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Subcutaneous Immunoglobulin Therapy for Hypogammaglobulinemia Secondary to Malignancy or Related Drug Therapy

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ABSTRACT

Immunoglobulin replacement therapy (IRT) has an important role in minimizing infections and improving the health-related quality of life (HRQoL) in patients with immunodeficiency, who would otherwise experience recurrent infections. These plasma-derived products are available as intravenous immunoglobulin (IVIg) or subcutaneous immunoglobulin (SCIg). The global demand for these products is growing rapidly and has placed pressure on supply. Some malignancies and their treatment (as well as other medical therapies) can lead to secondary hypogammaglobulinemia or secondary immunodeficiency (SID) requiring IRT. Although IVIg use in this cohort has well-established therapeutic benefits, little is known about SCIg use. A literature search in July 2015 found only 7 published articles on SCIg use. These articles found that both IRT modes had equivalent efficacy in regard to reduction of bacterial infections. In addition, SCIg was reported to produce higher serum IgG trough levels compared with IVIg on equivalent dosage with the added benefit of fewer adverse effects. Patient HRQoL reports demonstrate preference for SCIg because of reduced adverse effects and hospital visits. There are no health economic models published on SCIg use in SID, but models on primary immunodeficiency disease and IRT conclude that SCIg provided greater economic benefits than IVIg. The findings of this small number of reports suggest that SCIg therapy for patients with SID is likely to be beneficial for both the patient and health care providers. To substantiate wider use of SCIg in SID, larger and more detailed studies are needed to accurately quantify the effectiveness of SCIg.

Contents

Immunoglobulin (Ig) products have been administrated intravenously as replacement therapy to treat immunodeficiency since the 1980s [1-3]. Ig products are also used as immunomodulatory agents in autoimmune disease, but this will not be covered in this review. Both

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primary immunodeficiency (PID) and secondary immunodeficiency (SID) compromise an individual's ability to produce functional immunoglobulins and thus diminish their resistance to infection.

Ig products contain the spectrum of affinity-matured IgG derived from a large pool of healthy blood donors, which have immunological functions of neutralization, opsonization, sensitization, and activation of the complement system [4-6]. Although the mechanisms for the therapeutic effects of Ig products are not completely understood, the presence of F(ab') fragments in the product provides antigen recognition function, whereas the Fc fragments enable activation of immunity [7]. Readers are referred to a recent review of mechanisms of actions of Ig preparations by Matucci et al [7].

Patients with recurrent infections are considered for immunoglobulin replacement therapy (IRT) regardless of their serum IgG levels. However, the level of serum IgG which defines immunodeficiency varies with the patient's age, underlying disease, and clinical status. In lung transplant patients, IgG levels of 4.0-6.9 g/L are considered as mild immunodeficiency, and levels less than 4 g/L are considered severe immunodeficiency [3]. Pediatric hemopoietic stem cell transplant (HST) patients are considered immunodeficient when their serum IgG level falls below 4 g/L [8]. The IgG level used to define immunodeficiency in SID varies, as some studies use IgG levels of less than 5 g/L [9] and others levels of less than 5.5 g/L [10]. Nevertheless, IRT is warranted in patients with recurrent infections regardless of severity of the underlying immunodeficiency disease [3,9].

Both PID and SID can be treated by administration of Ig, either as intravenous immunoglobulin (IVIg) or subcutaneous immunoglobulin (SCIg). Although much is known about IVIg and SCIg therapy for PID patients, the same cannot be said for SID. This literature review will focus on SID patients using SCIg replacement therapy. The terms *acquired hypogammaglobulinemia* and *secondary immunodeficiency* are used interchangeably in this review and abbreviated to SID.

Hypogammaglobulinemia can be secondary to malignancies that affect immunoglobulin production, such as chronic lymphocytic leukemia (CLL) [9,11-14], multiple myeloma, B-cell lymphoma, primary amyloidosis, and monoclonal gammopathy of unknown significance [5,6,9,10]. Between 27% and 52% of patients with CLL are diagnosed with hypogammaglobulinemia [9,13], and depending on the stage of the disease, this can be as high as 85% of patients [11]. This places these patients at risk of developing infections, thus influencing their morbidity and mortality. Estimates indicate that 25%-50% of deaths in patients with CLL are due to infection [12,15]. However, one study reported that all their CLL patients had the same risk of infection (79%) regardless of their serum IgG levels [13]. Other mechanisms that influence the susceptibility to infection in CLL patients include lymphocyte dysfunction, neutropenia, and a defective complement system [12].

Immunodeficiency can also be secondary to treatment of the patient's underlying disease [10]. Up to 6.6% of patients treated with rituximab develop symptomatic hypogammaglobulinemia [10,16], with 38.5% experiencing transient hypogammaglobulinemia [9], with subsequent increased risk of infection [14,16,17]. Treatment with glucocorticoids [10,18] has been reported to cause decreased serum IgG levels in 12% of patients [9], and anticonvulsant therapy has also been associated with the development of antibody deficiency [10,18]. The immunosuppressive treatments received by recipients of solid organ transplants are estimated to cause hypogammaglobulinemia in 14%-37% of patients [3,18,19]. Similarly, more than a third of children who received a lung transplant developed prolonged hypogammaglobulinemia [8]. Some treatment-related hypogammaglobulinemias are short lived, whereas others can be long term.

Viral infections, including human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus, and parvovirus B19, have also been associated with antibody deficiency that can increase susceptibility to infections [9,18].

As multiple factors may contribute to reduced serum IgG levels (ie, malignancy, treatment regimens, renal dysfunction [10,18], and/or viral infections), SID patients are a heterogeneous group. Because of their complex clinical presentation, it is often impossible to establish the exact cause of the hypogammaglobulinemia. Hence, it is not always clear if IRT will be of benefit to these patients.

In recent years, some countries have developed guidelines for the appropriate use of IRT [20-22], although clinical classifications used are not consistent. The efficacy of IVIg replacement therapy for SID has been well documented, and there are clear guidelines on its use in hematological conditions [15,20,23,24]. Total IgG product use for SID patients is variably estimated at 35% in Canada [25] and 21% in Australia [26]. In the United Kingdom, 11% are hematology patients and 7% are hemato-oncology patients [27]. There are presently no specific guidelines or recommendations for SCIg use and only a very small number of published reports on the efficacy of SCIg programs in SID patients. This article begins to address this knowledge gap with a literature search on the use of SCIg in SID patients.

Strategies for Literature Search

A systematic literature search of the following databases: PubMed, Google Scholar, Web of Science, ProQuest Health & Medical Complete, Annual Review, Scopus, Informit, EBSCO, and Cochrane Library, was conducted on 24 June 2015 for studies related to SID patients treated with SCIg replacement therapy (Fig 1). The keywords used were *acquired hypogammaglobulinemia*, *secondary immunodeficiency*, *subcutaneous*, *SCIg*, and *malignancy* (Fig 1). Broad keywords were chosen to minimize risk of missing studies that used mixed cohorts and included patients with SID. Any studies that were on IVIg use only, literature reviews, meta-analyses, abstracts, meeting reports, and books were excluded. For the remaining studies, the title, abstract, and methods section were screened to assess relevance. The search was completed without further restriction and identified 7 articles that included SID patients treated with SCIg replacement therapy, which are summarized in Table 1.

The study cohorts in the 7 articles varied and included patients with CLL, non-Hodgkin lymphoma, HST, and lung transplant recipients (Table 1). There was significant variation in the age of patients. One study had a pediatric cohort [8], another covered an age range from 1 to 74 years [28], 3 studies had a cohort mean age between 60 and 70 years [3,14,29], and 1 did not indicate the age of patients [30]. The Canadian study [25] had no patients, as it was based on a population estimate and reported only on economic benefits from switching PID and SID patients from IVIg to SCIg.

Two studies, the Swedish study by Hammarström et al [30] and the American study by Koterba and Stein [29], only included patients who commenced on SCIg and were naive to prior Ig therapy, whereas 3 studies, Compagno et al [14], Hoffmann et al [28], and Shankar et al [3], also reported on patients who started with IVIg and subsequently switched to SCIg. In the pediatric study [8], they compared HST patients who continued with IVIg therapy with those who switched to SCIg. It is worth noting that the cohort numbers of all the studies were small, with the largest study cohort containing 61 patients split into 2 groups [14] (Table 1).

Clinical Outcome

Serum IgG Levels

Although IgG levels greater than 6 g/L are considered normal for adults, there appears to be no consensus on the serum IgG level which provides protection from infection. In SID patients, this is further complicated by the heterogeneity of their underlying disease. Six studies (total n = 111 patients) included data on serum IgG trough levels in patients with SID (Table 1). In the earliest report, SID patients, who received SCIg therapy at a dose of 50 mg/kg/wk, demonstrated an increase of serum IgG levels from 3.1 to 5.5 g/L posttherapy [30].