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### Will Immunoglobulin Therapy of Autoimmune Blistering Skin Diseases Survive the New Financial Management of Inpatients?

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#### Key Words

Immunoglobulin · Autoimmune blistering disease

Autoimmune blistering mucocutaneous diseases are rare but may be associated with high morbidity and a significant mortality rate. Treatment is cumbersome and the therapeutic armamentarium is limited. Mainly in pemphigus, high-dose systemic corticosteroids are still the first-line and cornerstone treatment. Due to long-term adverse effects, ‘steroid-sparing’ adjuvants are widely used, mostly without having proven their clinical efficacy in randomized controlled studies. Intravenous immunoglobulin (IVIG), however, has been evaluated in several randomized controlled trials [1, 2], and the levels and recommendations for evidence-based-medicine treatment of various autoimmune blistering skin diseases were listed recently [3]. Use of IVIG is attractive because of its low adverse event profile, and its use in children has also been addressed [4, 5].

IVIG therapy is expensive and usually needs inpatient health care professional assistance. In the setting of the diagnosis-related group type of financial management in hospitals there is some concern that patients unresponsive or showing severe adverse effects to the first-line therapy might be treated below optimum by avoiding the use of IVIG, neglecting the fact that in the long run, such suboptimal treatment might finally cause health care costs above those of IVIG therapy. Switching over to a semiambulatory setting, dispensing with postinfusion surveillance in these often severely ill patients might infringe on ethical standards. To overcome this dilemma, outpatient treatment with subcutaneous IgG (SCIG) might provide the solution.

Subcutaneous application of an immunoglobulin concentrate to patients with hypo- or agammaglobulinemia due to primary immunodeficiency (PID) has first been reported in 1952 [6]; the idea has been taken up in 1980 again [7], and treatment schedules

were elaborated in the 90s [8, 9]. In the first years of the new millennium, prospective controlled studies comparing intravenous and subcutaneous applications of immunoglobulin concentrates were performed [10, 11]. Thereby, the safety and efficacy of SCIG in previously untreated PID patients, including children, was high [12, 13]. Today, several immunoglobulin concentrates at strengths of 10 or 16% are registered for subcutaneous application in PID patients. The running marketing authorization process in the EU member states and Switzerland will soon make a 20% SCIG available. This preparation will enable to apply considerable doses at relatively low volumes (up to 0.5 g/single site of injection; application at several sites possible) [14]. Last but not least, from a social insurance’s perspective, evaluation of IVIG versus SCIG showed a potential for cost saving when using SCIG replacement therapy [15, 16].

According to a widely accepted belief, a hallmark of immunomodulation and control of inflammation in chronic autoimmune diseases by IVIG is a repeated, rapid enhancement of IgG in the circulation to levels considerably above the norm. The total amount applied per treatment is 1–2 g IgG/kg body weight over 2–5 days. Indeed, maintenance of IgG levels close to or within the norm was insufficient in preventing the development of immune thrombocytopenic purpura [17–19]. The question remains whether for immunomodulation SCIG, which does not induce the high peak levels, can replace IVIG, at least in some of the chronic inflammatory and/or autoimmune conditions responsive to IVIG. Actually, there are valuable hints that SCIG could indeed be immunomodulatory and anti-inflammatory in neurological conditions such as multifocal motor neuropathy [20–23] or chronic inflammatory demyelinating polyradiculoneuropathy [23–28] as well as dermatomyositis [29, 30]. Moreover, there is one publication of successful SCIG therapy in a patient with severe epidermolysis bullosa acquisita [31]. To the best of our knowledge, a ‘steroid-sparing’ effect of SCIG has not yet been studied in other autoimmune blistering skin diseases. To keep adjuvant immunoglobulin therapy available for severe cases, we propose a clinical trial in patients with recalcitrant pemphigus vulgaris assessing the ‘steroid-sparing effect’ of SCIG in a way similar to that of Amagui et al. [1].

#### Disclosure Statement

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