Unmasking a New Potential Role of Intravenous Immunoglobulins: Could It Stand the Cancer Challenge?

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Our understanding of the pivotal role the immune system plays in the pathogenesis of many diseases is continually expanding. Huge advances have been made in elucidating the complex immunologic background of several diseases, including Alzheimer's disease, Parkinson's disease, and asthma [1,2]. Recently, mounting evidence has been gathered in support of the central role of the immune system in cancer pathogenesis [2]. In addition to the normal physiological selective pressures against cancer propagation, new approaches that upregulate the immune system are therapeutically investigated to provide better control over carcinogenesis. Several immunotherapy protocols have demonstrated tangible effects, including monoclonal antibodies, adoptive transfer of genetically enhanced lymphocytes, and vaccines [3]. Current strategies used to combat carcinogenesis show modest effects. However, the combination of standard care regimens with novel immunotherapeutic strategies is postulated to provide a synergistic effect against cancer, decrease disease burden, and improve patients' quality of life [3].

Intravenous immunoglobulins (IVIG) are made from a pool of anti-idiotypic IgG molecules that bind to, and neutralize, autoantibodies. While their mechanism of action is not fully understood, IVIG is thought to downregulate the production of endogenous antibodies, cause differential macrophage activation, and modulate Fc receptors [4]. IVIG has multiple applications, including antibody replacement in immunodeficiencies or immunomodulation in patients presenting with autoimmune or autoinflammatory diseases [5,6].

IVIG is used in the management of a variety of medical conditions, including prevention of coronary aneurysm in Kawasaki disease, conditions associated with graft-versus-host disease, reduction of bacterial infections in certain populations, immune thrombocytopenic purpura, multifocal motor neuropathy, and chronic inflammatory demyelinating polyneuropathy [7,8]. Interestingly, the use of IVIG in the field of neurology has expanded substantially. IVIG is considered a first-line treatment for Guillain-Barré syndrome (GBS) and a second-line therapy for several diseases, including stiff-person syndrome and multiple sclerosis [9].

GBS is an acute inflammatory immune-mediated progressive polyradiculoneuropathy disease. GBS is idiopathic; however, the aberrant immune response is postulated to occur secondary to triggers such as immunizations, infections, or surgery [10]. The primary treatment routes in GBS include plasma exchange and administration of IVIG. Compared to supportive care, treatment with plasma exchange resulted in better recovery, better improvement of muscular strength, and reduced need for mechanical ventilation [11]. Furthermore, treatment with IVIG was shown to be as effective as plasma exchange in the treatment of GBS [12].

In this issue of the *Israel Medical Association Journal* (*IMAJ*), Shalem and colleagues [13] reviewed the records of all patients who were admitted to the Sheba Medical Center with a diagnosis of GBS between 2007 and 2015. Of the patients diagnosed with GBS who were also treated with IVIG, 71% percent reported improved motor function, as assessed by the motor disability grading scale (MDGS), within 14 days of treatment onset. Furthermore, MDGS improvement from admission to discharge was also statistically significant, $P < 0.001$. The data presented in their article reflects the effectiveness of IVIG in a clinical setting and thus substantiates the documented benefit of IVIG in the management of GBS.

To explore the broader application of IVIG, this therapy is also indicated for the prevention of recurrent bacterial infections due to B-cell chronic lymphocytic leukemia.

Because of the high adverse effect profile of modern chemotherapeutics, the search for safer treatment modalities remains a high priority. Our current understanding of the efficacy of IVIG in cancer treatment is based on conditions in which IVIG is administered for a concurrent immunodeficiency or autoimmune disease.

In a study of five patients with chronic lymphocytic lymphoma (CLL), treatment with IVIG for either autoimmune hemolytic anemia or immune thrombocytopenic purpura resulted in the recovery of the autoimmune condition with a concomitant maintenance of lymphocyte counts and infection rates. These results denote the putative role of IVIG in controlling CLL [14]. Similarly, the treatment of polymyositis in patients infected with human immunodeficiency virus who presented with with Kaposi's sarcoma resulted in improvement of the patient's symptoms with a concurrent

abrupt regression of Kaposi's sarcoma [15]. Moreover, IVIG delayed disease progression of metastatic melanoma with a documented regression of distant metastasis in some patients [15,16].

While much of the research on the use of IVIG in cancer therapy is relegated to treatment with a concurrent immunodeficiency, in this issue of the *IMAJ* Danieli and co-authors [17] describe a case report of a 60 year old male with metastatic pancreatic cancer with liver and lymph node involvement who was treated with subcutaneous immunoglobulin (SCIg) for concurrent common variable immunodeficiency (CVID). SCIg was used due to severe cardiovascular side effects with prior IVIG administration. Preceding the SCIg treatment, the patient had a life expectancy of a few months. After treatment with SCIg, clinical and laboratory improvements were noted. The patient survived for 10 months but eventually succumbed to hepatic and pulmonary impairment [12]. This case study suggests a potentially favorable role that pooled immune globulins play in slowing cancer progression, but the benefits should be further studied.

The unique effectiveness of IVIG in the treatment of immunodeficiencies, autoimmune diseases, and cancer raises questions concerning the drug's mechanism of action. It has been suggested that autoimmune diseases and cancer have several common baseline characteristics, including the presence of autoantibodies, genetic predisposition, viral based etiology, and frequent co-occurrence of the two conditions [18]. On that premise, several mechanisms have been proposed. In autoimmune diseases, IVIG action is based on the anti-inflammatory activity (classical, M-CSF), whereas in neoplasms a pro-inflammatory action is required, most probably involving the alternative granulocyte-macrophage colony stimulating factor (GM-CSF) pathway.

Several mechanisms have been proposed to explain the anti-metastatic effects of IVIG, such as the activation of interleukin 12 (IL-12) secretion, and the subsequent activation of natural killer cells, inhibition of metalloproteinases, inhibition of malignant cell line growth, and expression of pro-apoptotic genes and Fas expression [19]; however, the exact mechanism requires further elucidation.

The current paradigm in cancer therapy calls for effective, novel therapeutic regimens. Based on the evidence presented, IVIG therapy may present a new treatment modality. Accordingly, further research is required to delineate the molecular function and clinical efficacy of IVIG as an anticancer therapy.

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"Learning is not attained by chance, it must be sought for with ardor and attended to with diligence"

Abigail Adams, (1744–1818), wife of John Adams, second president of the United States

"Hope lies in dreams, in imagination and in the courage of those who dare to make dreams into reality"

Jonas Salk, (1914–1995), American medical researcher and virologist, developer of polio vaccine