Novel Aspects of Hypogammaglobulinemic States: Subcutaneous Immunoglobulin Treatment

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In recent years, increasingly more patients are receiving immunoglobulin infusions. This is due to better recognition of antibody deficiency, as reviewed elegantly in the current issue of *IMAJ* by Etzioni [1], and to the appreciation that such treatment reduces life-threatening infections and chronic lung damage [2]. Furthermore, the improved survival of patients with immunodeficiency and the immunomodulatory effect of immunoglobulin, which is beneficial in different chronic immune-mediated diseases, have resulted in a significant increase in the number of patients receiving regular immunoglobulin infusions. However, this has led to several problems. Although most patients require infusion only once every 4 weeks, and modification of preparation methods have allowed higher immunoglobulin concentration and faster infusion rates, many patients lose time from school or work with each treatment [3]. The cost to the health system has risen substantially, particularly due to the associated costs of hospital-based care. This prompted the establishment of an optional "self-infusion Ig administration at home" in some countries [4]. Several studies have indicated that after appropriate training many patients are able to continue IVIg treatment at home, without an increased incidence of side effects or adverse reactions [5]. In parallel, subcutaneous administration of Ig has been evaluated [6,7].

Small portable pumps usually infuse SCIg through a fine 25-G butterfly needle into the subcutaneous tissue in the thighs, buttocks or abdomen. If sufficient subcutaneous tissue is available 10 ml are injected at each site, while 5 ml are infused in areas with poor subcutaneous tissue [3]. More than one site may be used simultaneously. The initial trials with SCIg kept a low infusion rate of 1–3 ml/hour [8]. Further studies have indicated that a rapid (10–40 ml/hr) SCIg infusion at high concentration (16%) is possible [9].

IVIg is used as replacement therapy in patients unable to produce adequate immunoglobulin due to primary or secondary immune deficiency [2,10]. Monthly IVIg infusions have also been shown to improve the clinical status of patients with different autoimmune, rheumatologic and neoplastic diseases, possibly due to the immunomodulatory effect of immunoglobulin [11–15]. SCIg has been given only to patients with primary antibody deficiencies, initially to those who experienced an anaphylactic reaction to IVIg

IVIg = intravenous immunoglobulin
SCIg = subcutaneous immunoglobulin

[16] or with a difficult intravenous access route. It has been evaluated in pregnant women [17] and in children with antibody deficiency [3,18]. In the latter population, the low volume of SCIg that is given may overcome the increased risk for thromboembolic events associated with IVIg administration in neonates, related to the hyperviscosity state that is common in these patients [19].

Up to 87% of patients treated with SCIg experience some form of tissue reaction at the infusion sites at least once. Local swelling and soreness at the infusion site are reported by 66% of patients, while redness or itching occurs in less than 50% [20]. Rapid infusions (up to 40 ml/hr) are also safe and are not associated with increased adverse effects [21]. Abrahamsen and colleagues [22] reported that therapy with SCIg for up to 6 years with over 1,100 infusions among patients with immunodeficiencies was feasible and safe with no systemic adverse reactions. A pivotal study among 165 patients who received more than 33,000 SCIg infusions documented only six episodes of moderate systemic reactions, none of which required treatment such as adrenaline, hydrocortisone, etc. [20]. This is considerably less frequent than the rate of moderate or severe reactions associated with IVIg or intramuscular immunoglobulin infusions.

Several studies have shown that SCIg is at least as effective as IVIg in achieving adequate plasma levels of IgG and IgG subclasses [3,23], although it may take up to 6 months until the desired IgG levels are reached [24]. Furthermore, SCIg treatment in pregnant women results in normal total IgG and IgG subclass levels in cord blood [17]. Recently, a crossover study showed that there was no difference in the frequency or severity of infections over a one year period among patients with primary antibody deficiency syndrome when treated with SCIg or IVIg [25]. A small study has shown that SCIg given every 2 weeks achieved serum IgG levels similar to those with other replacement regimens (Hammastrom, Stockholm, 2000, personal communication), which may make the administration of SCIg even more appealing to some patients.

SCIg infusions are associated with considerably more needle punctures and possibly increased discomfort, as compared with IVIg, particularly in children. Several studies have assessed the satisfaction of patients and families with SCIg. The majority of families reported less inconvenience as compared to IVIg treatment, less discomfort to the child, and reduced school or work time loss [3]. There was also improved health-related function and self-rated

health. Among 165 patients treated with SCIg, only 3 patients elected to discontinue the infusions. One patient refused any form of replacement therapy after 6 years of treatment, and two patients elected to return to IVIg treatment after 95 and 173 infusions respectively, due to pronounced erythema, itching and soreness [20]. Thus, it seems that in most patients, the advantages of SCIg outweigh the local reactions.

The varying costs of immunoglobulin preparations and the different health systems in countries over the world do not allow a precise determination of the exact costs, however it is expected that home SCIg will significantly reduce the burden on the families and patients as well as on the healthcare system. In Sweden, home SCIg infusions are expected to reduce the yearly cost per patient for the healthcare sector by US$ 11,000 (76% reduction) compared to IVIg treatment [20]. In the Netherlands, the reduction in cost was estimated to be only 44%, however this is still substantial when considering the widespread use of immunoglobulin [26].

In conclusion, studies have shown that SCIg is as effective and safe as IVIg. There are frequent local reactions at the infusion site, however there is a very high rate of patient and family satisfaction mainly because of the time saved and the independence of home treatment. Further studies will clarify both the role of SCIg as a replacement therapy and immunomodulator in larger patient groups and its cost-effectiveness.

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