International Immunopharmacology 15 (2013) 752–755

Contents lists available at SciVerse ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Preliminary report

Subcutaneous IgG replacement therapy is safe and well tolerated in lung transplant recipients

T. Shankar [a], J. Gribowicz [b], M. Crespo [b], F.P. Silveira [c], J. Pilewski [b], A.A. Petrov [b,*]

[a] Department of Medicine, University of Pittsburgh Medical Center, United States
[b] Division of Pulmonary, Allergy and Critical Care Medicine, University of Pittsburgh Medical Center, United States
[c] Division of Infectious Disease, University of Pittsburgh Medical Center, United States

ARTICLE INFO

Article history:
Received 13 September 2012
Received in revised form 11 February 2013
Accepted 25 February 2013
Available online 15 March 2013

Keywords:
Lung transplant
Hypogammaglobulinemia
Subcutaneous IgG

ABSTRACT

Intravenous immunoglobulin (IVIG) replacement has been shown to decrease the risk of post-transplant infections secondary to hypogammaglobulinemia, however the use of subcutaneous immunoglobulin (SCIG) in this population has not been reported. A retrospective analysis of the efficacy and tolerability of subcutaneous immunoglobulin replacement on 10 lung-transplant recipients was performed. All 10 patients demonstrated an increase in IgG levels at three months that was sustained at 6–12 months with SCIG replacement therapy, with the majority (70%) tolerating infusion without complications. The results of this study suggest that subcutaneous IgG replacement therapy is a well tolerated alternative to IVIG.

1. Introduction

Lung transplantation is a critical therapeutic option in management of advanced pulmonary diseases. In spite of recent medical advancements, the 5 year survival rate remains suboptimal compared to that of other solid organ transplantation [1]. One important post-transplant complication is the increasing emergence of hypogammaglobulinemia (HGG), likely related to the increasing use of immunosuppressive therapies. Mild HGG (IgG 400–699 mg/dl) has been noted in 33–58% of lung transplant (LT) recipients and severe HGG (defined as IgG < 400 mg/dl) in 14–37% of LT recipients [2–4]. Moderate to severe hypogammaglobulinemia in LT recipients has been associated with increased occurrence of infections, longer hospitalizations, and acute cellular rejection [2,4].

Replacement therapy with human polyvalent IgG represents the gold standard in management of primary and secondary HGG [5]. Intravenous immunoglobulin (IVIG) infusions have long been the preferred method of replacement as subcutaneous immunoglobulin (SCIG) preparations, first introduced in the 1980s, were initially of low concentration requiring slow infusion rates, which made its use impractical for both patients and physicians [6,7]. New advances in IgG formulations, however, have resulted in low-viscosity rapid-infusion SCIG preparations that have been approved by the FDA in 2006 for use in primary immunodeficiencies as well as labeled for use in secondary immunodeficiencies outside the US. SCIG therapy is well tolerated with easy self-administration, results in high sustained IgG levels, and unlike IVIG, is not associated with renal injury [8]. While the use of IVIG therapy has been reported in heart and lung transplant recipients, the use of SCIG replacement therapy in LT recipients has not to date been reported [2,9,10].

2. Material and methods

2.1. Study design

We performed a retrospective analysis of lung-transplant recipients referred to an outpatient university clinical immunodeficiency center for evaluation of hypogammaglobulinema as defined by IgG below 750 mg/dl. We included all single or bilateral lung transplant recipients who had immunoglobulin levels assessed between January 2009 and December 2010 and were started on subcutaneous IgG replacement therapy. Patients with known pre-transplant immunodeficiencies were excluded from the study. The electronic medical record was reviewed and data related to medication tolerability, immunoglobulin levels, occurrence and treatment of infection, and allograft function were collected. The study was approved by the Institutional Review Board at our facility.

2.2. Study population

A total of 10 outpatient lung-transplant recipients were identified who had undergone subcutaneous IgG replacement at our facility. The diagnosis of hypogammaglobulinemia was based on post-transplant measurement of IgG level and defined as mild (IgG 500–750 mg/dl) or moderate to severe (IgG < 500 mg/dl). IgG levels were measured by nephelometry. In our center, patients were selected for IgG replacement if their IgG level was below 500 or if their level was below 750 and

* Corresponding author at: University of Pittsburgh Medical Center, Division of Pulmonary, Allergy and Critical Care Medicine, UPMC Montefiore NW 628, 3459 5th Avenue, Pittsburgh, PA 15213, United States. Tel.: +1 412 648 6215.
E-mail address: petrovaa@upmc.edu (A.A. Petrov).

1567-5769/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.intimp.2013.02.021

they had recurrent infections. The definition of recurrent infections used in our institution included 5 or more documented sinus infections per year, 2 episodes of pneumonia per year or 1 episode of pneumonia per year for 2 consecutive years, or 2 or more episodes of infectious bronchitis per year documented by positive bronchoscopic cultures. Baseline clinical and demographic characteristics included age, gender, reason for transplantation, induction therapy, severity of HGG, immunosuppressive regimen, years to initiation of IgG replacement therapy, presence of renal dysfunction and any IVIG use prior to transition to SCIG (Table 1). The mean age of patients was 59.9 years and 60% were male. The mean time from lung transplantation to initiation of SCIG replacement was 39.4 months and 70% of patients had been treated with IVIG continuously (30%) or intermittently (40%) prior to starting SCIG therapy. Renal dysfunction, as defined by glomerular filtration rate < 60 ml/min/1.73 m2, was present in 70% of patients.

2.3. Treatment protocol

Benefits and risks of IgG replacement were discussed with patients who provided informed consent. Two routes of the immunoglobulin replacement therapy (subcutaneous and intravenous) were discussed with each patient (Fig. 1). Patients who opted for SCIG were loaded with one IVIG dose of 5% Gammaguard liquid at 400 mg/kg. Patients who were already on IVIG received the last dose within a month of initiation of SCIG therapy. One week after IVIG loading dose, patients were started on SCIG (Vivaglobin, Hizentra CSL Behring) 100 mg/kg weekly, which was equivalent to a monthly IVIG dose. If renal dysfunction was present, SCIG was presented as the preferred route of administration, and patients did not receive the loading dose of IVIG. Patients who previously had tolerated IVIG infusion were set up with home infusion company for initial subcutaneous infusion at home. Patient education in home self-administration of SCIG was provided by home infusion nursing over a series of 2–3 visits after which time patients performed home infusions unsupervised. Patients who had never previously been exposed to IVIG, or who had previously not tolerated IVIG infusion were admitted to the infusion center for close monitoring during initial infusion. Subcutaneous infusions were started at home 1 week after the first, supervised, SCIG dose.

3. Results

A total of 10 lung transplant recipients were started on SCIG. 5 patients (50%) were started on SCIG without IVIG loading doses due to underlying renal dysfunction. Two patients (20%) were converted from IVIG to SCIG due to worsening renal function. One patient decided to change from IVIG to SCIG, and one elected to begin with SCIG, due to administration preference. One patient developed transfusion related acute lung injury (TRALI) after one dose of IVIG, and transitioned to SCIG without complications other than transient local swelling at infusion site.

All 10 patients demonstrated increase in IgG levels at three months that was sustained at 6–12 months with SCIG replacement therapy (Table 2). One patient experienced an initial increase in IgG level at 3 months followed by subsequent decline at 6–12 months, though IgG level remained above his pretreatment baseline.

Of the 10 patients, 7 (70%) were able to tolerate the infusion without complications. The remaining 3 (30%) experienced local infusion site reactions (swelling, erythema, soreness) that resolved spontaneously within 24 h. Two patients were on Vivaglobin therapy and one patient on Hizentra at time of local reaction. Patients continued to experience local reactions that resolved within 24 h with subsequent infusions. No patients experienced worsening renal function, respiratory distress, cardiovascular compromise, or required epinephrine treatment during this protocol.

4. Discussion

Infectious complications account for a large portion of the morbidity and mortality associated with lung and other solid organ transplantation [11,12]. Post-transplantation hypogammaglobulinemia, thought to be due to the use of potent immunosuppressive agents, confers an increased risk of infections and rejection episodes [2–4,13,14]. Recent studies describing treatment of post-transplantation hypogammaglobulinemia report use of intravenous immunoglobulin replacement only [2]. However, new advances in SCIG replacement therapy make this a particularly attractive option for transplant recipients. Renal dysfunction, also due to immunosuppressive agents, might be potentiated by the use of IVIG,

Table 1
Subject demographics and clinical characteristics.

Patient	Sex	Age (yr)	Reason for transplantation	Severity of HGG[a]	Induction therapy	Time to initiation of therapy (mo)	Presence of renal dysfunction	IVIG use prior to transition to SCIG	Immunosuppressive regimen	Type of SCIG initiated[b]	Adverse event with SCIG usage
1	M	67	Emphysema	Moderate–severe	Daclizumab	96	Y	Y	Prednisone, tacrolimus	Vivaglobin	N
2	M	58	IPF[c]	Moderate–severe	Daclizumab	12	N	Y	Prednisone, MMF[d], tacrolimus	Hizentra	N
3	M	64	COPD[e]	Moderate–severe	Alemtuzumab	36	Y	N	Prednisone, MMF, cyclosporine	Hizentra	Swelling/ erythema
4	M	50	Cystic Fibrosis	Mild	Alemtuzumab	24	Y	Y	Prednisone, cyclosporine	Vivaglobin	N
5	F	50	COPD	Moderate–severe	Alemtuzumab	12	Y	Y	Prednisone, MMF	Vivaglobin	Swelling/ erythema
6	F	66	Emphysema	Moderate–severe	Alemtuzumab	72	Y	Y	Prednisone, tacrolimus, MMF	Hizentra	N
7	F	66	Eosinophilic granuloma	Mild	Thymoglobulin	60	Y	Y	Prednisone, tacrolimus	Vivaglobin	N
8	F	51	IPF	Mild	Alemtuzumab	24	N	N	Prednisone, MMF, tacrolimus	Vivaglobin	Swelling/ erythema
9	M	58	IPF	Mild	Alemtuzumab	36	Y	Y	Prednisone, MMF, tacrolimus	Vivaglobin	N
10	M	69	COPD	Moderate–severe	Basiliximab	3	N	N	Prednisone, MMF, tacrolimus	Hizentra	N

[a] Hypogammaglobulinemia.
[b] All patients were eventually transitioned to Hizentra when production of Vivaglobin was discontinued.
[c] Idiopathic pulmonary fibrosis.
[d] Mycophenolate mofetil.
[e] Chronic obstructive pulmonary disease.