. Citing an article by ADELMAN *et al*. [17], the authors state that a specific cause of EPE could be identified in only 25% of patients [1]. We would like to emphasise that, although the paper by ADELMAN *et al*. [17] has long been one of the most important sources of our knowledge on epidemiology of EPE, it was based on analysis of 23 papers published between 1955 and 1982. Thus, the data from that study are quite old. However, even in this paper the cause of EPE could be identified in 65% of patients and only 35% of cases were classified as ''idiopathic'' EPE [17]. Recently, some relevant articles on EPE epidemiology have been published. Our analysis of the largest, single-centre treated group of patients with EPE showed that a causative diagnosis was not established in only 14.1% of these patients [18]. A similar result (15.6% idiopathic EPEs) was reported by MARTINEZ-GARCIA *et al*. [19]. It should also be noted that other authors reported a higher percentage of patients with EPE of unknown origin. This percentage, however, did not exceed 30–32% [2, 20]. A lower number of patients with unknown cause of EPE in the recent studies might be related to the advances in the diagnosis of pleural effusion, but also to changing aetiology of EPE. This was elegantly demonstrated in a paper recently