Liposteroid Therapy for Idiopathic Pulmonary Hemosiderosis: A Scoping Review of the Literature

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Abstract: Idiopathic pulmonary hemosiderosis (IPH) is a rare cause of diffuse alveolar hemorrhage (DAH). Glucocorticosteroids (CS) represent the first line therapy for IPH. Although most patients respond to CS, steroid refractoriness is seen in an appreciable minority of patients. This paper reviews and evaluates the efficacy and safety profile of liposomal dexamethasone 21-palmitate (liposteroid) for the treatment of IPH. Medline, Embase and Web of Science biomedical databases were searched between 1980 and 2020 to identify papers describing patients with IPH, who were treated with liposteroid. A total of five articles were identified. Four in the form of case reports and one as a case series. A total of 12 pediatric patients (5 boys, 7 girls) were identified, with a median age of 2.3 years (range 0.5–8.6). Liposteroid therapy in intravenous doses ranging 0.06–0.1 mg/kg body weight appeared to be effective for both remission induction therapy, and maintenance therapy. There was no mortality among patients treated with liposteroid, either in the acute phase or during follow-up. The majority of patients for whom long-term follow-up data were available, were cured or in disease remission. No acute adverse events were reported, and long-term side effects were minimal and tolerable. Liposteroid represents a potential alternative or supplement to conventional CS therapy, as it appears to be more efficacious and associated with fewer side effects. Larger prospective, controlled trials are necessary to be able to define more precisely the therapeutic role of liposteroid in IPH.

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Introduction

Idiopathic pulmonary hemosiderosis (IPH) is a rare cause of diffuse alveolar hemorrhage (DAH) (Milman and Pedersen, 1998). The classic presentation of IPH includes hemoptysis, radiologic chest infiltrates, and anemia. Although hemoptysis is present in the majority of patients, the classic triad is less common (Chen et al., 2017). In pediatric patients, the identification of hemoptysis may be challenging due to swallowing of the sputum, and patients may present with unexplained anemia. The intensity of DAH and the degree of respiratory impairment in IPH are highly variable (Saha, 2020). The majority of patients with IPH present with recurrent episodes of hemoptysis without respiratory failure. However, a minority of patients suffer from massive pulmonary hemorrhage resulting in acute respiratory failure and occasionally death (Gutierrez et al., 2014; Matsumoto and Nakagawa, 2019). Recurrent episodes of DAH may result in pulmonary fibrosis and progressive respiratory failure (Saha and Chong, 2022).

The etiology of IPH is so far unknown (Ioachimescu et al., 2004; Saha, 2020). Based on recent evidence, IPH appears to be a disease of immunologic origin with a possible genetic background (Taytard et al., 2013; Saha and Milman, 2021a). Therefore, clinicians are focused on using immunosuppressive agents, such as glucocorticosteroids (CS) and antimetabolites, for the treatment of IPH (Ali et al., 1998; Saha and Milman, 2021a). Early administration of these agents has significantly reduced overall mortality in IPH during recent years (Soergel and Sommers, 1962; Ohga et al., 1995; Kiper et al., 1999; Taytard et al., 2013). Currently, there is no consensus on a standardized treatment for IPH, and there is significant variability in the treatment regimens used throughout the world (Chin et al., 2015).

The treatment of IPH can be classified into "remission induction" and "remission maintenance" treatment phases. "Remission induction" treatment refers to the early therapy that is given during an acute episode of DAH. "Remission maintenance" treatment denotes the therapeutics employed to prevent the recurrence of DAH. Generally, systemic CS is the first line of therapy for remission induction. Although most patients improve on CS, steroid refractory cases are not uncommon. In these patients, second line therapy, such as cyclophosphamide or azathioprine, can be used as add-on therapy (Naithani et al., 2006; Flanagan et al., 2013). Liposteroid has shown promising results as a remission inducing agent, both as a single therapy and in combination with other CS. In addition, liposteroid has demonstrated efficacy as a remission maintenance agent.

Dexamethasone sodium phosphate (DSP) is a long-acting CS with a distinctly higher potency than prednisone or prednisolone, and liposteroid is the liposomal preparation of dexamethasone palmitate (Yokoyama et al., 1985; Furst and Saag, 2021). Due to its high lipid solubility and affinity for phagocytic and inflammatory cells, liposteroid achieves high concentrations in inflamed tissues (Yokoyama et al., 1985), and has an anti-inflammatory effect that is significantly higher than DSP

(Mizushima et al., 1982). The properties of liposteroid and the indications for treatment has recently been reviewed (Saha and Milman, 2021b).

The purpose of the present paper is to review and evaluate the efficacy and safety profile of liposteroid treatment in IPH, based on the existing reports. This may be of help to the clinician in the decision-making process of treatment modalities in the individual patient with IPH.

Methods

This manuscript is a scoping review of the literature. The literature was scrutinized to identify appropriate studies. The Medline, Embase and Web of Science databases were searched between 1980 and 2020 to identify all patients with IPH treated with liposteroid. The bibliographies of the identified reports were subsequently scrutinized to find additional reports. Both pediatric and adult patients were included in the search. Papers published in any language were included in this review. The databases were searched with the following terms: "idiopathic pulmonary hemosiderosis"; "idiopathic pulmonary hemosiderosis AND liposteroid"; "idiopathic pulmonary hemosiderosis AND treatment".

In total, 292 articles were found in the initial search. After examining the abstracts, full texts were reviewed for 13 papers. We finally identified five manuscripts that fulfilled our inclusion criteria. Out of the five papers, four were case reports (Table 1), and one was a small series of patients (Ohga et al., 1994; Doi et al., 2013, 2015; Sakamoto et al., 2018; Tobai et al., 2020). One article in Japanese (Sakurai et al., 1995) was translated into English.

Results

Demographics

A total of 12 patients were identified, 5 patients from case reports, and 7 from the patient series as shown in Tables 1 and 2. Two patients in the patients series (Doi et al., 2013) had previously been published as case reports (Ohga et al., 1994). All patients were Japanese children being started on liposteroid therapy at a median age of 2.3 years (range 0.5–8.6) (Table 2). Among the 12 children, 5 were boys and 7 girls. At birth, three were low birth weight babies being small for gestational age.

Autoimmune associations

All patients were examined for serum antinuclear antibody (ANA). Two patients had a positive ANA, but the titre was low in both, and none demonstrated symptoms or signs of autoimmune disease (Tables 1 and 2). The ANA developed during the follow up period in both patients (Doi et al., 2013). A positive serum antineutrophil cytoplasmic antibody (ANCA), milk protein allergy antibody or serum tissue transglutaminase antibodies were not reported in any patient. Two patients had trisomy 21, one of them developed thyroiditis during follow-up. Both patients with a positive ANA were alive at the end of the follow-up period.

Table 1 – Previous cases of IPH treated with liposteroid therapy

Report	Age	Sex	Country	First IPH diagnosis	Hemoglobin of presentation (g/dl)	Autoimmune workup	Diagnosis
Ohga	22 months	M	Japan	yes	6.1	negative	Sputum cytology and MRI
	14 months	F	Japan	yes	4.9	negative	Gastric aspirate cytology and MRI
Sakurai	6 months	M	Japan	yes	3.1	negative	Gastric aspirate cytology
Sakamoto	6 year	F	Japan	10 months of age	NR	NR	Gastric aspirate and sputum cytology
Tobai	2 year	F	Japan		2.2	negative	Gastric aspirate cytology

IPH – idiopathic pulmonary hemosiderosis; M – male; F – female; NR – not reported; MRI – magnetic resonance imaging

Treatment before liposteroid	Liposteroid dose	Outcome	Duration of therapy	Adverse effect	Recurrence
Methylprednisolone bolus Prednisolone 2 mg/kg Cyclosporin	0.05 mg/kg biweekly	Remission	14 months	none	One, upon discontinuation with a bacterial infection
Methylprednisolone	0.05 mg/kg every 10–14 days	Remission		none	Recurrence after 4 months managed with addition of azathioprine and inhaled corticosteroid
Methylprednisolone bolus (30 mg/kg/day × 5 days and prednisolone 2 mg/kg × 5 days failed, then another pulse steroid therapy was tried for 3 days with remission of symptoms	0.1 mg/kg/day every 2 weeks	Remission	7 months afterwards still no recurrence	none	none
Intravenous dexamethasone sodium	0.8 mg/kg/day for 3 days followed by maintenance dose weekly (0.5 mg/kg) with methyl prednisolone	Remission	NS	PRES Palmitate induced inflammation	Patients discharged from hospital 5 months after initiation of liposteroid
Intravenous prednisolone followed by oral prednisolone for maintenance Complicated by recurrent bleed and side effects	0.06 mg/kg/day for 3 days, followed by maintenance therapy every 4 weeks at the time of report		24 months		Recurrent bleed twice responded to bolus dose for 3 days

Table 2 – Demographic data, clinical presentation, and treatment in 12 children with idiopathic pulmonary hemosiderosis (IPH)

Variables	Number of patients /total number of reported patients
Sex	
– Boys	5/12
– Girls	7/12
Age (year)	2.3 (0.5–8.6)
Ethnicities	
– Asian	12/12
Admission hemoglobin (g/l)	4.8 (2.2–7.4)
Blood transfusion on admission	10/12
Antinuclear antibody	2/12
Genetic disorder	2/12
Liposteroid as remission induction therapy	10/12
– Steroid refractory patients	7/10
– Initial therapeutic agent	3/10
– Immunosuppressive agent before liposteroid	3/10
Liposteroid as maintenance therapy	2/12
– With corticosteroids	12/12
– With immunosuppressive agents	7/12
Follow-up period (years)	9.5 (0.6–16.9)
Hospitalizations during liposteroid therapy	7 (2.5–10.5)
Adverse effects	
Short-term adverse events	
– Posterior reversible encephalopathy	0/9
– Systemic inflammatory response	0/9
Long-term adverse events	
– Weight gain, cushingoid face, cataract, cutaneous striae, hypertension, low height	0/9
Reduced bone mineral density	4/9
Outcome	
– Cured	3/12
– Remission	6/12
– Active disease	3/12

Data presented as median (range)

Dosing of liposteroid therapy

Liposteroid given as intravenous infusion was initiated for remission induction treatment in 10/12 patients and for maintenance of remission in 2/12 patients (Table 2). For remission induction treatment, 8/12 patients received liposteroid

in doses ranging from 0.06 to 0.1 mg/kg body weight/day for three consecutive days and 2/12 received a dose of 0.05 mg/kg once every 10–14 days. In addition to liposteroid, 7/10 patients received other systemic CS as part of the induction treatment. Prior to treatment with liposteroid, 3/10 patients were treated with an antimetabolite.

The doses used for remission induction was also used for maintenance therapy. Typically, the maintenance therapy was initiated one week after the last induction dose, and the interval between the subsequent doses was gradually increased based on the patients' response. If the patients remained stable, without any evidence of relapse, the interval between infusions was increased up to every four weeks. If there was a recurrence of bleeding during the maintenance phase, the induction treatment regimen was repeated to control bleeding. During maintenance therapy, 7/12 patients required other immunosuppressive medications in addition to liposteroid.

Duration of liposteroid therapy

The duration liposteroid treatment was variable. Tobai et al. (2020) treated one patient with liposteroid for 2 years. In the study by Doi et al. (2013), all 9 patients received at least four years of monthly liposteroid treatment as maintenance therapy, and 2/9 patients received liposteroid therapy for more than 10 years. These 9 patients received liposteroid therapy for a median of 6.1 years, with a range of 2.3–15.6 years (Doi et al., 2013). In this review of 12 patients, the median duration of liposteroid therapy was 5.8 years, with a range of 0.6–15.6 years.

Efficacy of liposteroid therapy

Improvement during liposteroid treatment was reported in all 12 patients. The occurrence of respiratory failure requiring mechanical ventilation was not specified for all patients. However, two patients with respiratory failure could be weaned from mechanical ventilation after initiation of liposteroid therapy. Likewise, hemoptysis and anemia improved during liposteroid therapy. The long-term outcomes were assessed only in the study by Doi et al. (2013); all 9 patients were alive after a median follow-up period of 11 years (2.4–16.9 years); three patients remained symptom-free without medication for more than 1.4 years, three patients achieved long-term remission lasting more than two years, while the three remaining patients still had active disease.

The majority of patients did not report any limitation in physical activity during rest or exercise. At the end of the follow-up period, pulmonary function tests were available in 6/12 patients, while 6/12 patients could not cooperate. The forced vital capacity (FVC) was normal in three, mildly reduced in two, and moderately reduced in one patient. The only patient reporting exertional dyspnea during the observation period had a mild reduction of FVC, he was in the active phase of the disease and was reportedly non-compliant with the treatment (Doi et al., 2013). The serum

KL-6 level, an indicator for activity in pulmonary fibrosis was normal in all 9 patients (Doi et al., 2013).

Recurrence

After induction treatment, 11/12 patients had recurrence of bleeding, leading to hospitalization for median 7 times (range 2–20) (Table 2). The median blood hemoglobin concentration on first admission was markedly decreased, 48 g/l (normal reference interval 110–130 g/l) but had normalized without blood transfusion in all patients by the end of the observation period.

Adverse events

The long-term adverse effects of liposteroid therapy were assessed in the 9 patients of Doi et al. (2013). There were no cases of obesity, cutaneous striae or abnormal body fat distribution, such as cushingoid appearance, and no cases with hypertension or visual impairment. Low bone mineral density was found in four patients, but none had bone fractures. Although the final height of the liposteroid treated patient series was comparable to the normal population, no patient exceeded the 85th height percentile at the final follow-up.

Sakamoto et al. (2018) reported acute adverse events following the first infusion of liposteroid in a 6-year-old girl consisting of restlessness and irritability possibly due to posterior reversible encephalopathy syndrome. In addition, the patient presented a systemic inflammatory response due to palmitic acid causing elevated inflammatory markers, such as C-reactive protein (Sakamoto et al., 2018; Korbecki and Bajdak-Rusinek, 2019). However, this patient erroneously received an overdose of liposterid (see discussion).

Discussion

This paper discusses the role of liposteroid therapy in the management of DAH caused by IPH. Dexamethasone is a long-acting CS with antiinflammatory properties that is 6 times as potent compared to an equivalent dose of prednisone or prednisolone (Furst and Saag, 2021). Liposteroid is the liposomal preparation of dexamethasone palmitate (Yokoyama et al., 1985). The liposome particle is spherical in shape and composed of a phospholipid bilayer, which can be single or multi-lamellar (Benameur et al., 1993). The specific drug molecule is carried within the center of the liposome. Liposteroid was originally designed to target CS therapy to inflamed tissues, in order to reduce the unwanted systemic side effects of CS (Yokoyama et al., 1985). Liposteroid was developed in 1980 by Dr. Yutaka Mizushima in Japan and is currently approved for clinical use in several inflammatory disorders.

Compared to the conventional parenteral preparation of dexamethasone (DSP), which is hydrophilic, liposteroid is more lipophilic, and the tissue distribution and distribution half-life vary between these preparations. Liposteroid is administered

via the intravenous route as an infusion and taken up by phagocytic cells, e.g. macrophages in the reticuloendothelial system by phagocytosis; the rate of uptake is approximately 8 times faster than of free dexamethasone palmitate and DSP (Yokoyama et al., 1985; Wakiguchi and Ohga, 2016). Therefore, liposteroid achieves a higher concentration in the spleen compared to DSP (Mizushima et al., 1982). In contrast, due to its hydrophilic nature, DSP demonstrates a higher concentration than liposteroid in skeletal muscle. The elimination half-life is longer for DSP than for liposteroid (Yokoyama and Watanabe, 1996).

By virtue of its lipid solubility and predilection for phagocytic cells and other inflammatory cells, liposteroid achieves a two-fold higher concentration in inflamed tissues (Yokoyama et al., 1985), and the anti-inflammatory effect is 5–6 times more potent than DSP (Mizushima et al., 1982). Liposteroid exerts more potent inhibitory effect than DSP on the proinflammatory functions of the macrophages, such as receptor-mediated phagocytosis, production of superoxide, lipid peroxidation, and chemotaxis (Yokoyama and Watanabe, 1996).

As liposteroid is distributed primarily in the reticuloendothelial system, the suppression of the hypothalamic-pituitary axis is lower than by conventional steroid formulations. In animal studies, the level of dexamethasone in the pituitary was significantly lower with liposteroid compared to DSP (Mizushima et al., 1982) and there appears to be fewer metabolic side effects with liposteroid compared to the free dexamethasone palmitate (Schiffelers et al., 2006).

Liposteroid has been utilized for several rheumatologic and non-rheumatologic diseases. The role of liposteroid has been studied more comprehensively in patients with rheumatoid arthritis than in patients with other diseases (Mizushima et al., 1983; Hoshi et al., 1985). In a multicenter, double-blind comparative trial of 138 patients with rheumatoid arthritis, Hoshi et al. (1985) reported a significantly higher rate of improvement and lower adverse effects with biweekly intravenous or intramuscular liposteroid (0.05–0.08 mg/kg/body weight) compared to DSP. Efficacy of liposteroid has also been seen in patients with the macrophage activation syndrome or hemophagocytic lymphohistiocytosis, graft versus host disease, inflammatory myopathy, and immune thrombocytopenic purpura (Sakurai et al., 1999; Funauchi et al., 2003; Kobayashi et al., 2007; Nishiwaki et al., 2009, 2014; Filipovich et al., 2010; Wakiguchi et al., 2015; Wakiguchi and Ohga, 2016).

IPH is a rare disease. Based on the literature, IPH appears to be more common in children compared to adults (Ioachimescu et al., 2004). Among children, the incidence varies between 0.24 and 1.23 cases per million individuals per year (Kjellman et al., 1984; Ohga et al., 1995). Chen et al. (2017) reported only 37 adult cases in the period 2000–2015. We found that all reported patients who had received liposteroid therapy were in the pediatric age group. Based on the French database of rare pediatric diseases, IPH is more prevalent among girls (Taytard et al., 2013). This trend was present in our patient series as well. In contrast, there is a distinct male predominance among the reported adult cases (Chen et al., 2017). In

children, IPH frequently presents before the age of 10 years, as in this patient series. IPH in childhood appears to be more aggressive and difficult to treat compared to adult patients (Chen et al., 2017).

Despite first being reported by Virchow in 1864, the pathogenesis of IPH has remained obscure (Virchow, 1864; Zhang et al., 2019). There are significant suggestions of an immunologic and/or autoimmune pathogenesis for IPH (Saha, 2021). For example, autoantibodies are found in a considerable number of patients with IPH, either at diagnosis or later during the course of the disease (Iijima et al., 1988; Taytard et al., 2013; Freitas et al., 2015; Yanagihara et al., 2018; Stainer et al., 2019). Some patients with biopsy proven IPH have developed ANCA positive vasculitis many years after the initial diagnosis of IPH (Freitas et al., 2015). There may also be a genetic contribution (Milman and Pedersen, 1998; Watanabe et al., 2015; Alimi et al., 2018). IPH is often seen in patients with trisomy 21 and is in these patients associated with pulmonary hypertension and worse outcomes (Taytard et al., 2013). We have proposed renaming IPH to immune or pauci immune-mediated pulmonary hemosiderosis due to the immunologic association (Saha, 2021). In this liposteroid series, two patients had ANA without overt autoimmune disease. One patient with trisomy 21 developed thyroiditis during follow-up. A recent study found the overall prevalence of autoantibodies to be 26.4% in pediatric patients.

The diagnosis of IPH is often delayed (Chen et al., 2017). A definitive diagnosis of IPH requires histopathologic evaluation of lung biopsy specimens (Saha, 2020). DAH from IPH is often referred to as "bland pulmonary haemorrhage", denoting the absence of vasculitis and inflammatory cellular infiltration of the lung parenchyma. It is crucial to emphasize that other causes of "bland pulmonary haemorrhage" such as cardiac diseases, anticoagulation therapy, and some autoimmune/ rheumatologic diseases need to be ruled out before making a definitive diagnosis of IPH (Ioachimescu et al., 2004; Imtiaz et al., 2019; Saha and Chong, 2021; Saha et al., 2021; Saha et al., 2022). In children, IPH is often diagnosed by a compatible clinical history, radiologic findings, and identification of hemosiderin-laden macrophages from the sputum, bronchoalveolar lavage or gastric aspirate. However, this could lead to an erroneous diagnosis of IPH as patients with small-vessel vasculitis may have a negative serologic workup (Fullmer et al., 2005; Thompson et al., 2016). All patients in this liposteroid series were diagnosed with IPH without having a lung biopsy. Thus, there is a possibility that some of these patients may have suffered from a vasculitic disorder rather than IPH.

The treatment of IPH can be divided into remission induction and maintenance phases. There is no agreed-upon treatment regimen for IPH, and we have recently proposed a treatment algorithm (Saha and Milman, 2021a). Most clinicians would choose CS as the first-line therapy for inducing remission in the acute phase (Kiper et al., 1999; Chin et al., 2015). A questionnaire-based multinational study that surveyed pediatric physicians taking care of IPH patients revealed that CS was the medication

of choice during active bleeding (Chin et al., 2015). Similarly, CS also represented the first-choice treatment for maintenance therapy. The choice of a second-line agent varied among physicians. The majority favoured hydroxychloroquine, azathioprine, cyclophosphamide, and inhaled corticosteroids. Although some authors have questioned the long-term efficacy of the CS in the overall outcome, there appears to be a significant improvement in the outcomes among patients treated with CS. Indeed the survival rate in IPH has improved significantly during recent years, possibly due to the early initiation of immunosuppressive therapy (Soergel and Sommers, 1962; Kiper et al., 1999; Taytard et al., 2013).

Clinicians are often faced with challenges while treating patients with IPH. First, a subgroup of patients appears to be refractory to CS and requires additional immunosuppressive agents, such as cyclophosphamide or azathioprine (Colombo and Stolz, 1992; Rossi et al., 1992; Saeed et al., 1999; Airaghi et al., 2001; Helman et al., 2003; Naithani et al., 2006; Kamienska et al., 2009). However, these agents may be associated with severe adverse events, including the occurrence of malignancy (Radis et al., 1995; Bernatsky et al., 2008). Second, long-term use of CS therapy is associated with significant side effects, such as obesity, cushingoid appearance, cataracts, hyperlipidemia, hypertension, diabetes mellitus and osteoporosis.

The liposteroid was formulated as a targeted drug therapy to increase efficacy and reduce side effects from CS therapy. Liposteroid has been used as both induction therapy and maintenance agent. Intravenous methylprednisolone is typically used during acute IPH with respiratory failure (Li et al., 2017; Milman, 2020). As a remission inducing agent, liposteroid was predominantly used in the steroid-refractory patients in this review. In the majority of cases, liposteroid was used as add-on therapy to another CS. As liposteroid is a more potent anti-inflammatory agent and demonstrates enhanced inhibition of macrophage activation, a beneficial effect is seen even if the patients are refractory to conventional CS therapy. When liposteroid is used as a maintenance agent, the long-term side effects of CS are distinctly minimized. In a minority of patients, other immunosuppressive agents were used in addition to liposteroid therapy.

The dosing regimen used for liposteroid therapy was variable. During the acute phase of the disease with bleeding, the medication is typically infused for three consecutive days. Subsequently, infusion is performed at weekly intervals. When the pulmonary hemorrhage is controlled, the interval between infusions can be progressively increased from one to two weeks with the goal to have maintenance infusion therapy every four weeks. The dose used in maintenance therapy varied between 0.06 and 0.08 mg/kg body weight. Most patients also receive another systemic CS, the dose of which can also be tapered based on the response to liposteroid therapy. Doi et al. (2013) continued the maintenance liposteroid therapy for at least four years. The optimal duration of therapy for IPH is unknown. After a symptom-free period of 12–18 months without bleeding it seems reasonable to taper and discontinue liposteroid (Saha and Milman, 2021a).

The liposteroid was efficacious. Several patients were either cured or maintained long-term remission on liposteroid therapy. More importantly, all patients survived during the follow-up period. Also, the majority reported no functional impairment at exercise, and the pulmonary function tests revealed a relatively well-preserved lung function. There was no evidence of pulmonary fibrosis in any of the patients. End-stage lung disease can occur as a complication of IPH, but was not observed in this patient series. Lung transplantation represents the only available long-term therapy in patients with end-stage lung disease (Wroblewski et al., 1997; Calabrese et al., 2002; Ross et al., 2020; Gocho et al., 2021; Saha and Chong, 2022).

Liposteroid appears to be safe both in the short and long-term treatment regimens. Doi et al. (2013) did not report any acute adverse events. In contrast, Sakamoto et al. (2018) reported the development of posterior reversible encephalopathy syndrome and a systemic inflammatory syndrome following liposteroid infusion. However, the infused overdose of liposteroid was 0.8 mg/kg/day (Sakamoto et al., 2018), similar to the dosing regimen erroneously reported by Doi et al. in 2013, which in 2015 in an *erratum* was changed to the correct dose of 0.08 mg/kg/day (Doi et al., 2015). Therefore, Sakamoto's patient received a 10-fold higher dose than used in a standard dosage regimen (Sakamoto et al., 2018).

Long-term therapy with CS is associated with significant side effects. One of the reasons why liposteroid had been used was to reduce the cumulative steroid exposure and reduce overall side effects. Doi et al. (2013) did not report any patient with cushingoid appearance, metabolic abnormalities, or increased body mass index due to obesity in patients who received liposteroid therapy. The main concern was the overall height of this patient cohort. Although no patient was below two standard deviations in the final height, no patient was above their estimated 85th percentile.

IPH causes significant short and long-term morbidity and mortality, and can affect patients of any age. The mortality in the acute phase of the disease in adult patients., who often demonstrates relative refractoriness to CS, is approximately 14% (Chen et al., 2017). The mortality in pediatric patients can be as high as 100% within the first 2.5–5 years, unless an aggressive immunosuppressive regimen is used (Soergel and Sommers, 1962; Kjellman et al., 1984; Kiper et al., 1999). Liposteroid is a relatively less known formulation of dexamethasone palmitate that is not available globally. Based on the literature, liposteroid is more potent than DSP and causes more effective inhibition of proinflammatory cellular function than traditional CS preparations. It can be used as the stand-alone therapy for remission induction or used in association with other systemic CS in patients who demonstrate steroid refractoriness. The use of liposteroid as a maintenance agent could be associated with fewer adverse effects and possibly better outcomes.

Limitations of this study

Our study has several limitations. We identified a small series of 12 Japanese pediatric patients who received liposteroid therapy for IPH, and long-term follow-up was not

performed in all patients. None of the patients had a lung biopsy. Additionally, there might be a selection bias in the reported cases as all patients were reported from Japan because liposteroid is not available in many countries of the world, including the United States and Denmark.

Conclusion

IPH is a rare disease. Although the majority of patients respond well to CS therapy, a significant minority does not. Immunosuppressive agents have been tried in IPH patients with variable success. Liposteroid is a liposomal preparation of dexamethasone palmitate with an anti-inflammatory effect that is 25 times more potent than prednisone. Liposteroid appears to be an effective treatment in remission induction and remission maintenance regimens. Liposteroid should be considered in patients with refractory IPH, and in maintenance therapy to reduce the side effects of long-term steroid therapy. This review supports the efficacy and relative safety of liposteroid as a therapeutic option for IPH in children, while the efficacy in an adult population remains speculative.

Prospective studies in both pediatric and adult patients are needed to evaluate whether liposteroid has specific advantages compared to other CS, and whether it should be used as single treatment or in combination with other conventional CS and/or alkylating agents or antimetabolites.

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