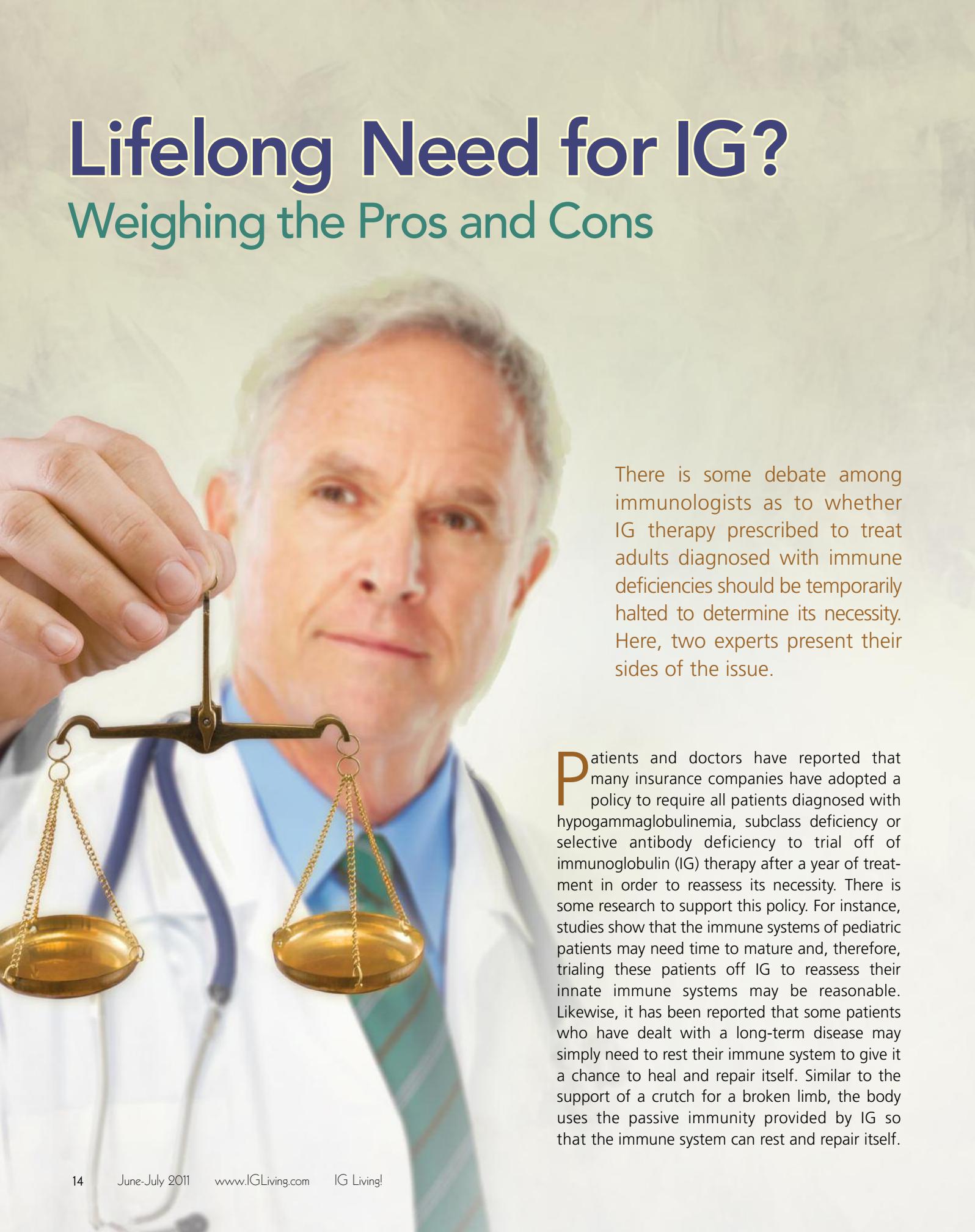


# Lifelong Need for IG?

## Weighing the Pros and Cons



There is some debate among immunologists as to whether IG therapy prescribed to treat adults diagnosed with immune deficiencies should be temporarily halted to determine its necessity. Here, two experts present their sides of the issue.

Patients and doctors have reported that many insurance companies have adopted a policy to require all patients diagnosed with hypogammaglobulinemia, subclass deficiency or selective antibody deficiency to trial off of immunoglobulin (IG) therapy after a year of treatment in order to reassess its necessity. There is some research to support this policy. For instance, studies show that the immune systems of pediatric patients may need time to mature and, therefore, trialing these patients off IG to reassess their innate immune systems may be reasonable. Likewise, it has been reported that some patients who have dealt with a long-term disease may simply need to rest their immune system to give it a chance to heal and repair itself. Similar to the support of a crutch for a broken limb, the body uses the passive immunity provided by IG so that the immune system can rest and repair itself.

Regardless, even expert clinical immunologists have a difference of opinion on the subject. Therefore, having a one-size-fits-all approach may not be in the best interest of the patient.

For this article, we invited two expert immunologists to present their analyses, pro versus con, on the issue of whether adults diagnosed with these immunodeficiency diseases should trial off IG after a period of therapy.

## Argument in Favor of Lifelong IG

By Francisco A. Bonilla, MD

Many clinical immunologists stipulate that following a correct diagnosis of antibody deficiency (or combined immunodeficiency) in adults, IgG replacement therapy should be lifelong. The reason for this is that these forms of immune deficiency are 1) genetically determined and unlikely to resolve spontaneously, 2) usually have a constant or gradually worsening clinical course over time, and 3) there is usually unequivocal evidence through experience regarding the benefit of IgG replacement for improving the course of the disease.

The most prevalent form of antibody deficiency in adults is common variable immunodeficiency (CVID), which may have its onset at any age. CVID is properly diagnosed when it is found that patients have a reduced number of two or more antibody classes (must include IgG with low IgA and/or IgM) and a clear impairment of antibody formation in response to vaccination, infection or both. In CVID patients, there are no well-described cases of resolution of the disease, and there is abundant evidence of the effectiveness of IgG therapy for reducing infections and improving other manifestations. Even after a period of relative clinical wellness, in properly diagnosed patients, it is expected that cessation of IgG therapy will result in a rapid waning of IgG levels, and a markedly increased risk of infection or worsening of chronic lung disease, etc. These complications may lead to an irreversible worsening of function that never would have occurred if therapy had not been temporarily halted, and does not return to baseline with its resumption.

Other antibody deficiency disorders in adults include X-linked agammaglobulinemia and various forms of hyper-IgM syndrome. Combined deficiencies include Wiskott-Aldrich syndrome, and additional forms of hyper-IgM syndromes, as well as others. These diseases almost always are diagnosed in childhood, but many individuals will survive into adulthood with appropriate therapy,

including IgG. Some patients may receive bone marrow transplantation in infancy for immunodeficiency. Many may fail to properly reconstitute B cell function and have persistent antibody deficiency. In all of these situations, spontaneous improvement in the course of the disease is not expected, and IgG therapy must be lifelong. Inappropriate cessation of therapy would expose these patients to the same risks described above.

Milder forms of antibody deficiency have been described in adults. These include hypogammaglobulinemia that does not meet criteria for CVID, IgG subclass deficiency with or without associated IgA deficiency and/or defects of specific antibody production, and defects of

*IgG replacement in properly diagnosed immunodeficient adults should never be discontinued.*

specific antibody production with normal immunoglobulins. These remain controversial as diagnoses of “true” immunodeficiency, and the natural histories of these “disorders” are less well-understood, and the role of IgG therapy in their management is less well-substantiated. For these reasons, many clinicians argue that IgG replacement is not indicated for these patients at all, and it should never be used. That being the case, then, IgG therapy is to be used only for those diseases described above for which therapy is expected to be lifelong, and for which interruption of therapy could be expected to have dire adverse consequences.

Thus, IgG replacement in properly diagnosed immunodeficient adults should never be discontinued.

## Argument in Favor of a Trial Discontinuation of IG Treatment

By Ricardo U. Sorensen, MD

Before discussing situations in which IG therapy may be discontinued, it is important to first consider the initial indications for IgG replacement therapy. These are largely based on the immunodeficiency with which each patient is diagnosed. If the immunodeficiency involves a deep decrease in IgG concentrations, as in agammaglobulinemia, hyper-IgM syndrome and in many patients with common variable immunodeficiency (CVID), there is little doubt that IG therapy is indicated and that there are no reasons to ever discontinue IG treatment.

*Discontinuing IG therapy should be considered only if patients have had a sufficiently long period of well-being on IG therapy.*

Second, it is important to consider the clinical severity, which refers mostly to the severity and frequency of infections. Clinical severity may vary even for some patients with agammaglobulinemia and CVID. And, an occasional X-linked agammaglobulinemic patient may have a very mild clinical course, and therefore, they may not be diagnosed until adulthood. Still, the need for treatment is rarely questioned if the patient came to clinical attention due to unusual or recurrent infections. However, some patients with CVID and many patients with immunologically milder forms of hypogammaglobulinemia need a clear assessment of their infection history as the need for IG therapy is considered.

If infections have already led to comorbidities like bronchiectasis or severe chronic sinus disease, these complications may become the strongest indication for long-term treatment, even if the immunologic severity is mild (e.g., mild hypogammaglobulinemia, IgG subclass deficiency with normal total IgG concentrations, or specific antibody deficiencies with normal immunoglobulins). Again, in these situations, IG therapy should be indicated and not discontinued.

So, when is a trial discontinuation of IG therapy warranted? There are several situations when this may be appropriate.

First, the need to continue treatment may no longer be present in patients who may have started therapy early in life. This is because the transient nature of an immune deficiency is not apparent at the time of initiation of therapy, despite a diagnosis of hypogammaglobulinemia stemming from significant infections that are affecting quality of life and the cost of medical care. Some of these patients could retrospectively be diagnosed with a transient hypogammaglobulinemia of infancy. In patients treated for hypogammaglobulinemia in the first years of life that do not have very low B lymphocytes, such as in an agammaglobulinemic patient, it is important to monitor IgM and IgA concentrations during IG therapy. Ideally, IgG trough levels also should be carefully monitored by keeping the dose of IgG per kilo and the interval of infusion constant. If the patient has improved clinically and the concentrations of immunoglobulins increase over time, a trial discontinuation of IG therapy should be considered.

There also are antibody and combined immunodeficiencies in which a limited period of IG therapy should be considered as part of the initial therapeutic plan. This includes some patients with IgG subclass deficiency and most patients with specific antibody deficiencies and normal immunoglobulin concentrations. In these patients, a limited period of IG therapy of one to two years should be planned from the start. This is recommended not so much to see if IG therapy works, since a well-designed treatment with appropriate concomitant management of infections will almost always be effective. Discontinuation of therapy is indicated because there is a reasonable expectation that, after a period of time, IgG replacement may no longer be needed.

An indication of IG therapy for a limited period of time also is almost always appropriate when IG is used as concomitant treatment for patients receiving a stem cell transplant or gene therapy. In many cases, these treatments offer a permanent cure for a primary immunodeficiency, enabling the patient to produce their own antibodies.

Another situation in which discontinuation of IG therapy should be considered is if there is an unclear indication for IG therapy when it is initiated at any age. For instance, patients may have been prescribed IG therapy without

solid evidence of an immunodeficiency or without a sufficiently documented history of infections. In these cases, patients may be re-evaluated, in some cases as a result of a request for a second opinion about the need to continue lifelong IG therapy. However, before discontinuing treatment, it would be appropriate to measure mature B lymphocytes and memory B lymphocytes by flow cytometry. If they are clearly below normal numbers, it is very likely patients will suffer from a recurrence of infections after discontinuing IG treatment. If treatment is discontinued, careful observation is advisable to avoid infections that may cause secondary damage.

In all of these situations, infections need to be monitored during IG therapy to ensure successful treatment. However, since the absence of infections is the main goal of IG therapy, this fact alone should not be an indication for discontinuation of therapy. Discontinuing IG therapy should be considered only if patients have had a sufficiently long period of well-being on IG therapy. This usually requires at least one and up to two years of treatment to allow mucosal surfaces to heal and normal clearing functions altered by recurrent or severe infections to be restored.

If no clinical improvement occurs with IG treatment, it is necessary to examine why this generally very effective therapy has failed. If failure to improve is due to an inappropriate indication for IG therapy, then it should be discontinued.

The decision to discontinue IG therapy should be made by the treating or consulting immunologist in agreement with the patient. And, each time IG therapy is discontinued, there

should be a period of at least four months prior to re-evaluating the need to restart it. The decision to restart IG therapy should be based more on the return of well-documented infections than on the depth of the immunological abnormality. This is because the presence of infections that improve on IG therapy and that return upon discontinuation of therapy is an indirect but very strong proof of a functional antibody deficiency.

## *The decision to discontinue IG therapy should be made by the treating or consulting immunologist in agreement with the patient.*

When there is a justifiable reason to stop IG therapy, it can be stopped at once, because the long IgG half-life will actually provide for a slow decrease in available circulating IgG over several months. Tapering off IG therapy by giving smaller doses of IgG or prolonging the interval between infusions is usually not done. It is recommended by many clinicians to discontinue IG therapy in the spring, when many patients experience a decreased number of infections even without treatment.

### **A Debate Among Shades of Gray**

As these two experts so expressly convey in their analyses, this issue of lifelong need for IG is far from black and white. Instead, whether pro or con, the grays in their lines of thinking come across explicitly: Determining when to treat primary immunodeficiency patients with IG must be based upon a proper diagnosis, severity of infections, patient response and the doctors' expertise.

No doubt, this debate represents just one of many differences of opinion that patients and immunologists will have concerning treatment with IG therapy. In the relatively young field of study of primary immunodeficiencies, the understanding of how and why IG treatment is and is not effective will continue to evolve. ■

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*Editor's note: This article refers to both IG and IgG. To clarify: IG is used when referring to the immune globulin therapy (the drug used to treat an immune deficiency). IgG is used when referring to the specific antibody found in the body that immune deficient patients are lacking.*