Short Review of Liposteroid: A Novel Targeted Glucocorticoid Preparation for Treatment of Autoimmune and Inflammatory Diseases

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Abstract: This paper briefly reviews the safety and efficacy of liposteroid in different inflammatory and non-inflammatory diseases. Corticosteroids (CS) are the first-line therapy in many inflammatory and autoimmune disorders. Although highly efficacious, long-term use of CS is limited due to the occurrence of significant side effects. Liposteroid, which is a liposomal formulation of dexamethasone palmitate, possess more potent anti-inflammatory and immunosuppressive properties compared to dexamethasone sodium phosphate. These two formulations have markedly different lipid solubility, resulting in different pharmacokinetic and pharmacodynamic properties. Liposteroid has been used with success in patients with rheumatoid arthritis, macrophage activation syndrome, and idiopathic pulmonary hemosiderosis. In addition, liposteroid has been used in some non-inflammatory diseases. Moreover, we conceive that liposteroid may have a beneficial effect in patients, who are critically ill due to COVID-19, and suffer from the macrophage activation syndrome.

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Introduction

Glucocorticosteroids alias corticosteroids (CS) is a class of potent anti-inflammatory and immunosuppressive medications used for treatment of many inflammatory and autoimmune diseases in clinical practice. CS exert their action by inhibiting transcription of proinflammatory genes and altering post-translational modifications of the cytokines, causing reduced secretion of cytokines from the cells (Tobler et al., 1992). Moreover, CS also decrease the production of arachidonic acid metabolites (Newton, 2000).

Dexamethasone is a potent CS with a long half-life. The duration of action ranges between 36 to 72 hours (Shefrin and Goldman, 2009). With equivalent systemic dosing, dexamethasone is 30 times more potent compared to hydrocortisone, regarding its efficacy as an anti-inflammatory agent. Similarly, dexamethasone is 6 times more potent than prednisone or prednisolone, which are the most commonly used systemic CS (Furst and Saag, 2020). Although highly effective, long-term CS therapy is associated with a significant risk of adverse effects, including the propensity of developing infections, metabolic changes (diabetes mellitus, hypertension, obesity) and bone abnormalities (osteoporosis), growth retardation in children, cataract formation, cushingoid appearance, and suppression of the hypothalamic-pituitary axis.

One potential method to reduce CS mediated side effects is the delivery of the necessary quantity of medication to the "site of interest", i.e., "targeted drug therapy". Such a strategy will result in a higher concentration of CS in the targeted inflammatory cells and tissues, and a lower systemic dose delivery to "non-target" tissues. In addition, increased potency compared to traditional drug preparations may further enhance the effect and decrease the necessity for a high CS dosing and reduce side effects. To this end, liposteroid represents an attractive and viable alternative to traditional CS therapy (Vishvakrama and Sharma, 2014).

What is liposteroid?

Liposteroid is the liposomal formulation of dexamethasone-21-palmitate (Yokoyama et al., 1985). The liposome vesicles are spherical and composed of a phospholipid bilayer. The lipid bilayer can be uni- or multi-lamellar (Benameur et al., 1993). The specific drug molecule is carried within the hydrophilic center of the liposome vesicle (Figure 1). The average liposomal sphere diameter varies between 0.1 and 0.3 μm, no vesicle being larger than 1 μm (Yokoyama and Watanabe, 1996). Liposteroid was manufactured by Dr. Y. Mizushima in Japan in 1981 and has been used in clinical practice since 1985 (Mizushima et al., 1982). Liposteroid has not yet been approved by the Food and Drug Administration (FDA) in the United States or the European medicines agency (EMA) to treat chronic inflammatory diseases. The medication is not currently manufactured in the United States. Liposteroid is manufactured and marketed as Limethason® in Japan for systemic administration and Lipotalon®

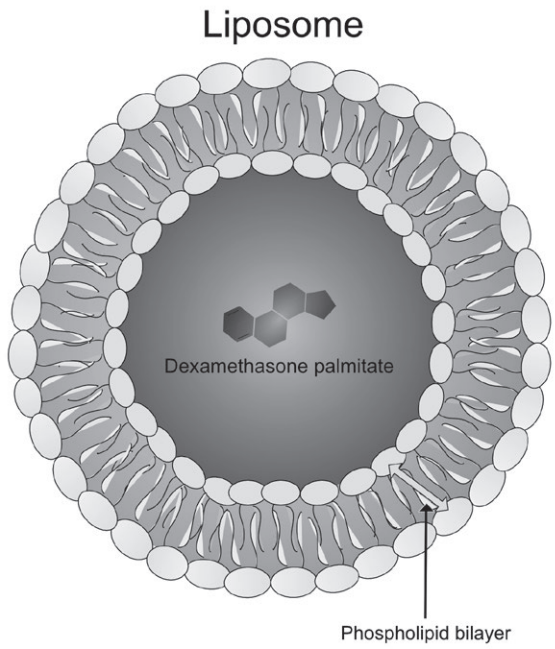

Figure 1 – Structure of the liposteroid. The hydrophilic dexamethasone palmitate is surrounded by a phospholipid bilayer.

in Germany for topical application. Liposomal preparations of other CS are also available (Schiffelers et al., 2006).

Pharmacokinetic and pharmacodynamic properties

Compared to the conventional parenteral hydrophilic formulation of dexamethasone (dexamethasone sodium phosphate – DSP), liposteroid is much more lipophilic. Consequently, there is a significant difference in the pharmacokinetic properties between liposteroid and DSP (Table 1). Following intravenous injection/infusion, some of the liposomes will undergo partial or total degradation of the lipid bilayer due to hydrolysis by esterases (Gregoriadis et al., 1984), and dexamethasone palmitate is then released into the plasma (Yokoyama and Watanabe, 1996).
The intact liposomes are taken up by various cells, either by fusion with the cell membrane or by phagocytosis (Vishvakrama and Sharma, 2014). In phagocytic cells, the liposomes are phagocytosed and the phospholipid wall is degraded by lysozymes, thereby releasing the active drug within the cell (Vishvakrama and Sharma, 2014).
The fraction of administered liposomes, which undergo degradation in the blood is dependent on the composition of their lipid structure and the size of the liposome vesicles, i.e., the larger the size, the lower the plasma degradation and the higher the fraction of liposomes being phagocytosed and incorporated into the target cells (Gregoriadis et al., 1984).

Table 1 – Comparison between dexamethasone sodium and liposomal dexamethasone palmitate (liposteroid)

	Dexamethasone sodium phosphate	**Dexamethasone palmitate**
Preparation	conventional preparation for intravenous and intramuscular administration	liposomal preparation = liposteroid
Plasma concentration following intravenous dose	low	high
Alpha half life due to drug redistribution	0.14 hours	0.32 hours
Elimination half life	5.48 hours	2.17 hours
Tissue concentrations		
Skeletal muscle	high	low
Liver, kidney, lung	similar	similar
Spleen	low	high
Inflamed tissue	low	high
ED_{50}	0.45 mg/kg	0.08 mg/kg
Potency		5.6 times more potent

ED_{50} – median effective dose to achieve a specific effect in 50% of the population

Following intravenous administration of liposteroid, the plasma concentration of free dexamethasone palmitate is actually higher than after administration of DSP in equipotent doses, indicating some liposome degradation in the blood. The maximal plasma concentration of dexamethasone palmitate is achieved approximately 1.5 hours after liposteroid administration (li et al., 1988). The tissue distribution and distribution half-life (alpha half-life) vary markedly between these preparations. Once administered, liposteroid is taken up by phagocytic cells including macrophages in the reticuloendothelial system, both as intact liposomes and at variable stages of degradation (Gregoriadis et al., 1984). The rate of uptake is approximately 8 times faster than that 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). The other organs with high liposteroid deposition are the liver and lungs (Yokoyama and Watanabe, 1996). In contrast, due to its hydrophilic nature, DSP demonstrates a higher concentration in skeletal muscle (Yokoyama et al., 1985). The liver is the primary site of metabolism and degradation of dexamethasone palmitate. After being excreted in the bile, dexamethasone palmitate enters the enterohepatic circulation. Within 48 hours, 60% of dexamethasone is cleared renally, whereas 40% is excreted via the fecal route (Yokoyama and Watanabe, 1996). The elimination or beta half-life also varies

between DSP and liposteroid. In humans, the elimination half-life of DSP is 5.48 hours compared to 2.17 hours for liposteroid (Yokoyama and Watanabe, 1996).

Due to its high lipid solubility and predilection for phagocytic and other inflammatory cells, liposteroid achieves a two-fold higher concentration in inflamed tissues (Yokoyama et al., 1985). The anti-inflammatory effect of liposteroid is 5–6 times more potent than DSP (Mizushima et al., 1982). Moreover, liposteroid exerts a 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 et al., 1985; Yokoyama and Watanabe, 1996). In experimental studies, receptor-mediated phagocytosis by macrophages was suppressed by 80% with liposteroid at a concentration of 0.03 mg/ml compared to a 30% inhibition with DSP at a 10-fold higher concentration of 0.3 mg/ml. Similarly, the superoxide production was reduced by 75% by liposteroid at a concentration of 0.03 mg/ml (Yokoyama and Watanabe, 1996). Based on animal studies, the ED_{50} (median effective dose to achieve a specific effect in 50% of the population) for liposteroid was 0.27 mg/kg and 0.072 to 0.15 mg/kg to prevent edema and granuloma formation, respectively (Yokoyama and Watanabe, 1996).

As liposteroid is distributed predominantly in cells in the reticuloendothelial system, the suppression of the hypothalamic-pituitary axis is lower than 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). Likewise, there appear to be fewer metabolic side effects with liposteroid than with DSP (Schiffelers et al., 2006).

Liposteroid in autoimmune and inflammatory diseases

Liposteroid has been utilized for several inflammatory and noninflammatory conditions. These autoimmune and inflammatory diseases include rheumatoid arthritis (RA), graft versus host disease (GVHD), hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS), and idiopathic pulmonary hemosiderosis (IPH). In addition, liposteroid has been used in patients with infantile spasms or refractory seizures and for vascular protection during intraarterial chemotherapy.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune systemic inflammatory disorder characterized by symmetric destructive polyarthritis. The role of liposteroid was studied early in patients with RA (Mizushima et al., 1983; Hoshi et al., 1985). In a multicenter, double-blind comparative trial of 138 patients with RA, Hoshi et al. (1985) reported a significantly higher rate of symptomatic improvement and lower frequency of adverse effects with intravenous/intramuscular liposteroid (2.5 mg dexamethasone) given every other week, compared to DSP. The study was conducted over a period of eight weeks. Unfortunately, no subsequent trials have been performed.

Macrophage activation syndrome/hemophagocytic lymphohistiocysosis
Macrophage activation syndrome (MAS) or hemophagocytic lymphohistiocytosis (HLH) is a life-threatening condition associated with profound immunologic activation, i.e., cytokine storm, tissue destruction, and multi-system dysfunction. HLH carries a high mortality rate. One of the primary cells involved in the pathogenesis of HLH is the macrophage. The absence of normal downregulation of macrophage activity plays a critical role in the pathogenesis of HLH (Filipovich et al., 2010). As liposteroid is a more effective inhibitor of proinflammatory macrophage activity, researchers have used liposteroid with success in patients with HLH who demonstrated relative refractoriness to conventional CS therapy. Funauchi et al. (2003) reported a case of HLH in a patient with systemic lupus erythematosus where the patient initially improved on intravenous methylprednisolone. However, the cytopenia and ferritinemia were refractory to traditional CS therapy, but normalized following liposteroid therapy (Funauchi et al., 2003). Kobayashi et al. (2007) reported a pediatric patient with familial HLH with perforin deficiency, who was managed with liposteroid prior to a successful bone marrow transplantation. MAS secondary to juvenile dermatomyositis has also been treated successfully with liposteroid (Wakiguchi et al., 2015).

Graft versus host disease
Graft versus host disease (GVHD) is often occurs after allogeneic stem cell transplant. Infiltration of the affected tissue by macrophages is thought to be refractory to therapy and carry a poor prognosis (Nishiwaki et al., 2009). In an animal model of GVHD, Nishiwaki et al. (2014) demonstrated that liposteroid was effective against activated macrophages infiltrating the skin, whereas DSP was not. GVHD refractory to high dose systemic CS has shown improvement with liposteroid therapy (Kurosawa et al., 2020).

Idiopathic pulmonary hemosiderosis
Idiopathic pulmonary hemosiderosis (IPH) is a rare disease characterized by recurrent episodes of diffuse alveolar hemorrhage (DAH) without any known etiology (Saha, 2020; Saha and Chong, 2021). IPH is more prevalent among children than adults (Chen et al., 2017). The latest evidence point towards autoimmune pathogenesis with a genetic predisposition (Saha, 2021). CS represents the first line of therapy both during the acute phase for remission induction and subsequently for maintenance of remission (Saha and Milman, 2021). A minority of patients are refractory to CS and require second-line immunosuppressive medications, such as azathioprine or cyclophosphamide, to achieve disease control (Saha and Milman, 2021). Unfortunately, these medications are associated with an increased risk of infections and malignancies.

Liposteroid has been used successfully in patients with IPH refractory to high dose conventional CS therapy (Sakurai et al., 1999; Doi et al., 2013; Sakamoto et al.,

2018; Tobai et al., 2020). Typically, liposteroid is infused for three successive days at doses ranging from 0.06 to 0.1 mg/kg body weight/day in order to induce remission. The subsequent maintenance dosing is usually started one week after the last induction dose, and subsequently, the interval between infusions is gradually increased, provided the bleeding remains under control. The maximal interval between maintenance doses is four weeks. Doi et al. (2013) reported 9 pediatric patients treated with liposteroid, with a median follow-up of 11 years; 3/9 patients were cured, and another three patients obtained long-term remission. Importantly, all patients survived during the observation period (Doi et al., 2013). This finding is crucial as pediatric patients with IPH have been reported to have a median survival of 2.5 years in previous studies (Ohga et al., 1995).

Other inflammatory diseases
Similar efficacy has been reported in patients with other inflammatory and autoimmune diseases, such as inflammatory myopathy, immune thrombocytopenia (idiopathic thrombocytopenic purpura), and gouty arthritis (Shimizu, 1996; Sakurai et al., 1999; Wakiguchi and Ohga, 2016; Wakiguchi, 2017). Table 2 summarizes the use of liposteroid in autoimmune and inflammatory disorders.

Use of liposteroid for noninflammatory disorders

Prevention of hepatic artery stenosis
Liposteroid also possesses protective effects on the vascular endothelium (Suzuki et al., 1992). Sadahiro et al. (2000) reported an exciting application of liposteroid therapy. The authors utilized liposteroid for the prevention of hepatic artery stenosis due to hepatic arterial infusion of chemotherapeutic drugs for liver metastasis in patients with colorectal cancer (Sadahiro et al., 2000). In their study, when liposteroid was simultaneously infused with 5-fluorouracil, none of the 12 patients developed hepatic artery stenosis. In contrast, 67% of patients in the control arm developed hepatic artery stenosis, defined as ≥50% narrowing of the artery. Liposteroid contained 4 mg of dexamethasone palmitate, was infused during each treatment session. For the comparison of efficacy, the reported incidence of hepatic artery stenosis due to hepatic arterial chemo infusion varies between 10–40% (Oberfield et al., 1979).

Infantile spasms and refractory seizures
"West syndrome" is a form of generalized childhood epilepsy characterized by refractory daily seizures and mental retardation. Although the exact mechanism is unknown, adrenocorticotropic hormone (ACTH) and CS represent first-line agents in the treatment of this disease. Liposteroid therapy has shown improved outcomes and fewer side effects compared to ACTH in several studies of infantile spasms and refractory epilepsy (Yamamoto et al., 1998, 2007; Yoshikawa et al., 2000).

Table 2 – Outcomes in patients treated with liposteroid for inflammatory and non-inflammatory diseases

Disease	Type of study	Patient population	Liposteroid dose	Outcome	References
Rheumatoid arthritis	double blind, prospective trial	adult	2.5 mg IV or IM every 2 weeks	Tendency to higher rate of improvement compared to DSP. Lower frequency of side effects with liposteroid.	Mizushima et al. (1983), Hoshi et al. (1985)
Hemophagocytic lymphohistiocytosis/ macrophage activation syndrome	case reports	pediatric	2.5 mg IV daily for 2 weeks, followed by 2.5 mg IV every other day for 2 weeks 7.5 mg/m^2/ day for 3 days followed by 3.75 mg/m^2/ day for 4 days	Decrease in pancytopenia, serum lactate dehydrogenase and ferritin. Marked regression of systemic symptoms and hepatosplenomegaly.	Funauchi et al. (2003), Kobayashi et al. (2007), Filipovich et al. (2010), Wakiguchi et al. (2015)
Graft versus host disease	case report	adult	10 mg/day three times a week gradually increased to 10 mg/day	Regression of pericardial effusion, ascites, and generalized edema. Decrease in serum ferritin and soluble interleukin 2 receptor.	Nishiwaki et al. (2014), Kurosawa et al. (2020)
Idiopathic pulmonary hemosiderosis	case reports and patient series	pediatric	0.06–0.08 mg/ kg/day IV for 3 days, followed by gradual increase in dosing intervals up to 4 weeks	Induction of remission and maintenance therapy.	Sakurai et al. (1999), Doi et al. (2013), Sakamoto et al. (2018), Tobai et al. (2020)

DSP – dexamethasone sodium phosphate; IV – intravenous infusion; IM – intramuscular

Different dosing regimens have been used without any significant adverse reactions (Yamamoto et al., 1998, 2007).

Adverse effect of liposteroid therapy

Liposteroid therapy is generally well tolerated. The incidence of acute toxicity is very low. Sakamoto et al. (2018) reported the development of restlessness, irritability, hypertension, and altered mental status secondary to the development of posterior reversible encephalopathy in a 2-year-old girl after the first dose of liposteroid. The authors also reported a systemic inflammatory syndrome due to the palmitate component of the liposteroid. However, the dose used in this child (0.8 mg/kg body weight/day) was erroneously 10 times higher than the normal standard dose (Doi et al., 2013, 2015). There are no reports of acute systemic toxicity from liposteroid infusion in standard dosing regimens.

There is more concern about possible adverse effects in patients receiving long-term CS therapy. Doi et al. (2013) reported no cases of obesity, hypertension, cushingoid appearance, metabolic- or bone abnormalities in children receiving liposteroid for 2.3–15.6 years. All children had body heights between the 80th to 85th percentiles for normal children, so it is possible that there may be a slight growth retardation.

What is the importance of liposteroid?

Glucocorticoids are the mainstay of therapy for many inflammatory and autoimmune diseases. Despite their usefulness, clinicians are wary of prolonged CS therapy due to the risk of adverse effects. Liposteroid is a unique targeted drug delivery formulation of systemic CS that is more potent and reaches higher concentrations at the sites of inflammation than conventional CS, thereby enabling the clinician to use a lower total systemic dose. This may translate into reduced adverse events while ensuring better outcomes and patient compliance. Although not available throughout the world, the data from Japan is intriguing regarding the safety and efficacy of liposteroid for a multitude of conditions. Large-scale prospective, controlled studies will be necessary to define the role of liposteroid in clinical medicine.

Potential use in COVID-19

Since the beginning of the coronavirus disease-19 (COVID-19) pandemic due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), researchers have been trying to find medications, which are effective in the treatment of both mild and severe disease (Saha et al., 2020). COVID-19 is associated with a significant inflammatory response, and treatment with low-dose dexamethasone has been shown to improve survival among critically ill patients with presumed MAS (RECOVERY Collaborative Group et al., 2021). Consequently, dexamethasone or an equivalent dose of other CS is currently standard of practice throughout the World in these patients. As liposteroid, by targeting the macrophages, has a more potent

anti-inflammatory effect than DSP, it is conceivable that liposteroid could provide a higher beneficial effect for patients with severe COVID-19 pneumonia than DSP. Although this issue so far has not been given attention in the COVID-19 pandemic, we suggest that this hypothesis requires further clinical investigations.

Conclusion

Liposteroid is a liposomal preparation of dexamethasone palmitate with significantly higher potency and anti-inflammatory properties compared to free dexamethasone. Liposteroid accumulates predominantly in phagocytic cells in the reticuloendothelial system and achieves a much higher concentration in inflammatory tissues than DSP. It also provides more effective inhibition of proinflammatory macrophage activity. Although positive outcomes have been reported in most trials with liposteroid, the actual number of trials are limited. This is likely due to the unfamiliarity of this preparation among clinicians as the medication is not available worldwide. Given the potential efficacy and the possibility of reduced adverse effects, further studies are necessary to define the role of this compound in clinical medicine.

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