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Safety and Efficacy of Immunoadsorption as an Add-On to Medical Treatment in Patients with Severe Idiopathic Pulmonary Arterial Hypertension

Christian Nagel[a, b, h, i] Ralf Ewert[c] Benjamin Egenlauf[a, h, i] Hans B. Lehmkuhl[d] Stephan Rosenkranz[e] Nicola Benjamin[a, h, i] Vedat Schwenger[f, g] Felix J.F. Herth[h, i] Ekkehard Grünig[a, h, i]

[a]Centre for Pulmonary Hypertension, Thorax Clinic at the University Hospital Heidelberg, Heidelberg, [b]Lung Centre, Klinikum Mittelbaden, Baden-Baden, [c]Clinic for Internal Medicine, Greifswald University Hospital, Greifswald, [d]Medical Practice for Cardiology, Berlin, [e]Department of Cardiology, Heart Center at the University Hospital Cologne and Cologne Cardiovascular Research Center, Cologne, [f]Department of Nephrology, Klinikum Stuttgart, Stuttgart, and [g]Department of Nephrology, University Hospital Heidelberg, [h]Department of Internal Medicine, Pulmonology and Critical Care Medicine, Thorax Clinic at the University Hospital Heidelberg, and [i]Translational Lung Research Center Heidelberg (TLRCH), Member of the German Center for Lung Research DZL, Heidelberg, Germany

Keywords

Immunoadsorption · Plasmapheresis · Pulmonary arterial hypertension · Autoantibodies

Abstract

Background: Despite optimized medical therapy, severe idiopathic pulmonary arterial hypertension (IPAH) is a devastating disease with a poor outcome. Autoantibodies have been detected in IPAH that can contribute to worsening of the disease. ***Objectives:*** The objective of this prospective, open-label, single-arm, multicenter trial was to evaluate the safety and efficacy of immunoadsorption (IA) as an add-on to optimized medical treatment for patients with IPAH. ***Methods:*** A total of 10 IPAH patients received IA over 5 days. Their clinical parameters, including hemodynamics measured by right heart catheter, were assessed at baseline and after 3 and 6 months. The primary endpoint was the change in pulmonary vascular resistance (PVR). Secondary endpoints included the change in 6-min walking distance, quality of life, safety, and plasma levels of IgG and autoantibodies. ***Results:*** The evaluation of the 10 IPAH patients (75% female; 51 ± 12 years; 166 ± 10 cm; WHO functional class III; 53% on combination therapy) revealed that IA was a safe procedure that efficiently removed IgG and autoantibodies from the circulation. After 3 months, the mean PVR improved significantly by 13.2% ($p = 0.03$) and the cardiac index improved by 13.1%, but no significant changes were found in 6-min walking distance. The quality of life physical functioning subscale score significantly improved after 6 months. The serious adverse events in 3 patients were possibly related to IA and included pneumonia, temporary disturbance

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E-Mail karger@karger.com
www.karger.com/res

Christian Nagel, MD
Centre for Pulmonary Hypertension
Department of Internal Medicine, Pulmonology and Critical Care Medicine
Thorax Clinic at the University Hospital Heidelberg, Röntgenstrasse 1
DE–69126 Heidelberg (Germany), E-Mail christian.nagel@med.uni-heidelberg.de

in attention, and thrombocytopenia. ***Conclusions:*** IA as an add-on to targeted medical treatment for IPAH is a safe procedure with beneficial effects on hemodynamics, especially in patients with high levels of autoantibodies. Larger-scale controlled studies are needed to assess its efficacy in IPAH and to identify responders.

Introduction

Idiopathic pulmonary arterial hypertension (IPAH) is characterized by increased pulmonary vascular resistance (PVR) and right heart failure [1]. A pathologic immune response is a major constituent of the molecular pathogenesis of PAH [2, 3]. This has been demonstrated not only in connective tissue disease-associated PAH but also in pulmonary hypertension (PH) due to infectious diseases or pollution [4]. An increased autoimmune response has also been shown in idiopathic [5] or heritable [6] PAH and in PH due to lung disease [7] or left heart failure [8].

Autoantibodies (AAB) against endothelial cells, fibroblasts, and smooth muscle cells have been detected in IPAH and in connective tissue disease-associated PAH. Although they are not specific for PAH, they can contribute to the pathogenesis of the disease [9, 10]. It has been shown that immunoglobulins isolated from animals with monocrotaline-induced PH can induce the disease in previously non-PH animals [11]. Circulating AAB against the α_1-adrenergic, angiotensin II, and endothelin-1A receptors, which contribute to the remodeling of pulmonary vessels, have been identified in the sera of patients with PAH [12]. It was proposed that these antibodies lead to long-lasting activation of the target receptors, causing proliferation and hypertrophy of endothelial cells and fibroblasts, vascular remodeling, and vasoconstriction [13].

These findings led to the hypothesis that removal of AAB from the circulation by immunoadsorption (IA) might improve the disease. Using IA, antibodies were nonspecifically removed by an adsorber [14] without any need to substitute blood products. IA has previously been used for various indications such as dilated cardiomyopathy (DCM) [15, 16], connective tissue diseases [17, 18], and myocarditis [19], as well as during heart transplantation [20]. First experiences with IA using the medical device TheraSorb™ – Ig Flex Adsorber with a LIFE 18® Apheresis System in 4 PAH patients were encouraging and revealed good tolerability of the treatment and improvements in noninvasively measured right ventricular size, pulmonary artery pressures, peak oxygen uptake, and 6-min walk distance [12].

The objective of this prospective study was to investigate the safety and efficacy of IA in patients with IPAH.

Subjects and Methods

Study Population and Design

The study was designed as a prospective, open-label, single-arm, multicenter clinical trial. Five centers participated. Patients aged 18–80 years old with IPAH and right heart insufficiency in WHO functional class (WHO-FC) II–III on stable, optimized, disease-targeted medication were assigned to the study. Exclusion criteria were pregnancy and/or lactation, walking inability, inability to perform the 6-min walk test (6MWT), or right heart catheterization (RHC). The medication remained unchanged during the study period. RHC was performed at baseline and after 3 months. The primary endpoint was the change in PVR. Secondary endpoints were hemodynamic changes, the change from baseline to 3 months in 6MWT distance and WHO-FC, quality of life (36-Item Short-Form Health Survey [SF-36]), reduction in the plasma IgG concentration (IA efficacy), and safety (adverse events and all-cause mortality).

All patients gave written informed consent to the study. The protocol was approved by the Central Ethics Committee of the University of Heidelberg, Germany, on May 23, 2012, as well as by local ethics committees. This study was conducted in accordance with good clinical practice and the current version of the revised Declaration of Helsinki (World Medical Association Declaration of Helsinki). Written informed consent was obtained from all subjects prior to the conduct of any study-specific activities. The first patient entered the study on July 13, 2012, and the last patient completed the study on November 26, 2013.

Procedure of IA

For IA, the medical device TheraSorb™ – Ig Flex Adsorber was used with the LIFE 18® Apheresis System (Miltenyi Biotec GmbH, Bergisch Gladbach, Germany). The TheraSorb™ – Ig Flex Adsorber column removes human IgG (all subclasses, IgG1–4), IgA, IgE, and IgM, as well as immune complexes, from the circulation [17].

The treatment procedure followed a standardized scheme and included the control of alternating cycles of two adsorber columns during treatment, as described previously [13]. The therapeutic system consists of two regenerable TheraSorb™ – Ig Flex Adsorber columns attached to a disk separator. Within the disk separator, plasma and the cellular components of venous blood are separated, and the plasma is directed alternately into one of the adsorbers, while the other adsorber is regenerated. After passing through the adsorber matrix, the plasma is recombined with the cellular components of the blood and returned to the patient.

To perform IA, the patients stayed in hospital for at least 5 days, received a Shaldon catheter, and underwent apheresis every day for 2 h. The Shaldon catheter was inserted into the internal jugular vein directly after RHC with the Seldinger wire technique during the same procedure. Safety parameters were assessed at baseline, every day during in-hospital stay, and at day 9, as well as 1 month, 3 months, and 6 months after IA had been initiated.

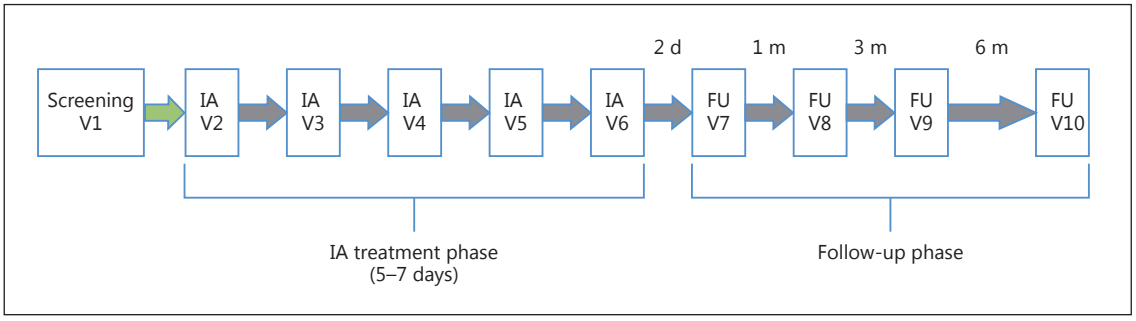

Fig. 1. Trial timeline showing the immunoadsorption treatment visits (IA) followed by a series of follow-up visits (FU) over a period of approximately 6 months. d, day; m, month.

The trial consisted of a screening visit and recruitment of eligible patients (V1), followed by 5 inpatient IA treatment visits (V2–6). The primary endpoint of the trial was assessed after 3 months (V9). The timeline for the trial is shown in Figure 1.

Outcome Measures

The efficacy parameters were prospectively evaluated at baseline and 3 months. The 6MWT was carried out under standardized conditions [21]. Health-related quality of life assessment was performed with the SF-36 [22]. The completed SF-36 questionnaire at baseline was compared to the results after 3 and 6 months.

RHC was performed at baseline and 3 months. The examination at rest was performed in a supine position using the transjugular approach with an 8-Fr introducer set. RHC was performed with triple-lumen 7-Fr Swan-Ganz thermodilution catheters. Cardiac output was measured at least in triplicate by thermodilution with a variation of <10% between the measured values. PVR and the cardiac index (CI) were calculated. All pressures were recorded at the end of expiration. The zero reference point for the pressure recordings was set at 1/3 of the thoracic diameter below the anterior thoracic surface at the level of the right atrium in the midaxillary line (phlebostatic axis) [23].

Measurements of AAB

To investigate the influence of baseline AAB levels on treatment outcome, subgroups (SG) with different numbers of AAB at a level above a specified threshold (corresponding to a normal AAB concentration) were analyzed. The following patient SG were formed on the basis of their specific number of AAB (α_1-adrenergic receptor antibodies, endothelin-1A receptor antibodies, and angiotensin II receptor type 1 antibodies) at an above-threshold level at baseline. The threshold value of 10.0 U/mL was used to determine the four SG based on the number of antibodies at a concentration above this level (SG1 = 0 AAB above threshold; SG2 = 1 AAB above threshold; SG3 = 1–3 AAB above threshold; SG4 = 2–3 AAB above threshold; thus, SG2 and 3, as well as SG 3 and 4, overlap). A value <10.0 U/mL was defined as "normal" by our central laboratory.

Safety Assessment

Safety assessments included monitoring of adverse events and serious adverse events, clinical laboratory evaluations, and monitoring of vital and physical signs throughout all visits. All adverse events and serious adverse events were assessed by the respective investigators for associations with the trial procedure or the trial device.

Table 1. Baseline characteristics of the safety set and the efficacy (per protocol) set of patients

Baseline characteristics	Safety set	Per protocol set (efficacy)
Patients, *n*	12	10
Gender male/female, *n*	9/3	8/2
Age, years	51.5±12	53.2±12
Height, cm	166±10	167±9
Weight, kg	76±25	78±26
WHO functional class at baseline, *n* (%)		
III	12 (100)	10 (100)

Values are presented as mean ± SD unless specified otherwise.

Statistical Analysis

Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). In general, the data are summarized by scheduled assessment. Descriptive statistics are given using the usual scale statistics including sample size, mean, and standard deviation. Frequency statistics are displayed by *n* and %. Paired-sample *t* tests were carried out to compare values between the different time points. The results are presented with 95% confidence intervals for the difference and a descriptive *p* value. The efficacy analysis was based on the per-protocol analysis set. All safety analyses were based on the safety analysis population.

Results

Baseline Characteristics and Patient Disposition

The patients' disposition and baseline demographics are summarized in Table 1. A total of 12 subjects received all IA treatments and were included in the safety set for

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Table 2. Changes in mean PVR between V2 (baseline) and V9 (3 months after IA) for the PPS and the 4 SG of patients, as well as individual values for each patient

Group	*n*	PVR, dyn × s × cm^{-5}						Reduction in PVR, %
		baseline (mean)	baseline (SD)	3 months (mean)	3 months (SD)	reduction in PVR (mean)	SD	
PPS	10	816.39	299.88	707.92	239.24	108.50[a]	135.89	13.2
SG1	3	672.73	178.00	600.07	277.06	72.67	99.08	10.8
SG2	4	1,019.90	245.55	883.50	165.31	136.40	146.60	13.4
SG3	7	877.95	331.05	754.14	227.94	123.80	153.34	14.1
SG4	3	688.72	379.93	581.67	191.82	107.10	193.81	15.6
PVR values for individual patients								
10102		474		291.5		182.5		38.50
10103		898.5		652.5		246		27.38
10104		884		680		204		23.08
50501		917.5		728		189.5		20.65
50502		1,318		1,030		288		21.85
40401		726		681.2		44.8		6.17
10101		603		538		65		10.78
20201		765		818		–53		–6.93
20202		817.5		827.5		–10		–1.22
20203		855		863.5		–8.5		–0.99

IA, immunoadsorption; PVR, pulmonary vascular resistance; PPS, per protocol set; SG, subgroup according to autoantibodies above threshold; V, visit. [a] Statistically significant (paired sample *t* test).

Table 3. Mean change in 6-min walking distance at each follow-up visit compared to the baseline measurement at V1

Group	Subjects, *n*	Change in 6-min walking distance (compared to V1), m							
		V7		V8		V9		V10	
		mean	SD	mean	SD	mean	SD	mean	SD
All[a]	9	1.78	37	16.11	28	7.11	24	2.22	73
SG1	2[b]	–25.50	5	–19.00	6	–18.50	8	–37.00	61
SG2	4	3.75	44	19.50	20	10.00	23	–7.00	29
SG3	7	9.57	39	26.14[a]	23	14.43	22	13.43	76
SG4	3	17.33	37	35.00	28	20.33	23	40.67	118

The first line gives the data for all eligible patients recorded at the follow-up visits (V) 7–10. SG, subgroup. [a] Statistically significant (paired sample *t* test). [b] Patient 40401 was excluded from the analysis because the 6-min walking distances were not measured at all times.

analysis. Two of the 12 patients were excluded from the per protocol set (PPS) due to missing hemodynamic values. In 1 patient, cardiac output was not measured at baseline; another patient had no RHC after 3 months. Thus, only 10 patients performed RHC with hemodynamic measurements at baseline and after 3 months and could be entered into the PPS for analysis of treatment efficacy. All 10 patients completed the treatment and follow-up visits. The mean baseline 6-min walking distance was 441.11 ± 76 m. All subjects were in WHO-FC III at baseline.

Table 4. Change in per protocol set parameters between baseline and 3 months (visit 9)

Per protocol set (efficacy)	Baseline	3 months
WHO functional classification at baseline, *n* (%)		
III	10 (100)	6 (60)
6-min walking distance, m[a]	441.11±76	448.22±62
Quality of life		
Physical functioning index	75.11±16.71	74.33±18.19
Right heart catheterization		
Mean pulmonary arterial pressure, mm Hg	55.1±11.16	55.95±19.54
Pulmonary vascular resistance, dyn × s × cm^{-5}	816.39±299.88	707.92±239.24
Cardiac index, L × min × m^{-2}	2.45±0.57	2.77±0.86

Values are presented as mean ± SD unless specified otherwise. [a] Only 9 patients were included in the 6-min walk test results due to protocol deviation in 1 patient (40401).

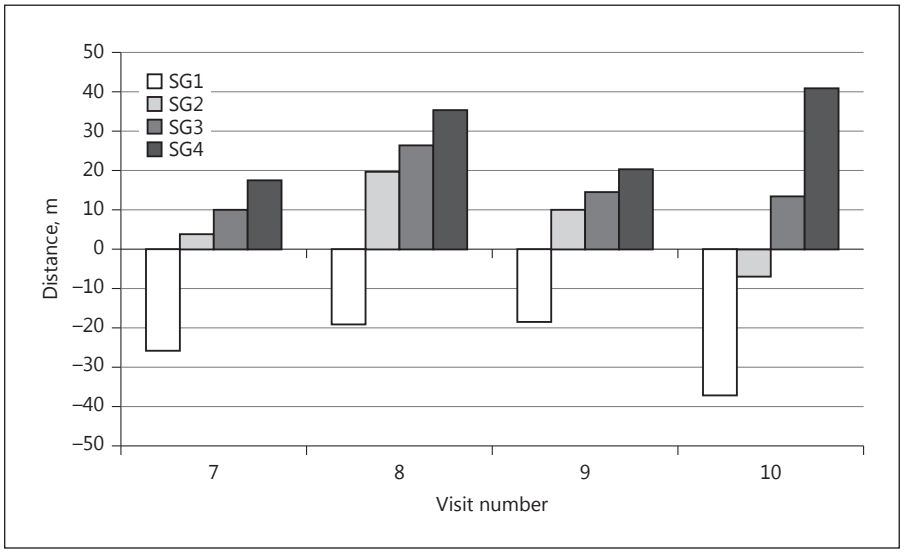

Fig. 2. Mean change in 6-min walking distance (compared to visit 1) (data from Table 3). SG, subgroup.

Reduction in PVR and Increase in Cardiac Function

After 3 months, the patients in the PPS showed a statistically significant ($p = 0.03$) decrease in mean PVR of 13.2% (Table 2). The CI improved by 13.1% from 2.45 ± 0.57 to 2.77 ± 0.86 L × min × m^{-2} (Table 4). The analysis of the patient SG revealed a PVR reduction of 15.6% in SG4 and of 14.1% in SG3, while SG2 and SG1 exhibited reductions of 13.4 and 10.8%, respectively (Table 2). Five of the 10 patients showed a PVR reduction between V2 and V9 of >20%.

6-min Walk Test

The mean values for the secondary endpoint 6MWT distance for the overall PPS population (excluding patient 40401, whose 6MWT values were not measured at all times) from V7 to V10 were improved when compared to the baseline value at V1 (Table 3) and showed the highest mean increase of 16.1 m (3.7%) at V8, 1 month after IA. However, there was no significant difference in mean values compared to V1.

The patient SG also showed a trend towards the walking distance increasing with the number of AAB above the threshold (SG1 < SG2 < SG3 < SG4) (Table 3; Fig. 2). A summary of the changes in parameters measured in the PPS is given in Table 4. At 3 months, 4 patients (40%) had improved their WHO-FC from III to II, and they remained in class II when assessed at V10 (6 months after initiation of IA).

Table 5. Concentrations of AAB at baseline (V1) and at each follow-up visit (n = 10 patients)

Visit	n	AAB concentration, U/mL					
		α1-AR-AAB		ETA-AAB		AT1-AAB	
		mean	SD	mean	SD	mean	SD
V1	10	12.22	4.39	5.77	4.75	7.65	4.73
V7	10	6.31	5.17	4.44	3.78	4.93	4.31
V8	10	13.16	6.09	7.28	4.65	9.00	4.43
V9	10	13.81	7.1	7.65	4.77	9.07	4.47

AAB, autoantibody; α1-AR-AAB, α_1-adrenergic receptor antibodies; ETA-AAB, endothelin-1A receptor antibodies; AT1-AAB, angiotensin II receptor type 1 antibodies.

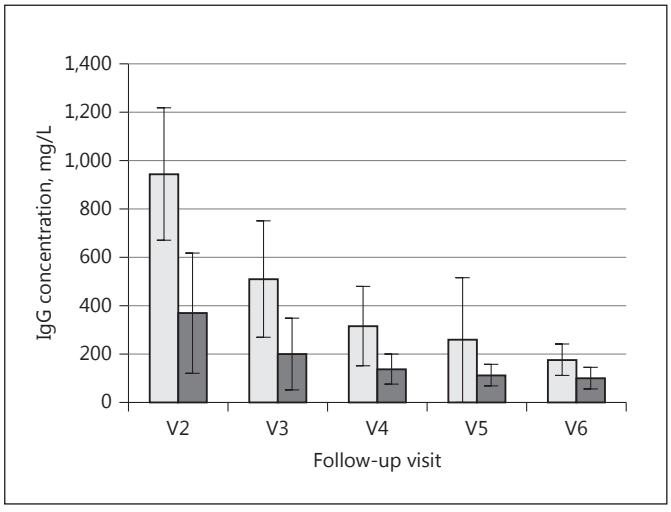

Fig. 3. Mean IgG concentrations (±SD) for the per protocol set of patients (n = 10) before (light gray) and after (dark gray) each IA treatment at visits (V) 2–6.

Removal of IgG

IA led to an average reduction of IgG at each IA treatment of approximately 56% (mean values ± SD from –576.5 ± 120.58 mg/L at baseline to –76.56 ± 44.85 mg/L on the last day of IA treatment). Figure 3 shows a reduction of the mean IgG concentrations in the plasma from V2 to V6 of almost 90% (mean values of 943 mg/L before IA at V2 and 100 mg/L after IA at V6).

Reduction in AAB Concentration

All mean AAB concentrations were reduced at V7, 9 days after the start of the IA treatments (Table 5). One month and 3 months after the first IA treatment (at V8 and V9, respectively), the AAB concentrations had increased; at V9, they were exceeding the initial mean concentrations.

Quality of Life

The mean scores on the SF-36 physical functioning for the overall population beginning at V8 until V10 were improved – but not significantly – when compared to the baseline value at V1 (from 52.78 ± 18.05 [SD] at V1 to 60.56 ± 19.44 [SD] at V10). The highest increase of 14.7% was observed at V10 (p = 0.10), 6 months after IA.

Safety Assessment

All safety analyses were based on the safety set of patients (n = 12). During the entire trial period, a total of 41 adverse events were reported in 10 patients. Of the 41 events reported, 38 were nonserious events and 3 were classified as serious. The latter included disturbance in attention, mild thrombocytopenia, and mild atypical viral pneumonia. The CT scans of this patient showed mild ground-glass opacities in both upper lobes, no typical signs of lobar pneumonia, and only a mild elevation of infectious parameters. This atypical pneumonia was most probably a viral pneumonia due to concomitant prophylactic postprocedural antibiotic treatment with levofloxacin 500 mg per day. Both the mild thrombocytopenia and the mild atypical viral pneumonia occurred in the same patient.

These adverse events were adjudged by the investigator as possibly related to the trial device, as well as possibly to the trial procedure. None of the serious adverse events was suspected to have a definite causal relationship to the device or to the trial procedure (Table 6).

Discussion

Our proof-of-concept study is the first to investigate the safety and feasibility of IA in IPAH patients. In our IPAH cohort, IA was a rather safe and feasible procedure. Furthermore, the results of our study indicate that IA may significantly reduce PVR and increase the CI after 3 months of IA treatment. The rationale behind using IA was based on an earlier study, where it had been used to treat 5 patients with IPAH to remove IgG from the plasma. The patients in that study were all positive for AAB against the α_1-adrenergic receptor, angiotensin II receptor subtype 1, and endothelin-1A receptor, as shown by a beating rat cardiomyocyte stimulation assay. Subsequent to IA, they showed sustained disappearance of

Table 6. Adverse effects adjudged to be associated with the procedure or with the device

System organ class	Adverse event	Patients, *n*	Patients at risk, %	Adverse events, *n*
Procedure-related adverse events				
General disorders and administration site conditions	Application site pain	1	8	1
	Edema	1	8	1
Infections and infestations	Lung infection	1	8	1
Nervous system disorders	Paresthesia	1	8	1
	Dizziness	2	17	2
	Headache	1	8	1
	Grand mal convulsion	1	8	1
Blood and lymphatic system disorders	Thrombocytopenia	3	25	3
Metabolism and nutrition disorders	Hypocalcemia	2	17	2
Gastrointestinal disorders	Nausea	1	8	1
Investigations	C-reactive protein increased	1	8	1
Device-related adverse events				
Nervous system disorders	Paresthesia	1	8	1
	Dizziness	2	17	2
	Headache	1	8	1
Blood and lymphatic system disorders	Thrombocytopenia	2	17	2
Metabolism and nutrition disorders	Hypocalcemia	2	17	2
Gastrointestinal disorders	Nausea	1	8	1
Infections and infestations	Infection	1	8	1

AAB, a reduction in mean pulmonary arterial pressure, and an increase in cardiac output and exercise capacity [12, 24].

Safety of IA Treatment and Immunoglobulin Levels

IA efficiently removed IgG and AAB from the circulation and demonstrated a high level of safety. Although temporary mild adverse events were common, no clinical worsening of the IPAH or deterioration of right heart function was detected. None of the serious adverse events was adjudged to have a definite causal relationship to the device or to the trial procedure. The 5 IA sessions resulted in a 90% reduction in mean IgG level in plasma. The IgG concentration was monitored continuously at all treatment visits and showed a continuous decrease.

Hemodynamic Changes and AAB Levels

IA treatment led to a significant reduction in PVR of 13.2%; 5 of the 10 patients in the PPS responded to treatment with reductions in PVR of >20% when measured at V9. Seven of the 10 patients showed a reduction in PVR and 3 showed an unchanged or mildly elevated PVR 3 months after IA. The patients with the highest number of AAB at an above-threshold concentration at baseline showed the highest reduction in PVR (up to 15.6% in SG4). Additionally, cardiac function improved after IA, marked by an increase in the CI by 13.1% after 3 months. Similarly, in patients suffering from DCM, Trimpert et al. [25] detected a significant improvement in left ventricular function due to a reduction in cardiotropic AAB (AAB against sarcolemmal and mitochondrial proteins, surface receptors [β_1-adrenoreceptor and M_1 muscarinic receptor], and heat shock proteins) and therefore an increase in contractility of the left ventricle. Several earlier studies have detected that IA combined with subsequent IgG substitution (IA/IgG) improves the left ventricular ejection fraction, enhances the CI and NYHA class [26–28], reduces inflammation [29], and decreases plasma levels of the prognostic heart failure markers nt-BNP and

nt-ANP [30] in patients suffering from DCM. An improvement in right ventricular myocardial function after IA could therefore be a possible explanation for the increase in CI in our IPAH patients and should be targeted by further studies.

In the present study, a more significant effect of IA was not seen 3 months after IA, when the AAB concentrations had returned to, or even surpassed, the levels measured at baseline. Trimpert et al. [25] observed a longer-lasting beneficial effect on cardiac function in DCM patients up to 6–12 months after IA in combination with subsequent IgG substitution. IgG substitution was primarily carried out for safety reasons to avoid acute infections, but it influences the immune system through various mechanisms at the same time. One of those mechanisms is prevention of antibody production rebound [19]. This could be an explanation for a prolonged beneficial effect of IA/IgG in DCM compared to IA without IgG substitution in IPAH, and might therefore also be considered for IPAH patients to prolong the beneficial effect of IA. In DCM, cardiotropic AAB are not detectable in all patients [25]. The same could apply to our IPAH patients and could be the reason for the nonresponse of those 3 of our patients that did not show any improvement in PVR. Detection of cardiotropic AAB at baseline in addition to AAB associated with vascular remodeling is therefore paramount to identify potential responders before conducting IA.

Frequency of IA Courses

The optimal frequency of IA courses over time for responders is unknown. Trimpert et al. [25] demonstrated in patients suffering from DCM that 4 monthly repeated courses of IA/IgG therapy were not superior to a single course of 5 consecutive IA sessions and IgG substitution. The reason for that was the nearly complete removal of cardiotropic AAB until 6 months after the initial IA/IgG course, so that additional IA courses would have no additional effect. Future studies need to address the progression of antibody titers over time to adapt the frequency of IA courses for responders.

IA in Other Forms of PAH

Assuming that levels of AAB do play a pathologic role in the genesis of PAH, the results of a current trial with patients suffering from systemic sclerosis-associated PAH are awaited with interest. That trial is studying the effect of rituximab on PVR. Rituximab is an agent that targets and eliminates B lymphocytes and has been reported to significantly improve PAH parameters [31, 32]. It would also be interesting to investigate the effect of a combination of IA treatment and rituximab on systemic sclerosis-associated PAH. This therapeutic option has recently been shown to be effective in the long-term removal of ABO and HLA antibodies from the circulation of solid organ transplant patients and has led to an improvement in the long-term survival of ABO-incompatible grafts [33]. This positive outcome suggests that the combination of pan-Ig IA and rituximab leads to a sustained depletion of those antibodies that would otherwise have an adverse effect on clinical outcome.

Study Limitations

The present study was a proof-of-concept trial of IA in IPAH. Although IA was safe and feasible in IPAH and led to an improvement in hemodynamics, the number of patients included was too small to assess the efficacy of IA and no control group was available.

Conclusion

IA in IPAH is a safe and feasible procedure and is a promising therapeutic approach to improve the pulmonary vasculature and right heart function in severe IPAH. Further research is needed to assess its efficacy in IPAH, to identify responders to IA, and to evaluate strategies for prolonging the effect of IA in IPAH before conducting this procedure routinely as add-on treatment to medical therapy.

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Financial Disclosure and Conflicts of Interest

The authors declare that they have no competing interests.

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