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Bruce Mazer Is a Pediatric Allergist and Immunologist and Professor of Medicine at McGill University, Senior Scientist at the Research Institute of the McGill University Health Center and is currently the Associate Scientific Director (Strategy) of Canada's COVID-19 Immunity Task Force. He is a graduate of McGill's Faculty of Medicine and Health Sciences and has been a faculty member in the Department of Pediatrics since 1991. From 2000 to 2015, he served as Division Head of Allergy and Immunology at the MCH. In 2015, he was appointed Head of Child Health Research at the Research Institute of the McGill University Health Centre (RI-MUHC). In October 2016, he became Interim Executive Director and Chief Scientific Officer of the RI-MUHC, a role he held until July 2020. He has published over 120 papers and held continuous research funding since 1993. Dr. Mazer's research focuses on the role of B-cells in regulating inflammation in allergic diseases and antibody responses in immune-deficient patients. His early research on intravenous immunoglobulin influenced the treatment of asthma, Kawasaki disease and immune defects in children. Dr Mazer later led the creation of Canada's first food allergy consortium which led to multiple food allergy oral immunotherapy trials and genetic biomarkers of food allergy. This CIHR-funded network is generating new insights into life-threatening food reactions and testing new treatments – some based on studies by the Mazer lab. An award-winning mentor who held many leadership positions at McGill, Dr Mazer has played a national role in pandemic-related research as director of scientific strategy for the Canadian COVID-19 Immunity Task Force.

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THE USE OF IVIG FOR ALLERGY CONSULTANTS

Introduction

IgG plays multiple roles in the immune system. Best known as an effector molecule in host defence, infusions of polyclonal IgG have been employed as the mainstay of treatment for patients with immunodeficiency diseases affecting the humoral immune system. IgG preparations are fractionated from pools of several hundred to several thousand donors or more[1] and therefore contain a broad spectrum of antibodies, capable of providing protection against many bacterial and viral diseases. Preparations of human IgG are available for intravenous (IVIG) or subcutaneous (SCIG) administration, allowing individuals with both primary and secondary immune defects to have significantly fewer infections, decreased hospitalizations and overall improved quality of life (QOL)[2]. Moreover, IVIG has been employed as a regulator of a large number of autoimmune and inflammatory conditions since the 1980s.[3]

IgG Replacement for Immune Deficiency

How do you choose who should receive immunoglobulin therapy? Is it simply a history of recurrent infections, such as frequent ear infections or pneumonia? Should all individuals with risk factors such as immune suppressive therapies, cancer treatments or hematologic malignancies be considered for immunoglobulin replacement? The scarcity of plasma for fractionation, exacerbated by the recent COVID-19 pandemic, led to shortages of raw materials for IVIG. This demands that practitioners carefully scrutinize the use of immunoglobulin replacement, and employ

caution not only in prescribing, but in over-rationing this essential therapy, to the detriment of patients with primary antibody immune deficiency.[4]

Physicians evaluating individuals who may potentially benefit from IVIG replacement therapy should take a systematic approach to their assessment **(Figure 1**). The patient's history is commonly that of an unusual number of sinopulmonary infections, but can also include unexplained severe infections including sepsis, meningitis, osteomyelitis, and unusual abscesses in the upper or lower respiratory tract. All suspected patients should have a complete blood count (CBC) performed, looking for deficiencies in total lymphocytes, as well as measurements of IgG, IgA, IgM and IgE. The key to this evaluation is the demonstration of poor production of IgG (<4.0 g/L), as well as impaired production of specific antibodies. This is most easily performed by measuring antibody levels against common vaccines, such as diphtheria, tetanus, pneumococcus, measles, mumps, rubella, or hepatitis A or B. If the initial vaccine antibody levels are low, a booster vaccine followed by a repeat blood sample drawn 28 days later will demonstrate if the subject has responded appropriately.[5] In addition to antibody levels, evaluation of total T and B lymphocytes can illuminate deficiencies in the antibody producing B-cells or defects in T-cells which contribute to combined immune deficiencies. Indeed, the evaluation can also include additional studies of B and T-cell memory, T-cell function, complement studies, and neutrophil studies as appropriate. It is important to remember two important caveats: first, if IgG is low, but response to booster vaccination is normal, the benefit of IgG replacement is very suspect and other causes of IgG loss should be evaluated; second, IgA deficiency alone is not an indication for IgG replacement.[2]

Secondary immune deficiencies are an increasingly important group of conditions that may require long-term IgG replacement therapy. Although there are numerous conditions that lead to secondary hypogammaglobulinemia, broad indications are hematologic malignancies including chronic lymphocytic leukemia (CLL) or multiple myeloma (MM), diseases that lead to protein or immunoglobulin loss, or medications that decrease antibody production. Recent practice guidelines have reviewed the approach to the diagnosis and treatment of secondary hypogammaglobulinemia.[6] In particular, it is important for practitioners to be aware of the long-term effects of anti-CD20 B-cell ablation therapies including rituximab and ocrelizumab.[7] Used extensively for rheumatologic, hematologic and neurologic conditions, the increased use of these highly effective therapies has led to long-term decreases in B lymphocytes, impaired antibody production and increased susceptibility to infections. This has been identified in 3%-15% of individuals treated with anti-CD20 therapies. It has been postulated that secondary immune deficiency following anti-CD20 therapies may be a sign that the autoimmune or inflammatory process was due to an underlying primary humoral immune defect that was completely unmasked by the anti-CD20 therapy. Therefore, guidelines from multiple societies have recommended at minimum to evaluate serum immunoglobulins prior to initiating anti-CD20 therapy. However, a strong argument can be made for evaluating B-cell numbers as well, prior to initiating therapy, to document pre-existing B-cell lymphopenia. Follow-up should include IgG, IgA and IgM levels 3-6 months and one year post-therapy to ensure they are at normal levels, with more frequent measurements if the patient is suffering from recurrent or severe infections. A summary of guidelines suggests IgG replacement therapy for IgG levels below 3 or 4g/L in the context of severe or recurrent infections[6] **(Figure 1).**

Antibody replacement therapy can be achieved with either IVIG or SCIG IgG therapy. These are both very effective and can be administered at home, in an infusion centre or in hospital. SCIG is generally prescribed at 100-150 mg/kg SC weekly, with the dose titrated based on IgG levels, the patient's clinical status and provincial guidelines. As replacement therapy in primary immunodeficient patients, IVIG is dosed at 400-800 mg/kg.[2] IVIG is generally prescribed every 3-4 weeks and is similarly adjusted based on the patient's clinical parameters (infection frequency, general status , etc.) and IgG trough levels obtained at 3-6-month intervals. As IVIG contains antibodies to diverse pathogens, the primary objective of low-dose replacement therapy is to prevent recurrent infections in primary immunodeficient patients or in patients with recurrent infections with secondary immunoglobulin deficiencies.

IgG Replacement for Autoimmune disorders

IVIG is employed as an effective treatment for many autoimmune and inflammatory disorders. This commonly entails doses 3-5-fold higher than those employed for immune deficiency, ranging from 1-2gm/kg. IVIG has been consistently and successfully used for numerous conditions, including immune thrombocytopenic purpura (ITP), Kawasaki Disease (KD), Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), systemic lupus erythematosus, dermatomyositis, and other autoimmune and neurologic disorders.[8] Indeed, the number of conditions for which IVIG is used "off label" outnumbers that of the conditions with regulatory approval.[9,10] This is due to the wide-ranging interaction of various components of IgG molecules with multiple targets in the immune system, including immune cells, epithelial cells, cytokines, and other soluble molecules including complement. Studies on IVIG in these conditions have uncovered naturally occurring regulatory molecules that represent a small percentage of pooled IVIG, such as anti-idiotype antibodies, fractions that have specific glycosylation, and other components.[3] A more complete discussion of the

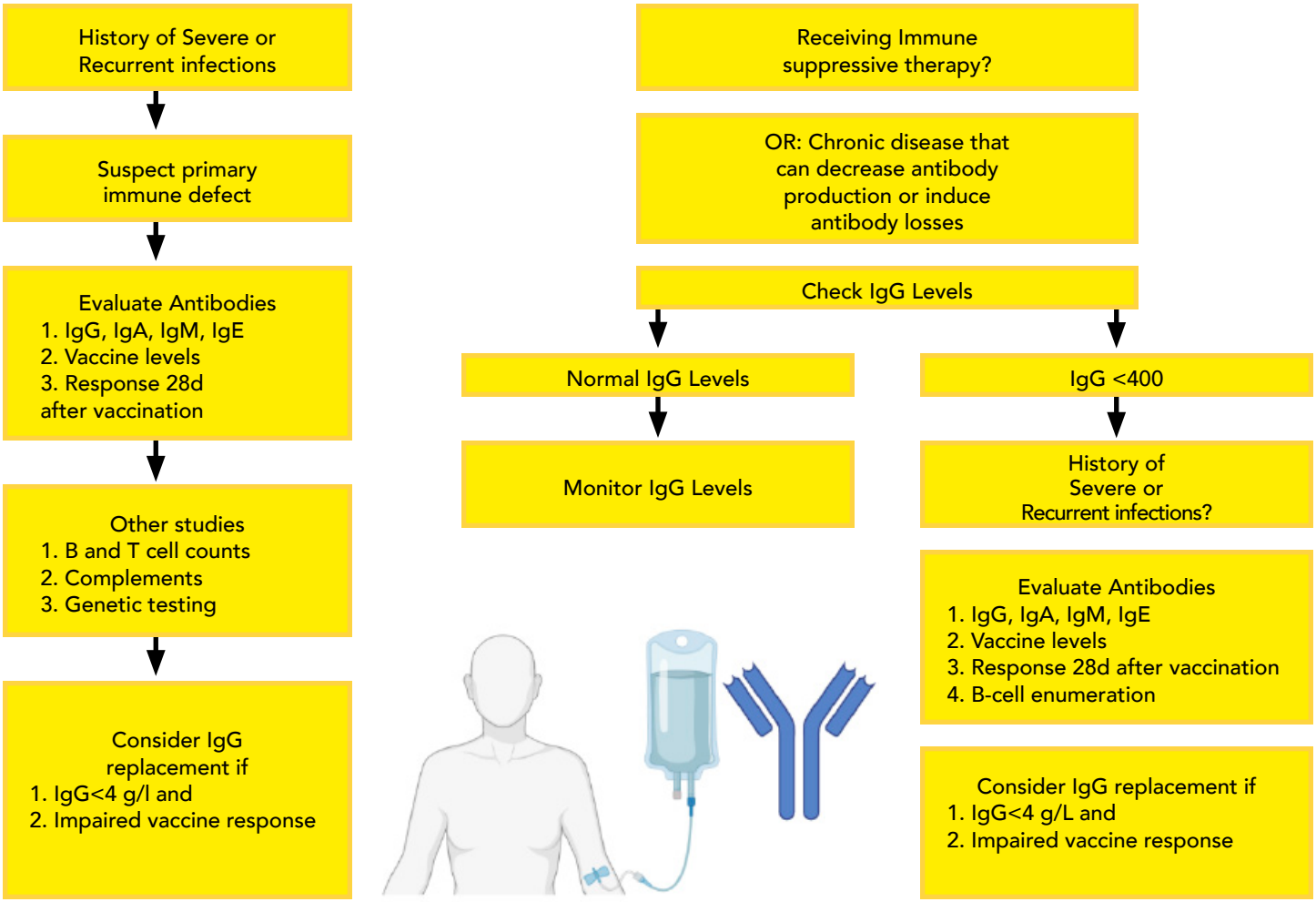

Figure 1: *Evaluation of primary and secondary antibody deficiencies; courtesy of Bruce Mazer, MD*

mechanism of action of IVIG in autoimmunity has recently been published.[11]

In individuals with inflammatory disorders on high-dose IVIG therapy, there is no clear IgG level that correlates with success; therefore, clinical scoring systems for patients with chronic diseases such as dermatomyositis[12] or neurological conditions are essential tools for monitoring therapy.

Safety of IVIG

The safety of IgG therapy is frequently questioned. It is, after all, a blood product derived from human plasma sources. How then can IgG products be made secure with relation to infectious viruses such as hepatitis and human immunodeficiency virus (HIV)? The procedure varies depending on the plasma fractionation facility or manufacturer; however, there are currently several very common steps that ensure product and patient safety.[13] Donors are screened and blood samples taken to ensure that signs of diseases such as transaminase levels are not elevated. All plasma is fractionated using cold ethanol in a process known as Cohn-Oncley fractionation. This step disrupts enveloped viruses such as HIV. However, a hepatitis outbreak in the 1990s led to important steps taken to ensure that non-enveloped viruses were deactivated or eliminated. Currently, virtually all plasma products undergo steps in which solvent-detergent is added, followed by other viral inhibitors, and finally nanofiltration.[14] These steps are highly effective in eliminating pathogens of concern and can even completely eliminate SARS-CoV-2 if it is present in the plasma of a donor.[14]

IVIG for the COVID-19 Virus

During the recent SARS-CoV-2 pandemic, clinicians showed extreme interest in antibody therapies that could mitigate the severity of acute COVID-19-related disease, particularly during the first waves of the pandemic when hospitalization was very common, particularly in the elderly. These treatments were shown to be highly instructive and provided insights into what antibodies can and cannot do in the setting of acute infections. Trials of hyperimmune plasma therapy (IgG infusions of plasma from patients recovering from severe SARS-CoV-2infection) were unsuccessful and, at times, worsened outcomes.[15] Similarly, IVIG infusions in hospitalized patients with severe COVID-19[16,17] were not successful at altering the clinical course of the virus.

Even Multi-systemic Inflammatory Syndrome of Children (MIS-C), which is highly analogous to Kawasaki Disease, was initially treated with IVIG; however, therapy has migrated to a combination of IVIG and corticosteroids or other biologic anti-inflammatory treatments.[18] Even monoclonal antibody agentsagainst SARS-CoV-2, while initially showing some promise, were unable to maintain pace with the changing landscape of COVID-19 variants and therefore had a very narrow window of usefulness.

The experience with COVID-19 has underscored some valuable teaching points regarding harnessing the power of IgG replacement therapy. First, although antibodies are an excellent first line of defence against bacterial and viral invaders, they have demonstrated greater efficacy in prevention than in treatment. As a result, vaccination or prophylactic infusion of an appropriate monoclonal antibody is generally more effective than antibody treatment in established disease. Second, IVIG therapy can only prevent COVID-19-related disease in individuals who require antibody supplementation when there was a high level of population immunity through vaccination and/or infection. This means there was a lag time between the acquisition of donor plasma and the appearance of relevant antibodies against SARS-CoV-2. IVIG varies in effectiveness depending on the variants in the community. Third, antibody levels to coronaviruses wane significantly within a short period of time vs other vaccine-preventable diseases.[19] This suggests that IVIG will have variable effectiveness for protection against SARS-CoV-2 and its variants, unless tailored COVID-19 vaccination becomes a regular feature of adult immunization programs.

Conclusion

IVIG remains an extremely useful tool and is the mainstay of treatment for individuals with impaired antibody production. It is essential for allergy and immunology clinicians to ensure that they thoroughly evaluate patients with frequent infections and initiate IVIG therapy for those patients with primary immune defects and the increasing population with secondary immune deficiencies. Moreover, while IVIG has had an excellent track record of both safety and efficacy, the COVID-19 pandemic has underscored several limitations of antibody therapy.

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Financial Disclosures:

None declared

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