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Rational use of immunoglobulins (IVIgs and SCIgs) in secondary antibody deficiencies

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Summary

Immunoglobulins for intravenous use (IVIgs) and subcutaneous use (SCIgs) can prevent recurrent and severe infections in patients with secondary antibody deficiencies that are frequently linked to haematological/oncological malignancies as well as other clinical conditions and their respective treatments. Even so, as IVIgs and SCIgs are costly and their supply is limited, their clinical use must be optimised. The aim of this position paper is to provide structured practical guidance on the optimal use of IVIgs and SCIgs in secondary antibody deficiencies, particularly in haematological and oncological practice.

The authors agree that the occurrence of severe infections is a prerequisite for the use of IVIgs. Serum IgG levels in general as well as IgG subclass levels can be additional indicators of whether a patient could benefit from IVIgs. Responsiveness to vaccines can help to identify immunodeficiency. Patients with chronic lymphocytic leukaemia or multiple myeloma who are receiving respective treatment, especially B-cell depletion therapy, but also some patients with autoimmune diseases are prone to antibody deficiencies and need IVIgs. For the optimal use of IVIgs and to maximise their potential benefit, the indication must be individually assessed for each patient. As a primary treatment goal, the authors define a sufficient prophylaxis of severe infections, which can be supported by normalising IgG levels. If the initiated treatment is insufficient or linked to intolerable adverse reactions, switching the product within the class of IVIgs or changing to a different batch of the same product can be considered. Pausing treatment can also be considered if there are no infections, which happens more frequently in summer, but treatment needs to be resumed once infections return.

These structured recommendations for IVIg treatment in patients with secondary antibody deficiency may provide guidance for clinical practice and therefore help to allocate IVIgs to those who will benefit the most, without overusing valuable resources.

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Introduction

Immunodeficiencies are characterised by malfunctioning of the innate and/or adaptive immune system. They are classified into primary immunodeficiency diseases and secondary immunodeficiency diseases, and are associated with complications such as infections, autoimmunity and a variety of malignancies. Whereas primary immunodeficiency diseases are of mono- or polygenetic origin, secondary immunodeficiency diseases are acquired and may have a variety of causes, including haematological malignancies, metabolic disorders, infections and medical treatments [1–3].

Secondary antibody deficiency, a type of secondary immunodeficiency disease, is often multifactorial in aetiology, related to both the underlying condition and its treatment. Secondary antibody deficiencies are estimated to be 30 times more common than primary antibody deficiencies. Moreover, their prevalence is increasing, not least due to the growing number of novel therapies, especially the B-cell- and plasma cell-targeting drugs used to treat haematological malignancies [3]. Secondary antibody deficiencies are most commonly caused by haematological malignancies, such as chronic lymphocytic leukaemia (CLL), lymphoma and multiple myeloma, but they can also be associated with other conditions, such as inflammatory and autoimmune diseases. As severe infections due to secondary antibody deficiencies can be life-threatening, especially for patients with haematological malignancies and those on chemotherapy or immunotherapy, optimising the treatment and management of secondary antibody deficiencies is of broad interest among clinicians. The diagnosis and the decision on appropriate treatment should always be based on careful clinical and laboratory risk assessment and must be individualised for each patient. Cur-

rent treatment of symptomatic secondary antibody deficiencies includes a range of interventions and preventive measures, including antibiotic prophylaxis, non-live vaccines and immunoglobulins for intravenous or subcutaneous use [3].

Immunoglobulin substitution has evolved to become an important treatment option for secondary antibody deficiencies in the last few decades, especially for patients with myeloma or chronic lymphocytic leukaemia, with increasing clinical experience suggesting that many of these patients receiving immunoglobulin therapy experience fewer and less-severe infections [4–7].

However, the supply of immunoglobulins is limited, as they are derived from healthy plasma donations and their production is time-consuming, with multiple steps of fractionation, purification and strict quality control [8].

Until recently, the indication for IVIgs had formally been restricted to patients with myeloma or chronic lymphocytic leukaemia with secondary antibody deficiency and recurrent infections, excluding their wider use in the treatment of immune defects from other causes, especially drug-induced conditions due to long-term immunosuppressive medication. In 2018, the European Medicines Agency (EMA) extended the therapeutic indication of IVIgs to include *"SID [secondary immunodeficiency disease] in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either serum IgG level of <4 g/l or proven specific antibody failure (PSAF = failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines)"* [9] This label extension has been endorsed by Swissmedic for various IVIgs, meaning that today many IVIgs are approved and can be reimbursed for the treatment of secondary antibody deficiencies irrespective of the underlying cause [10]. The extension of the label is mainly based on evidence and clinical studies including patients with primary antibody deficiencies [5]. Currently, prospective clinical data from controlled trials regarding the use of IVIgs in secondary antibody deficiencies are lacking. A blueprint for an intergroup cooperative effort to address this important clinical shortcoming could be the investigator-initiated UK trial TEAMM [11].

As clinical experience shows, the use of IVIgs represents a major opportunity for patients with secondary antibody deficiencies but the potential side effects, such as infusion reactions, as well as the relatively high costs and the limited availability must be considered when allocating treatment and optimising resources. Even so, straightforward guidance on the use of IVIgs in secondary antibody deficiencies is difficult to find. Experts in immunology, haematology and oncology from Switzerland therefore met to discuss the diagnosis, treatment and management of secondary antibody deficiencies, and the appropriate role of IVIgs. The resulting position paper aims to provide practical guidance to clinicians from different specialties to optimise the use of IVIgs in secondary immunodeficiency disease and to suggest clinical situations in which IVIgs can be paused or stopped. Subcutaneous use of Ig is not explicitly discussed in this position paper but can be considered within the respective indications listed in table 1.

Methodological approach

The interdisciplinary group of authors consists of clinicians from the German- and French-speaking parts of Switzerland. These oncologists, haematologists and immunologists met to discuss the practical implications of the

Table 1:
Authorised Ig products for immunoglobulin replacement therapy in Switzerland [32–35]. Note regarding the marketing authorisation status in Switzerland for the subcutaneous administration of immunoglobulins: While Hizentra® is approved for the treatment of secondary immunodeficiency diseases irrespective of the underlying cause, subcutaneous Cutaquig® and Cuvitru® for secondary immunodeficiency disease are only indicated in the context of myeloma and chronic lymphocytic leukaemia [32–35] and subcutaneous Hyqvia® is not indicated for secondary antibody deficiency [35].

Drug	Administration	Composition	Swiss market authorisation (regarding secondary immunodeficiency disease)
Privigen® (CSL Behring)	i.v.	Human plasma protein, ≥98% IgG; IgG1 69%, IgG2 26%, IgG3 3%, IgG4 2%; Max. 25 µg/ml IgA; anti-A 1:8, anti-B 1:4	**Indications:** severe or recurrent infections, ineffective antimicrobial treatments and either a proven specific antibody failure or IgG <4 g/l. **Contraindications:** IgA-deficiency with anti-IgA-antibodies; hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (CLL) in whom prophylactic treatment with antibiotics has failed or is contraindicated; hypogammaglobulinaemia and recurrent bacterial infections in patients with multiple myeloma; hypogammaglobulinaemia in patients before and after allogeneic haematopoietic stem cell transplantation (HSCT)
Octagam® (Octapharma)	i.v.	Human plasma protein, ≥95% IgG; IgG1 60%, IgG2 32%, IgG3 7%, IgG4 1%; max. 0.4 µg/ml IgA	
Intratect® (Biotest)	i.v.	Human plasma protein, ≥96% IgG; IgG1 57%, IgG2 37%, IgG3 3%, IgG4 3%; max. 1.8 mg/ml IgA	
Klovig® (Takeda)	i.v.	Human plasma protein, ≥98% IgG; IgG1 ≥56.9%, IgG2 ≥26.6%, IgG3 ≥3.4%, IgG4 ≥1.7%; max. ≤140 µg/ml IgA	
Hizentra® (CSL Behring)	s.c.	Human plasma protein, ≥98% IgG; IgG1 69%, IgG2 26%, IgG3 3%, IgG4 2%; max. 50 µg/ml IgA. No information on isoagglutinins	**Indications:** severe or recurrent infections, ineffective antimicrobial treatments and etiher a proven specific antibody failure or IgG <4 g/l.
Cuvitru® (Takeda)	s.c.	Human plasma protein, ≥98% IgG; IgG1 ≥56.9%, IgG2 ≥26.6%, IgG3 ≥3.4%, IgG4 ≥1.7%; max. 280 µg/ml IgA. No information on isoagglutinins	Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (CLL) in whom prophylactic treatment with antibiotics has failed or is contraindicated; hypogammaglobulinaemia and recurrent bacterial infections in patients with multiple myeloma; hypogammaglobulinaemia in patients before and after allogeneic haematopoietic stem cell transplantation and SID
HyQvia® (Takeda)	s.c.	Human plasma protein, ≥98% IgG; recombinant human hyaluronidase (rHuPH20), IgG1 ≥56.9%, IgG2 ≥26.6%, IgG3 ≥3.4%, IgG4 ≥1.7%	**Indication:** primary immunodeficiency diseases and SID

extended indication for IVIgs in secondary antibody deficiency and to contribute to the creation of this paper. The roundtable took place in Zurich on 25 August 2020, with optional virtual attendance via Skype, and was chaired by the first author (JSG). Participation was based on an invitation to physicians from the mentioned disciplines with experience in IVIg and SCIg therapy; we make no claims as to completeness.

The subsequent manuscript, created with the help of a medical writer (J. Keim, Iaculis GmbH) involved two feedback rounds with the authors, as well as substantial feedback and critical discussion from two initially non-participating experts (NK), who contributed to the discussion of the second manuscript from the infectious disease expert position and ATP, a haematologist, who contributed the haemolysis paragraph and more detailed product information resulting in a consensus for the next version. The literature search and further writing from then on was the sole responsibility of the authors, led by JC and FS. The final manuscript reflects, to our mind, a representative consensus opinion of the respective authors on the current practice of IVIg and SCIg use in Switzerland. It does not fulfil the requirements of formal guidelines but provides structured recommendations from the authors, based on their clinical experience, on the use of IVIgs to treat secondary antibody deficiencies.

Identification of patients who can potentially benefit from IVIgs

To identify patients who can potentially benefit from IVIgs and to optimise the use of IVIgs in clinical practice, several parameters, including the occurrence of infections, serum IgG levels and response to vaccination, can be assessed. The authors suggest a treatment algorithm that can aid clinical decision-making, which is summarised in figure 1 and described in more detail below.

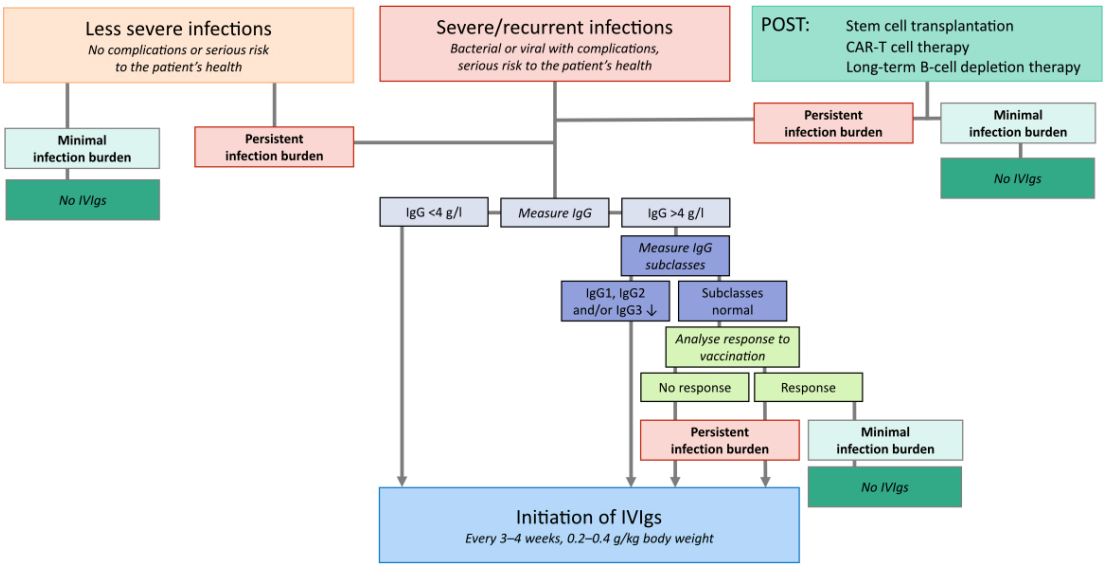
Infections

The authors agreed that the most obvious and important reason why patients with secondary antibody deficiencies would potentially benefit from IVIgs is the presence of recurrent and, most importantly, severe infections with serious complications. According to a recently published European expert consensus paper on the topic, recurrent infections can be defined as at least three infections in a 12-month period despite appropriate anti-infective treatment. Furthermore, an infection can be regarded as severe if it requires an acute i.v. intervention, immediate or prolonged hospitalisation, or emergency intensive care [12]. In the recommendations presented herein, we decided to use the term severe infections to refer to infections leading to complications or posing a serious risk to the patient's health. In addition to assessing the occurrence of recurrent severe infections, the authors recommend evaluating the overall clinical status of the patient and the respective psychological stress when deciding which patients would be good candidates for IVIgs. Secondary antibody deficiency-related infections can be of bacterial or viral origin and mainly affect the upper and lower respiratory tract. In patients with secondary antibody deficiencies, IVIgs are commonly prescribed after two or more infections or after the first severe infection.

IgG levels

Most importantly, if a patient does not have an infection, IVIgs are not indicated, irrespective of serum IgG levels. In the case of recurrent infections, however, serum IgG levels can be an additional marker indicating whether a patient could benefit from IVIgs. Even though IVIg label specifications define IgG levels below 4 g/l as the threshold for the use of IVIgs, there are patients with Ig levels below this threshold who do not show infections and therefore do not need IVIgs; conversely, there are patients with IgG levels above 4 g/l who have serious infections. In patients with extremely low IgG levels (<2 g/l), especially

Figure 1: Selecting patients suitable for IVIgs. A treatment algorithm that can aid clinical decision-making. Severe infections were those leading to complications or posing a serious risk to the patient's "health", e.g. infections requiring an acute i.v. intervention, immediate or prolonged hospitalisation, or emergency intensive care [12]. Recommendations are based on the authors' clinical experience.



in combination with extremely low IgA levels, initiation of IVIg substitution should be considered on an individual basis to prevent a first severe and potentially life-threatening infection. This is in line with the American Society for Transplantation and Cellular Therapy (ASTCT) consensus recommendations for CAR-T treatment [13].

In patients with normal IgG levels and recurrent severe infections, determining the levels of the individual IgG subclasses IgG1, IgG2 and IgG3 can be revealing. IgG subclass deficiency is typically diagnosed when one or more IgG subclass levels are two standard deviations below the age-adjusted range in patients with normal total IgG levels [14, 15]. IgG1 and IgG3 production are induced by exposure to soluble and membrane protein antigens. IgG2 plays an important role in the response to bacterial capsular polysaccharide antigens. The clinical significance of subnormal IgG4 subclass, if any, is unclear. Patients with IgG subclass deficiency with infections might benefit from IVIgs [16].

Preventive measures

Substitution of Igs in patients with Ig deficiencies could potentially be prevented or its frequency could be reduced by sufficient preventive measures. Not least for resource-saving purposes, sufficient vaccination should be offered to all patients at risk. By analogy with the evidence of patients with multiple myeloma**,** who have a minimum NCCN (National Comprehensive Cancer Network) level of 2b, physicians caring for patients with Ig deficiencies should promote all indicated immunisations, particularly those for seasonal influenza viruses. Passive immunisation should be considered in patients with Ig deficiencies after exposure with hepatitis A, varicella or measles and active immunisation with varicella zoster vaccine where indicated, regardless of vaccination status (NCCN level 2b). For best use of vaccinations, outside the scope of this paper, please refer to Kroger A, et al. (Best Practice Guidelines for Immunization, https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/intro.pdf, accessed on 5 May 2024). Alternatively, the recommendations of the Federal Office of Public Health (FOPH) can serve as a reference in this regard [40].

Prophylactic antibiotic therapy is not recommended for patients with Ig deficiencies; however, early use of antibiotics in infections in these vulnerable populations should be considered and ideally discussed with an expert in infectiology.

Response to vaccination

Bacterial antigens are either proteins or complex polysaccharides. When evaluating suspected immunodeficiency, responsiveness to vaccines containing each distinct type of antigen should be assessed separately. Depending on the immunological defect present, a patient may respond poorly to one or both types.

The polysaccharide pneumococcal vaccine is usually used to assess the response to polysaccharide antigens, which requires functional B-cells only. The response to pneumococcal vaccines can be analysed with two consecutive standard serology assays. Protein vaccines, such as tetanus, are the most common vaccines used to evaluate the antibody-mediated response to protein antigens. Responses to protein antigens require intact B and T cell function. An adequate immune response is demonstrated if at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines is measured after four weeks. It is important to consider that potential co-medication, such as chemotherapy in haematological conditions, can affect the response to vaccination. However, in the case of continuous co-medication, the response to vaccination would partially reflect the patient's clinical situation.

Pathological conditions and respective treatments that are typical for patients needing IVIgs

Based on their clinical experience, the authors have identified patient populations that are more likely to require IVIgs to a certain extent. Table 2 contains an overview of these treatment groups. Table 1 summarises the available products for immunoglobulin replacement therapy in Switzerland and their respective indications.

Patients with haematological malignancies

Patients with chronic lymphatic leukaemia (CLL) or multiple myeloma (MM) are at an increased risk of developing secondary antibody deficiencies and are therefore more vulnerable to infections [17, 18]. Consequently, IVIgs are frequently indicated to prevent infections in these malignancies, but their use should be considered on an individual basis. Over 30 years ago, a study demonstrated that administering IVIgs to patients with CLL, hypogammaglobulinaemia or a history of infection significantly lowered bacterial infections over one year compared to those treated with a placebo [6]. In the more recent German prospective non-interventional SIGNS study, including 307 patients with secondary immunodeficiency disease due to CLL, multiple myeloma, indolent lymphoma or other malignancies, immunoglobulin treatment was associated with a decrease in overall infection rates and improved quality of life. Additionally, IVIgs were reported to have very good tolerability [18]. Besides a reserved use of immunoglobulin replacement therapy in CLL, the European Society for Medical Oncology (ESMO) practice guidelines recommend restricting the use of immunosuppressive agents, e.g. corticosteroids [19].

For patients with multiple myeloma the European Myeloma Network (EMN) has defined a small subset with an immunoglobulin replacement therapy indication. This subset encompasses: patients with a high tumour burden, sepsis with organ dysfunction (neutropenia or renal failure) [20].

Both guidelines (ESMO and EMN) limit immunoglobulin replacement therapy to patients with serum IgG concentrations below 400 mg/dL and who have severe and recurrent infections by encapsulated bacteria (or other pathogens reasonably thought to be due to hypogammaglobulinaemia), despite appropriate antimicrobial prophylaxis and immunisation (NCCN level 2A) [19, 20].

According to the clinical experience of the authors, patients with Hodgkin's lymphoma hardly ever need IVIgs, whereas they are frequently administered to patients with Burkitt's lymphoma.

Generally, the type of treatment rather than the pathological condition itself is considered to affect the severity of immunodeficiencies. Based on clinical experience, pa-

tients who undergo long-term B-cell depletion therapies often require IVIgs. Some patients with follicular lymphoma who receive rituximab as a long-term maintenance treatment may be at risk of developing secondary antibody deficiencies. Additionally, the use of cladribine and fludarabine, or a combination of fludarabine and rituximab, can lead to significant and lasting secondary antibody deficiencies.

There is also some, probably non-representative, clinical experience with patients treated with the tyrosine kinase inhibitor (TKI) ibrutinib. Even though IgG levels are often low during ibrutinib treatment, most patients do not develop infections and therefore do not require IVIgs. This could imply that ibrutinib and other tyrosine kinase inhibitors might be less immunosuppressive than classic chemo-immunotherapies. However, serious infections have been reported for ibrutinib [21] and should be considered when treating and monitoring patients taking Bruton's tyrosine kinase inhibitor (BTKi).

For patients on the BCL2 inhibitor venetoclax, the clinical experience is limited but may be like that of ibrutinib. It is worth noting that ruxolitinib, a JAK1/2 inhibitor, displays significant immunosuppressive capabilities and carries a heightened risk of infections [22]. In summary, patients un-

Table 2:
Therapies associated with secondary antibody deficiencies and the resulting potential benefit forIVIgs. Recommendations by the authors based on clinical evidence. Level of evidence (LoE).

Treatment	Mode of action	Examples	Potential benefit for IVIgs	Comments / recommendations by the expert panel
Anti-B-cell monoclonal and *bispecific* antibodies	Deplete B-cells or plasma cells*	Rituximab (a-CD20)	Often (symptomatic hypogammaglobulinaemia in patients receiving rituximab that prompts immunoglobulin replacement therapy is 6.6% LoE 3 [36]; Bispecific antibodies in multiple myeloma hypogammaglobulinaemia in 34 (87%) patients, immunoglobulin replacement therapy needed in 18 (53%) LoE 3 [37])	Depends on the dosage, the treatment duration and respective concomitant immunosuppression.
		Belimumab (a-BlyS/BAFF)		
		Blinatumomab (a-CD3/CD19)		
		Glofitamab (a-CD3/CD20)		
		*Daratumomab** (a-CD38)		
		*Teclistamab** (a-CD3/BCMA)		
Tyrosine kinase inhibitors	Inhibit B-cell proliferation and survival	Imatinib	Rarely	
		Dasatinib		
		Ibrutinib		
		Bosutinib		
		Nilotinib		
		Asciminib		
BCL-2 inhibitors	Induce apoptosis of B-cells	Venetoclax	Occasionally	
Janus kinase inhibitors	Modulate cytokine response and proliferation factors	Ruxolitinib	Rarely (increased infectious risk for herpes zoster 8%, bronchitis 6% and urinary tract infections 6%LoE 3 [22])	
Purine analogues	Supress T-cells and B-cells	Azathioprine	Rarely	
		Fludarabine	Occasionally	
		Cladribine		
CAR-T	Suppress B-cells	Tisagenlecleucel (Kymriah®)	Kymriah® (Hypogammaglobulinaemia 45% in ALL patients. 15% in DLBCL patients; immunoglobulin replacement therapy in 19% (DLBCL) [38])	
		Axicabtagen ciloleucel (Yescarta®)	Yescarta® (11% hypogammaglobulinaemia prolonged hypogammaglobulinaemia 6%; immunoglobulin replacement therapy in 16.5% [39])	
Alkylating agents	B-cell and T-cell death	Cyclophosphamide	Rarely	
		Chlorambucil		
		Melphalan		
Anticonvulsants	Arrested B-cell development	Carbamazepine	Rarely	
		Valproate		
		Phenytoin		
		Lamotrigine		
Autologous and allogeneic stem cell transplantation (SCT)	Replenishment of blood cells		Occasionally (but routine prophylaxis is not recommended. LoE 1 [13])	More frequent if SCT is due to haematological malignancies than due to solid tumours. Revaccination after stem cell transplantation.
BTKi	Suppress B-cells	Ibrutininb	11.4% serious infections in the 1st year, 14% of these patients died [21]	The risk of fungal infections appears to be increased
		Acalabrutinib		
		Zanubrutinib		
		Pirtobrutinib		
Other		Clozapine	Rarely	Long-term steroid therapy in combination with other immunosuppressive drugs may be an indication for IVIgs.
		Steroids		
		Methotrexate		
		Mycophenolate		
		Hydroxychloroquine		

der chronic tyrosine kinase inhibitor treatment should be carefully monitored for infections and have their Ig levels measured at reasonable intervals.

Based on clinical experience, patients who undergo CAR-T cell therapy often have low levels of lymphocytes and IgG, yet they do not frequently experience infections. However, long-term data are so far limited, as CAR-T cell therapy has only recently become available in clinical practice. It should therefore be carefully considered in these patients whether the administration of IVIgs is necessary, and management should be focused on prophylactic treatment, e.g. with cotrimoxazole, acyclovir or valacyclovir. Furthermore, patients with haematological malignancies may require IVIgs following autologous or allogeneic stem cell transplantation [23].

Patients with solid tumours

Patients with solid tumours are generally considered to need IVIgs less frequently, as they are usually prone to infection only during chemotherapy and not after the completion of their treatment. Even patients with testicular cancer who undergo high-dose chemotherapy along with autologous stem cell transplantation generally have a good recovery rate, and therefore, may not require IVIgs.

Patients outside of haematology and oncology

Outside of haematology and oncology, there are conditions in which patients are also prone to develop secondary antibody deficiencies. The following paragraph intends to give a concise summary of these conditions, but it does not claim to be comprehensive. In autoimmune disorders, including vasculitis and collagenosis, the rate of secondary antibody deficiencies seems to be low in patients who are treated with conventional disease-modifying drugs such as methotrexate, azathioprine, mycophenolate and hydroxychloroquine. However, repeated courses of anti-CD20 treatment in combination with glucocorticoid therapy or other immunosuppression/chemotherapy, older age and pre-existing hypogammaglobulinaemia are risk factors for developing hypogammaglobulinaemia. In addition, individuals with autoimmune conditions who take steroids and other immunosuppressive medications over an extended period are at a higher risk of developing secondary antibody deficiencies. It is possible that prolonged exposure to low doses may have had an impact on B-cells and resulted in a deficiency in immunoglobulins. Assessing baseline serum IgG, IgA and IgM levels and peripheral lymphocyte counts (B-cells) prior to the initiation of anti-CD20 therapy, during long-term treatment and after treatment is recommended. It is worth noting that patients who are taking anticonvulsants may require IVIgs.

Overall, the authors conclude that most patients who need IVIgs have haematological/oncological or autoimmune diseases and receive the respective treatments.

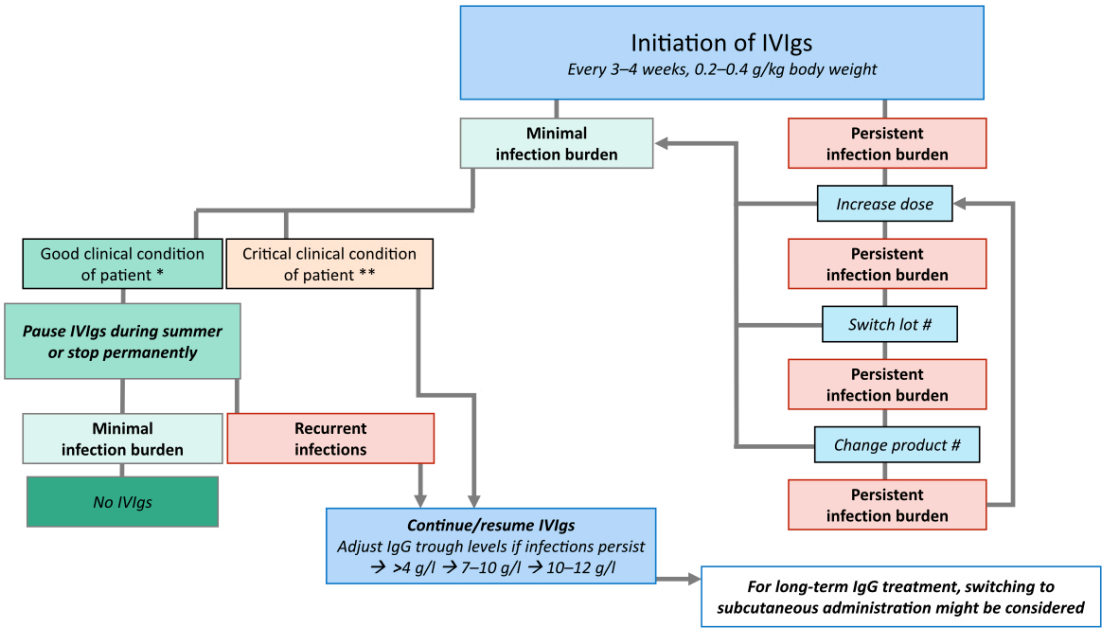
Treatment goals and management of IVIgs

To optimise the use of IVIgs, defining treatment goals as well as adequate therapeutic management concerning the choice of product, dosage, administration and potential side effects are of great importance. The authors' recommendations are illustrated in figure 2 and described below.

Treatment goals

The primary goal of treating patients with IVIgs is to prevent infections. Therefore, the dose as well as the administration route and frequency should be optimised for each patient individually to maintain acceptable plasma IgG levels and a substantial reduction of infection rate. IgG levels in the range 7–10 g/l are desirable, lower IgG levels in the

Figure 2: Management of IVIg therapy. Recommendations are based on the authors' clinical experience. * e.g. therapy-free and in remission; ** e.g. receiving immunosuppressive therapy and prone to complications; # also in case of adverse events if lowering the dose/infusion rate or premedication do not help.



range 4–7 g/l or even <4 g/l are acceptable if there are no infections.

Treatment optimisation

If infections still occur with normal IgG levels (>4 g/l), trough levels of IVIgs can be increased, first to 7–10 g/l and, if infections persist, to 10–12 g/l. All IVIgs should be considered as individual therapies and switching from one product to another is an option in situations where inefficacy or resistance is clinically suspected or likely [24, 25]. Based on their clinical experience, the authors agree that switching products within the class of IVIgs and switching to a different batch of the same product can both be considered if infections continue to occur.

Practical implications of administering IVIgs and managing adverse reactions

The suggested treatment interval for IVIgs in secondary antibody deficiency is three to four weeks and the suggested dose is 0.2 to 0.4 g/kg body weight. In general, no premedication is required. Patients who have adverse reactions to the infusion can be treated with premedication, such as paracetamol or antihistamines. Steroid treatment is not recommended unless there is a serious reaction. Furthermore, IVIgs should be administered slowly, and the infusion should be interrupted if necessary. First administrations can take place in the ambulatory setting. According to some of the authors, the first treatment should preferentially be given early in the morning, and the administration rate should initially be slow. To shorten the duration of the first treatment, administering a lower starting dose can be considered. If the treatment is well tolerated, dose and rate can be increased at the next session. However, it must be taken into consideration that even if the first administration is well tolerated, there is no guarantee that this will also be the case for subsequent administrations, due to batch-to-batch variability of IVIgs. In the event of adverse reactions, changing to a different batch of the same product or changing the product within the IVIg class can also be considered. If long-term immunoglobulin treatment is needed, switching from intravenous to subcutaneous administration (subcutaneous Ig can be self-administered by the patient at home) may be an option, taking the patient's preferences into consideration.

Clinical situations that require cautious use of IVIg and potentially repetitive small doses are for example increased blood viscosity, unstable angina pectoris, renal insufficiency, uncontrolled hypertension and thromboembolic disorders.

IVIg-associated haemolysis

IVIg administration may result in mild and usually self-limiting haemolytic reactions. In rare cases, significant haemolysis due to ABO blood group antibodies (isoagglutinins) contained in the product can occur as a serious complication of IVIg use and may result in renal and multiorgan failure and even death.

In clinical trials and observational studies, the incidence of IVIg-associated haemolysis ranged from 0 to 20% [26].

Factors associated with haemolysis frequency are:

- IVIg doses: higher frequency with high IVIg doses, i.e. >2 g/kg, as in the context of autoimmune disorders [27], low incidence in doses as applied in the context of antibody deficiency (<0.5 g/kg); one trial reported a frequency of 3.7% [28].
- ABO blood group: higher frequency for blood groups A and AB, less frequent for blood group B [13, 29].
- IVIg preparation methods: IVIg are derived from large human plasma pools, evidently comprising donors with very variable isoagglutinin titres. Most modern Ig manufacturing processes consist of precipitation and chromatographic steps to separate IgG from albumin and increase IgG purity, followed by additional purification steps to remove isoagglutinins from the product. The majority of reported haemolytic events occurred with IVIg products produced by ethanol-octanoic acid (OA) fractionation given at a high dose (≥2 g/kg). Only a few haemolytic events have been reported when products produced by Cohn fractionation, ethanol-PEG, immunoaffinity chromatography (IAC) and ethanol-OA plus IAC were applied [26, 30, 31].

Patients treated with IVIg should be monitored for signs of haemolysis and, in case haemolysis occurs, treatment interruption and product switch should be considered. According to the European Pharmacopoeia, the anti-A titre in IVIg preparations may at a maximum be 1:64. At the time of writing this article, anti-A content of the respective products in the vendor's product information were for Privigen® 1:8 (1 Oct 2016 – 30 Apr 2019). This was a reduction from 1:32 (1 Jan 2008 to 31 Dec 2021) by exclusion of donors with high anti-A titres and a refined isoagglutinin A and B reduction process by immune affinity chromatography (IAC). Data regarding anti-A/B reduction and titres for Octagam (10%)®, Intratect® and Kiovig were unavailable [32–35].

Treatment duration, interruption and discontinuation

In the absence of infections, pausing the administration of IVIgs over the summer months (April–October in the Northern hemisphere) can be considered. This decision should depend on the individual risk situation of the patient, which must be carefully and repeatedly assessed. If infections recur, IVIgs should be reinitiated. In some patients with lymphoma and secondary antibody deficiencies, B-cells might recover after stopping treatment when the patient is in long-term remission: in these patients, IVIgs can be stopped.

Discussion and conclusions

IVIgs play a crucial role in assisting patients with secondary antibody deficiencies by substantially elevating their IgG levels, reinforcing their immune response, and efficiently averting infections. This is reflected by the relatively broad indication for the use of IVIgs that has been implemented by the EMA and endorsed by Swissmedic. The effectiveness of IVIgs in treating secondary antibody deficiencies varies due to the diverse patient profiles and the numerous possible underlying causes. The high costs, the limited availability and an expected increasing worldwide demand for IVIgs derived from the plasma of healthy donors make optimal use of this symptomatic treatment

a necessity. This necessity became especially evident and important during the global COVID-19 pandemic.

The objective of this paper is to offer practical guidance to physicians from diverse fields based on the interdisciplinary clinical experience of the authors with IVIgs.

When making the decision on whether to administer IVIg treatment to a patient with secondary antibody deficiency, it is crucial to carefully consider if any severe infections have negatively impacted their overall health and wellbeing. Patients who are susceptible to infections should be recommended IVIg treatment. This usually applies to individuals undergoing treatment for haematological/oncological conditions, occasionally for those with autoimmune disorders and rarely for those with solid tumours. When making the decision to use IVIgs, it's important to consider the levels of both IgG and IgG subclasses. If there are any doubts about whether there is an indication for IVIgs in a patient, their response to vaccination can be analysed. When deciding to use IVIgs, it is important to adjust the starting dose and administration rate based on the individual's tolerance. If a patient experiences adverse reactions to an IVIg infusion or if the initially chosen product does not produce the desired effect, switching to a different IVIg product or batch may be helpful. For patients with a lower risk of infection, such as those with post-treatment CLL in long-term remission, stopping IVIgs may be an option, but treatment should be resumed if recurrent infections occur. The treatment of various secondary immunodeficiency disease patients is continually improving through clinical experience, and it is vital to have interdisciplinary discussions to establish the best criteria for using IVIgs.

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