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Use of intravenous immunoglobulin therapy in autoimmune blistering diseases

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Abstract

Autoimmune mucocutaneous blistering diseases (AMBD) are an interesting group of rare diseases that affect the mucous membranes and the skin and are frequently or potentially fatal. The clinical presentation is significantly variable, as is the course and prognosis. The immunopathology is well characterized and the target antigens to which the autoantibodies are directed have been studied by various investigators. A significant majority of the patients respond to conventional therapy, which consists of high-dose long-term systemic corticosteroids and immunosuppressive agents. This treatment program has significantly improved the prognosis in many patients. In such patients, significant side effects of the drugs may appear and produce a very poor quality of life. In patients with progressive diseases, especially those with mucous membrane pemphigoid, the significant sequela; such as blindness, aphonia, and stenosis of the anal and vaginal canals can occur. In several patients treated with conventional immunosuppressive therapy, death occurs as a consequence of prolonged immune suppression leading to opportunistic infections. In this manuscript, the published data on the use of immunoglobulins intravenous (IGIV) in patients with AMBD is presented. The most important features of IGIV in patients with AMBD are: 1) the ability to clinically control the disease; 2) the ability to induce and maintain a long-term clinical remission; 3) a lower incidence of side effects; and 4) a higher quality of life. The important characteristic of the IGIV therapy in the AMBD is two-fold. First, the therapy, when given according to a published protocol, produces a lasting and long-term clinical remission, rather than a temporary arrest of the disease. Second, the therapy, as described in the protocol, has a very definitive endpoint. Consequently, once the patients are treated and go into long-term remission, the therapy is no longer required. The significant positive results obtained with IGIV are to a large extent also due to the associated aggressive topical therapy that was used and the frequent use of sublesional injections with triamcinolone. The rapid and early detection of cutaneous and mucosal infections and their treatment with systemic antibiotics is also a very important feature of IGIV therapy. When patients are under long-term conventional therapy, the infections are often not detected because they lack the ability to mount signs of inflammation. It is also becoming increasingly clear for patients to have a successful outcome, in treatment with IGIV therapy, it is critical that the physician spends a significant amount of time with each patient, monitor the therapy closely, and be familiar with the overall health of the patient. It is also best if the therapies are instituted by a physician who has significant interest and experience in blistering diseases and IGIV therapy.

Keywords: Pemphigus vulgaris; Pemphigus foliaceus; Bullous pemphigoid; Cicatricial pemphigoid; Epidermolysis bullosa acquisita; Intravenous immunoglobulin therapy; IGIV protocol; IGIV treatment outcomes; Effects of early IGIV therapy termination; Conventional immunosuppressive therapy

1. Introduction

Autoimmune mucocutaneous blistering diseases (AMBD) are a group of rare diseases that affect the

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skin and multiple mucous membranes. These diseases have several features in common [1–6]. They often involve the skin and one or more mucous membranes, which are derived from the stratified squamous epithelial. They have variable clinical presentations, course, prognosis, and response to therapy. There is significant data to suggest that they have an autoimmune basis and that the pathogenesis of the disease process is linked to autoimmunity. In a significant number of patients in whom the disease is progressive, the clinical course can result in the development of serious complications and sequela. The long-term use of immunosuppressive agents can also produce death, secondary to opportunistic infections. Therefore, autoimmune blistering diseases were considered to be fatal prior to the advent of the corticosteroid era, but continue to be potentially life threatening because of the side effects of conventional therapies that are traditionally used in most treatment centers [1–11].

Over the last few years, a novel approach to their treatment has been reported [12]. Some patients who are non-responsive to high-dose systemic corticosteroid therapy and immunosuppressive agents have been successfully treated with IGIV [13–47]. This chapter, provides a review on the current use of IGIV in the management of AMBD. The focus of this inquiry is on the practical dimensions of the use of this agent in clinical practice. This manuscript deals with the treatment of five diseases in which IGIV has been successfully used and recommended. These five diseases are: 1) pemphigus vulgaris (PV), 2) pemphigus foliaceus (PF), 3) bullous pemphigoid (BP), 4) mucous membrane pemphigoid (MMP), also known as cicatricial pemphigoid (CP), and 5) epidermolysis bullosa acquisita (EBA). Some reports indicate that IGIV may also be effective in the treatment of linear IgA or bullous diseases (LABD), herpes gestationis and other blistering diseases. These two disease entities will not be discussed here. AMBD are relatively rare diseases. As readership of this journal is widespread and covers multiple areas of clinical medicine and practice, the author will briefly discuss epidemiology, clinical profile, diagnostic criteria, and current therapy. This background will help put into perspective the advantages of using IGIV, especially in cases where attempts to control the disease or attempts to achieve long-term remission is difficult, has several obstacles, or results in very serious side effects, affecting life; as well as, the long-term prognosis.

2. Epidemiology

PV has been reported in most countries of the world [1–3,48–61]. While the majority of cases in North America were in the fifth decade, it has been reported in children and in older patients. It affects males and females. It is reported that the incidence of PV is between 0.1–3.2 cases per 100,000 individuals per year. This incidence is higher in patients of Ashkenazi Jewish descent [53]. The incidence in Jerusalem is reported to be 1.6–2.7 per 100,000; and in Greece, 0.9 per 100,000. In Finland, it is reported to be 0.08 per 100,000 [53–56]. In the United States, one study was done in Connecticut, where the incidence was found to be 0.5 per 100,000 [53]. The incidence of pemphigus foliaceus is approximately 0.75 per 100,000 per year [1–3]. It appears to be higher in Tunisian women, whose annual risk is about 1.5 per 100,000 individuals [58]. In Brazil, there is an endemic form of pemphigus foliaceus referred to as fogo selvagem. It is also reported in other parts of South America. The fogo selvagem has an incidence as high as 5 per 100,000, and a prevalence rate of approximately 3.4%.

BP is a disease that affects predominantly the elderly [1,2,5]. The median age of onset is 65. The incidence has been reported to be 7 patients per 1,000,000 individuals in 2 different studies [62,63].

MMP is also a disease of the elderly and the mean age of onset is about 73 [64–66]. Women are affected twice as frequently as men and there is no racial predilection. The reported incidence of MMP varies from 0.87–1.6 per 100,000 individuals [64–66].

EBA is exceedingly rare [4]. The mean age of onset is approximately 50 years, but it has been observed in both very young and older patients [4,67,68]. The incidence is reported to be above 0.25 cases per 1,000,000 [63].

3. Clinical features and diagnostic features

3.1. Pemphigus vulgaris

The hallmark of PV is flaccid blisters on the skin that rupture easily and leave denuded, painful surfaces [1–3] (Fig. 1). In the majority of patients, the disease begins in the oral cavity [69]. The skin of the scalp, face, chest, back, and upper extremities is involved more frequently than below the umbilicus. Involvement of ocular, nasal, pharyngeal, laryngeal, esophageal, vaginal, penile, and anal mucosa is seen in patients who have severe and generalized disease. Skin biopsies from early lesions demonstrate a characteristic intact layer of basal cells with acantholysis [1–3]. Acantholysis refers to the loss of adhesion between epidermal cells, which are often seen floating in the cavity of the blister. Direct immunofluorescence (DIF) studies is absolutely essential. A perile-