The Grey Zone between Vaccination and Immunoglobulin Treatment in Patients with Secondary Immunodeficiency (SID)

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Abstract - in this editorial, the author address current views on treatment and definition of secondary immunodeficiency a heterogeneous but growing group of patients

Key words: secondary immunodeficiency vaccination immunoglobulin treatment

Primary immune deficiencies are genetic diseases caused by more than 200 single mutations. Each one of these mutations may/will affect the function of a cell activation pathway, a single cell population or a defined subset in innate or adaptive immunity.[1,2] Patients with secondary immunodeficiencies are a heterogenous group[3], comprising different disease entities: patients with HIV, patients with cancer including systemic/metastatic disease, hematological malignancies and HSCT, as well as patients on immunosuppressive treatment.[4] Secondary immunodeficiency has also been detected in patients with chronic diseases of the heart, lung, liver, kidney [5], and in patients with diabetes, with and without chronic organ involvement.[6] A large group of secondary immunodeficiency is caused by immune-suppressive treatment in solid organ transplants, cancer chemotherapy, and patients with rheumatic disease with immune suppression.[7] All of these patients are at an increased risk for infectious complications. The impairment of immune function in patients with SID often involves different levels of the immune response. Innate and adaptive immunity, as well as T-cell or B-cell function may be affected simultaneously.[8,9] Patients with combined T- and B cell involvement may present with a phenotype of severely impaired T-cell function, even resembling severe combined immunodeficiency e.g. patients with HIV and CD4-cells <200 mm³/µl and antibody failure. Patients with severe impairment of T-cell function may develop severe viral and fungal infections and bacterial infections with microorganisms of low pathogenicity, lengthy and chronic bacterial infections.[10] The most frequently diagnosed immune impairment in different forms of SID is predominantly antibody deficiency.[11,12] this may be mild or severe, with antibody response of lower height and shorter persistence[13,14], or severe up to antibody failure to protein and/or polysaccharide antigens. Patients with predominantly antibody deficiency syndromes are especially susceptible to infections by encapsulated bacteria; they develop recurrent infections of the upper respiratory tract or present with bacteremia and severe infections, e.g. bacterial pneumonia, purulent meningitis.[15] Impairment of immune function might arise as a consequence of disease, e.g. in patients with HIV, and in patients with hematological malignancies in patients after cardiac surgery etc. Hypogammaglobulinemia is frequent in multiple myeloma, CLL, B-cell lymphoma, etc., and may be a surrogate marker for antibody deficiency in these diseases.[16]

Patients with SID are unduly susceptible to infectious complications. The patients have been characterized as being at high or low risk for infection, based on 1) immune-suppressive treatment and 2) immunological status of the host [4,17]

In the course of immune-suppressive treatment, in cancer, SOT and autoimmune disease, immune suppression might be severe or low grade. [18,19,20,21]

Ad 1: High risk for infectious complications is likely to occur in patients receiving:

- high dose cancer immune therapy
- high level immune suppression within 2 months after solid organ transplantation
- receiving daily corticosteroid therapy with a dose of ≥ 20 mg (or more than 2 mg/kg/day) of prednisone or equivalent for ≥ 14 days receiving biological immune suppressants – rituximab – or immune modulators – TNF alpha blockers.

The diagnosis of high level immune impairment will also rely on the immunological status of the host by taking the following criteria into consideration:

- CBC (complete blood count) (granulocytopenia)
- CD 4 T-cells (< 200 cells/mm³)
- serum IgG concentration (< 400 mg/dl)
- antibody assessment, including response to diagnostic vaccination. (failure to respond)

Lower risk for infectious complications with low level immune suppression:

- Those receiving lower daily dose/less 14 days of systemic corticosteroids
- Those receiving methotrexate (MTX) lower equal 0.4 mg/kg/week, azathioprine lower equal 3mg/kg/day, or 6-mercaptopurine lower equal 1.5 mg/kg/day.

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Lower degree of immune impairment of the host:
• CD 4 T-cells (> 200 mm³ (200-500 mm³))
• serum IgG level (> 400 mg/dl (400-700 mg/dl))
• antibody assessment, including response to diagnostic vaccination (antibody response decreased)

Infectious complications are second or third major cause for mortality in the individual disease entities in SID patients. Infections may be lethal, may cause recurrent infections and facilitate the development of chronic disease. It may lead to chronic organ damage causing, e.g. chronic lung disease.

Numerous studies demonstrated high/increased morbidity and mortality by infectious complications of vaccine-preventable diseases in immunocompromised populations. Several of the studies have been performed in patients with hematological malignancies and HSCT, in patients with cancer, solid organ transplants, and diabetes.[22] High increased mortality by influenza and its complications by bacterial pneumonia, but also by invasive haemophilus influenzae, have been reported. Increased numbers of severe disease with meningococcal infections and severe and prolonged Hepatitis B infections were observed.[23] Several studies demonstrated the efficacy of vaccination against influenza, pneumococcal pneumonia and bacteremia,[24] systemic disease by Haemophilus influenza b, meningococcal disease and Hepatitis B.[25] Live vaccines are contraindicated in all patients with severe (high level) immune suppression with high level impairment of immune function. Killed/inactivated vaccines have been shown to be safe in numerous studies and to reduce hospitalization, intensive-care treatment, and cost in different disease entities.[26,27] They also show a trend in reducing mortality. Even though vaccination has been shown to be effective and widely suggested in small and medium-sized studies, the patient population, especially adult patients with SID, is highly under-vaccinated (figures range between 5 and 20 % with 40 % in a single report).[28]

Results of large controlled vaccination studies in SID patients are lacking, recommendations for vaccination have still been given based on results of numerous small and medium-sized studies by several health care agencies, as well as guidelines for the treatment of individual diseases (CDC/ACIP, IDSA, etc).[4,29]

Monitoring of the immune response by measuring titers of binding antibodies (by ELISA, hemaglutination and/or bactericidal and neutralization tests) has also been suggested and performed in numerous studies[30,31]. It has also been demonstrated that partial protection by vaccination is even provided to SID patients in whom the immune response is significantly lower than in the general population. However, there is a small segment of patients with antibody failure: patients who do not mount a response, even by a 2-fold increase of antibody titers. These patients are the most susceptible for infectious disease and they cannot benefit by vaccination.

Recommendations by health care agencies, infectious disease specialists and professional experts agree to start vaccination as early as possible in the course of the disease, if possible already after initial clinical presentation, before high level immune suppression.

At present, however, severe immune suppression has to start mostly right after presentation and this treatment cannot be delayed. Vaccination is likely to be ineffective until several weeks or up to a few months after intensive chemotherapy in this population during this high level immune suppression. During this time, the patients are at highest risk for infectious complications. Diagnostic vaccination cannot be performed until several weeks to 4 to several months after treatment. In these patients, diagnostic vaccination, mainly with pneumococcal polysaccharide with a PPV vaccine, and a protein antigen, have been suggested. Yearly influenza vaccine may be used as a primary protein antigen. As monitoring of the antibody response against these vaccination antigens has been widely recommended and used worldwide, in vaccination studies in immunocompromised patients, it could also be suggested for diagnostic vaccination in SID.

Killed/inactivated vaccines are standard in the care of patients with secondary antibody deficiency. Monitoring of the vaccine response by measuring binding antibodies to vaccine antigens has been recommended. The antibody response to pneumococcal polysaccharide after vaccination with PCV and/or PPV has been recommended for immunological assessment.[32]. The response to a protein antigen in addition has been suggested/applied.[33] Vaccination with seasonal influenza and pneumococcal vaccine (PCV or PPV) are recommended as priority in guidelines for individual diseases, e.g. Diabetes Care, 2014.[34] Patients who are unable to mount an immune response, as demonstrated by sero-conversion of antibody titer >2, are the most vulnerable patients in whom immunoglobulin treatment is recommended. Vaccination of household members and medical care takers, especially against influenza and pneumococcal disease, but with all available vaccines as applied for the general population, is strongly recommended to reduce the danger of infection in this patient group. Patients with antibody failure, who do not mount an immune response to vaccination, less than a 2-fold increase in antibody titer, will be the population that has to be considered for immune globulin treatment.

While indication for immunoglobulin treatment by the WHO/UIUS Classification Group[11] in PID and SID has been based on antibody failure – after diagnostic vaccination – recommendations more recently have mainly relied on hypogammaglobulinemia or switched memory B-cells, antibody failure and recurrent infections.[35,36,37]

The question whether hypogammaglobulinemia or antibody failure are better indications for treatment with immunoglobulin, or whether clinical markers such as severe and/or recurrent infections should be taken into account, has already been raised in the 1990ies, and discussion is still ongoing. Results of a controlled study showed that antibody failure after diagnostic vaccination with pneumococcal polysaccharide vaccine correlated with severe and multiple infections.[38].

In most studies, hypogammaglobulinemia and recurrent infections were applied as criteria for immune-globulin
treatment. Diagnostic assessment of the antibody response has been recommended, but less frequently used in patients.

Ig treatment, the provision of antibodies, is the mainstay of treatment in patients with the most severe forms of primary and secondary antibody deficiency (antibody failure) who are unable to mount an immune response – seroconvert with a 2-fold increase to vaccination. These patients are at highest risk for infectious complications.

Polyclonal immunoglobulin products applied for replacement in patients with PID and SID contain antibodies with a vast variety of immunological specificities and antimicrobial function: neutralization of bacterial exotoxins, opsonization for complement-mediated lysis, opsonization for uptake/killing by phagocytes, conditioning for cell-mediated (nk-cell and/or phagocyte) killing of microbial agents or infected cells.

The protective effect of antibodies is mainly prophylactic against recurrent infections. Recurrent infections will impair the quality of life and lead to chronic organ damage, especially, but not limited to, chronic lung damage. Early diagnosis of antibody deficiency could facilitate early treatment and could thus be beneficial.

The recommended dose of immune globulin in PID and SID patients is 400 mg/kg bodyweight IVIg every 3-4 weeks, or 100 mg subcutaneous Ig weekly.

Hitzig/Imbach[39] made the observation that pediatric patients who had antibody deficiency and thrombocytopenia not only responded to immune globulin treatment with a reduction of infectious episodes, but also with a rise of thrombocytes. Subsequently, Imbach reported that pediatric patients with acute and chronic thrombocytopenia responded to immunoglobulin treatment albeit to a much higher dose to 400 mg/kg bodyweight for 5 consecutive days (2 gr/kg) with increased to normal thrombocyte counts. This immune modulatory effect is mainly related to the interaction of the Fc fragment of IgG (reacting with Fc receptors on immune cells). This first study demonstrated an immune-suppressive effect of immunoglobulin at a dose of 2gr/kg. This study paved the way for high dose immunoglobulin treatment in autoimmune diseases. The immune suppressive effect of Ig is also important in the treatment of sensitized patients in HSCT and SOT.

In addition to the immune suppressive effect of Ig, modulation of inflammation has also been demonstrated. Hyperinflammation has also been observed in patients with PID e.g. chronic granulomatous disease, inflammatory bowel disease, etc. [40,41]

Based on early studies of the 1980ies and 1990ies clinical trials with immunoglobulin treatment in patients with hematological malignancies demonstrated a significant reduction of infectious episodes and of severe and recurrent infections. Indication for immune globulin treatment in early studies was antibody failure after diagnostic vaccination with pneumococcal polysaccharide and hypogammaglobulinemia. Treatment was initiated – in different forms of hematological malignancy, such as CLL, multiple myeloma, B-cell lymphoma etc. – in patients with stable disease. Thus, the indications for immune globulin treatment are hypogammaglobulinemia and recurrent infections not only in patients with different forms of hematological malignancies, but also for SID patients in general. Accordingly immunoglobulin treatment is recommended late in the course of the disease.

Grosbois et al. reported the first results of a prospective study of patients at the beginning of immune globulin replacement relying on serum immunoglobulin concentrations and recurrent infection: immunoglobulin replacement is proposed as serum Ig concentrations of less than 5gr/l, and recurrent infections in the patient’s history. Based on the results of studies performed over 20 years ago, the objective of a French study, the EPICURE, is to assess the clinical and immunological state of the patients with hematological malignancies and SID, who just start immune globulin treatment. EPICURE is a prospective observational, longitudinal, multicenter study involving 40 French centers. Baseline data on 130 patients are reported.

The patient population aged 67 +/- 12 years with myeloma and CLL, (aggressive or indolent) non-Hodgkin B lymphoma, and other hematologic malignancies. 10 patients presented with autoimmune cytopenia, 50 patients were on anti-cancer chemotherapy, 6 were on immune-suppressants, and 34 patients have received a bone-marrow transplant. Serum Ig Levels were 5g/l of patients who had no monoclonal peak. Clinical history of the year before Ig treatment has been taken.

119 patients have a history of infection within the last 12 months, with a total 236 infectious episodes. 66 of these episodes have been severe, and led to hospitalization for a total number of 972 days. According to the conclusion, patients with SID and haematological malignancies who start Ig replacement therapy were at high risk of severe infection and most of them had a low level of IgG.

Florucesco et al discuss the impact of hypogammaglobulinemia on the rate of infection and survival in solid organ transplantation in a meta-analysis which included in 1756 patients with hypogammaglobulinemia in 18 studies[42], during the first year post-transplantation. The study included patients with kidney or heart transplants, as well as liver transplants, with both prospective and retrospective analyses of cohorts, with those who were not transplanted as disease controls, the rate of severe hypogammaglobulinenia (IgG below 400 mg/dl) was 15 %. Severe hypogammaglobulinemia at his time significantly increased the risk of CMV, fungal and respiratory infections and was associated with higher 1-year all-cause mortality as originally described by Rubin [43].

IgG hypogammaglobulinemia was associated with mortality during the first year post transplantation.[44,45,46] In a retrospective cohort of patients with 37 solid organ transplants with severe hypogammaglobulinemia and with IgL levels <400 mg/dl, the question has been asked whether increasing sero Ig levels will have an effect.

Log rank test has been used to compare survival distribution between the groups and Fischer’s exact test has been used to
determine the association between hypogammaglobulinemia and rejection. The patients ranged all from 0.7-67.3 years with a mean of 3.8 years at a time of severe hypogammaglobulinemia was diagnosed 5.6 months after transplantation. Transplants, liver – small bowel 17, liver – small bowel – kidney 2, liver 5, small bowel 4, liver-kidney 1, kidney – pancreas 3, heart 3, heart – kidney 1, heart – lung 1. The 3 year survival after diagnosis was 49.5%, patients were divided based on IgG level at last follow-up with IgG more than 400 mg/dl, 23 patients and IgG less than 400, 14 patients. There was no difference in survival in rejection rate, graft loss, and death between the two groups and the conclusion was severe hypogammaglobulinemia following SOT was associated with high mortality rates, but increasing IgG levels did not result in better prognosis when started late in the course of disease.

SUMMARY AND FUTURE PERSPECTIVE:

Infectious complications are second and third major cause of mortality in patients with secondary immune deficiency. Live vaccines are contraindicated in the severely immune suppressed, but killed/inactivated vaccines are strongly recommended by health care agencies and infectious disease specialists. Low rate of vaccination in this population poses a major problem. Different health care agencies and professional groups recommend that vaccination, as a state of care, should be applied as early in the disease as possible. In patients with antibody failure who are severely immune suppressed and who do not respond to vaccination, immunoglobulin is the mainstay of treatment.

Indication for immunoglobulin treatment in patients with SID is based on hypogammaglobulinemia and recurrent infections; e.g. in hematological malignancies and SOT, in patients with stable disease.

FUTURE PERSPECTIVE – LARGER STUDIES WILL BE NEEDED:

1) Studies will have to clarify whether antibody deficiency (antibody failure) to diagnostic vaccination is an earlier and more sensitive indication for immune globulin treatment than hypogammaglobulinemia and recurrent infections.

2) Vaccine/immunoglobulin trials based on immunological assessment and immune suppressive treatment of the patient could facilitate larger studies through the analysis of various disease entities.

3) Larger studies will be needed to fill in the gap between vaccination and immunoglobulin treatment in patients with SID.

References


