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A personalized approach to choice-making of an immunoglobulin for the replacement therapy in patients with primary immunodeficiency – is the way to success

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ABSTRACT. Immunoglobulin replacement therapy is the most important treatment for the majority of Primary immunodeficiency (PID) forms. It is very important not only to prescribe replacement therapy, but also to choose the appropriate one according to individual patient's needs at the very moment. Furthermore, in reallife clinical practice some comorbid conditions, which can occur in patient, necessitate the choice of a specific drug from a wide range of IVIG preparations presented on the Russian pharmaceutical market.

Keywords: primary immunodeficiency, PID, replacement therapy, IVIG

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Персонифицированный подход – основа успеха при выборе препарата для заместительной терапии у пациентов с первичным иммунодефицитом

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РЕЗЮМЕ. Заместительная иммунотерапия препаратами иммуноглобулина человека нормального – это основа терапии большинства форм первичного иммунодефицита (ПИД). Очень важно не только назначить заместительную терапию, но и правильно подобрать дозу, исходя из индивидуальных потребностей пациента на текущий момент. Кроме того, в реальной клинической практике мы довольно часто сталкиваемся с ситуаций, когда некоторые коморбидные состояния обусловливают необходимость выбора конкретного препарата из широкого спектра иммуноглобулинов для внутривенного введения – внутривенных иммуноглобулинов (ВВИГ), представленных на российском фармакологическом рынке.

Ключевые слова: первичные иммунодефициты, ПИД, заместительная иммунотерапия, ВВИГ

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Primary immunodeficiencies (PIDs) are a group of congenital diseases of the immune system which includes more than 400 nosologies associated with loss, decrease or incorrect function of one or several its components [1–4]. It is a very heterogeneous group: each form has its unique spectrum of signs and different age of symptoms manifestation. Combining feature of most forms of PIDs is a presence of relapsing infections, mainly those of sinopulmonary tract [5]. A typical feature of infectious processes is torpidity to standard schemes of antibiotic therapy and absence of predisposing factors for occurrence of severe infections (e.g., smoking, unfavourable work conditions) [6]. The therapy of many forms of PIDs is based on replacement therapy with normal

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human immunoglobulin [3]. This is blood product that mainly consists of immunoglobulin G (IgG) obtained from plasma of large number of healthy donors. The main objective of replacement therapy is to achieve control over infectious processes. Trough level of IgG with target values not less than 700–800 mg/dL is used as a "surrogate" marker of therapy efficacy [7].

The importance of replacing normal human immunoglobulin products in patients with PID is stressed by the fact that they are listed in the List of Essential Medicines for Children and Adults by the World Health Organization (WHO) [8]. Moreover, placebo-controlled studies of these medicinal products are recognized as impossible due to ethic reasons [9].

Normal human immunoglobulin products are classified by the route of administration:

• Intramuscular normal human immunoglobulin (IMIG);

• Intravenous normal human immunoglobulin (IVIG);

• Subcutaneous normal human immunoglobulin (SCIG).

At present, IMIGs are not recommended for use in patients with PID because of inefficacy due to inactivation at administration site and low systemic bioavailability and due to high frequency of side effects. Besides, intramuscular products do not allow achieving necessary blood IgG level [10, 11].

SCIGs appeared on the pharmacological market relatively recently and have already proved themselves to be safe and effective products for patients with PID. Unfortunately, they are not widely used in Russia [12]. The greatest experience has been accumulated for IVIGs in patients with PID, therefore, this article will be focused on these very products.

Recommended dose for replacement therapy with IVIG for patients with PID is 0.4–0.8 g/kg of body weight once per 3–4 weeks [3, 13–18]. Meanwhile, the prescription of IVIG products at higher doses (0.6–0.8 g/kg of body weight) may be necessary in therapy initiation, after more than 3-month breaks in replacement therapy, during epidemically significant infectious episodes, if there is concomitant abnormality and/or complications which result in protein loss (bronchiectases, enteropathy, nephrotic syndrome) [16, 19].

The first IVIG products appeared in the 1960th. These products had a number of significant disadvantages. First of all, IgG molecules were split in manufacture (Fc fragment was either inactivated, or deleted, this technology leads to decreasing the product efficacy). However, it became later clear that Fc fragment is of not less importance than Fab to achieve effective protection against infectious agents. Secondly, the first products had low degree of purification, high level of IgA. Moreover, these products were not safe from the point of view of transmission of transmissive infections which caused special concerns in the context of administration in patients with PID. The manufacture procedure modified storngly during the following 60 years, by introduction of new steps which allowed to increase efficacy, safety and usability of IVIG products. The main landmarks in the IVIG evolution are as follows: use of new stabilizers, implementation of additional for virus inactivation, increased standards of purification degree of IVIG products, achievement of functional activity of IgG molecule (due to preserved both Fab and Fc fragments). Today we deal with modern generation of IVIG which have high efficacy, safety and tolerance profile. Meanwhile, modern manufacturers are in continuous search for additional abilities to increase the quality of their products (Table 1) [20].

Table 1. Evolution of IVIG products

Generation	Manufacture methods	Particularities
Generation 1 (1960-ies)	Enzymatically (pepsin and plasmin) and chemically (alkylation) modified IgG without functional Fc fragment (with the objective to improve tolerance).	Low efficacy of products
Generation 2 (1970-ies)	Amino acids and carbohydrates are used as stabilizers	• Intact molecule of IgG • Fc fragment activity 70–75% • Low degree of purification • High level of IgA
Generation 3 (1980-ies)	New steps for virus safety were introduced in the manufacturing process for the first time	High purity full activity of Fc fragment, high degree of virus safety
Generation 4 (1990-ies - present)	Increased standards of products manufacturing Appearance of products which may be stored at room temperature Occurrence of more concentrated solutions (10 %)	High content of IgG with normal distribution into subclasses, monomer and dimer content of more than 95%. Activity of Fc fragment of IgG close to 100%. The products are produced by use of multi step scheme of virus activation which includes not less than two independent methods (processing with solvent-detergent + incubation at low pH or pasteurization in combination with processing with polyethylene glycol)

At present, there is wide choice of IVIG by different manufacturers. A wide spectrum of different IVIGs has been registered in the Russian Federation:

- Octagam and Octagam 10% [21, 22];
- Gabreglobine IgG [23];
- Gamunex C [24];
- I.G. Vena [25];
- Imbioglobulin [26];
- Immunovenin [27];
- Normal human immunoglobulin [28];
- Intratect [29];
- Privigen [30];
- Sigardis and Sigardis-MT [31, 32];
- Flebogamma [33].

Normal human immunoglobulin products by different manufacturers cannot be considered as equivalent and are not generic. They are comparable in respect of efficacy, however, have differences caused by the manufacturing process (different populations of donors, distribution of IgG subclasses, level of IgA, stabilizers, pH, viral safety and other characteristics) which determine the safety and tolerance. To achieve the best treatment result, normal human immunoglobulin product should be selected based on patient's individual particularities [17, 18, 34, 35].

Despite significant alleviations in the methodology of clinical studies of IVIG, their manufacturing process as well as composition are clearly regulated by the WHO, only compliance with these requirements may guarantee treatment safety and efficacy. Data on compliance with the requirements set by the WHO should be reflected in the prescribing information, efficacy and safety should be confirmed with the results of clinical trials performed in compliance with Good Clinical Practice (GCP) [9, 36–40]. A number of products marketed in Russia do not comply with the WHO's requirements (regarding both manufacturing process and information on IVIG product).

As specified above, despite of common indications, IVIG products have serious differences. One of the most important features of the IVIG product is variability of antibodies. According to WHO, plasma from not less than 1000 donors should be used for normal human immunoglobulin production [40]. Compliance with this rule guarantees that the product contains sufficient variability of antibodies to assure effective protection against wide spectrum of infectious agents [41]. It should be noted that donor population plays an important role as well. The spectrum of encountering infections depends on climatic zone of residence and may differ significantly. Product by Chinese manufacture (Sigardis and Sigardis-MT) have been actively launched to Russian market. The donor's blood which is used by the company to prepare immunoglobulin product are residents of Chinese province Szechuan. This province is in the south of China, in subtropic climatic zone where the structure of infectious morbidity and therefore spectrum of antibodies in donors' blood differ from midland and north of the Russian Federation. The era of evidence based medicine requires confirmation of efficacy and safety of these products in patients with PID who live in Russia with comparative studies.

One of the most important efficacy characteristics of IVIG products is IgG level which should not be less than 95% (with the content of IgG dimers and monomers not less than 90%). The distribution of IgG subclasses should be specified in the prescribing information and comply with that physiological values. Today, not all IVIG products reflect these data in the prescribing information (Imbioglobulin, Immunovenin, Normal human immunoglobulin) [26–28], therefore, it is very difficult to foresee treatment efficacy since the above dosage regimen with IVIG has been developed with a view that manufacturers guarantee compliance with the requirements [40].

Switching from IVIG efficacy questions to safety aspects, it should be noted that safety and tolerance of IVIG depend on qualitative elimination of pathogens and removal of impurities which may cause the side effects. Taking into account that all normal human immunoglobulin products are blood products, they are associated with the risk of transmission of infections, thus, WHO's compulsory requirement is virus safety assurance [40]. This parameter has been also highlighted by Russian allergists-immunologists (Figure 1) as the most priority feature in choice of IVIG (the survey was performed on independent platform for anonymous voting "survey monkey" and included 86 respondents of the members of Russian Association of Allergists and Clinical Immunologists prescribing therapy with IVIG).

During manufacture process of modern IVIG products they undergo complex multi-step process to achieve virus safety (Figure 2). At step 1, the selection of donors includes physical examination and collection of history to exclude donors with risk of infectious diseases. Step 2 is the examination of each donation for HIV, hepatitis B and C viruses using valid laboratory tests. All samples with confirmed presence of at least one pathogen are excluded from further manufacture. At the third step, the whole plasma pool is tested before the manufacturing process starts. To achieve effective elimination of virus, not less than 3 steps of inactivation and elimination of viruses are used, which differ in different manufacturers. Used methods should be effective against both enveloped viruses (e.g., HIV, hepatitis B virus, hepatitis C virus) and non-enveloped viruses (e.g., parvovirus B19, hepatitis A virus) [41]. Product batches are multiply tested for virus safety during the whole manufacturing process.

In the setting of patients with PID, parvovirus B19 requires special attention, since it is able to cause severe hematopoiesis aplasia which may be fatal complication in patients with PID [42–44]. Some products (e.g., normal human immunoglobulin and imbioglobulin) do not declare safety of their products for this pathogen in

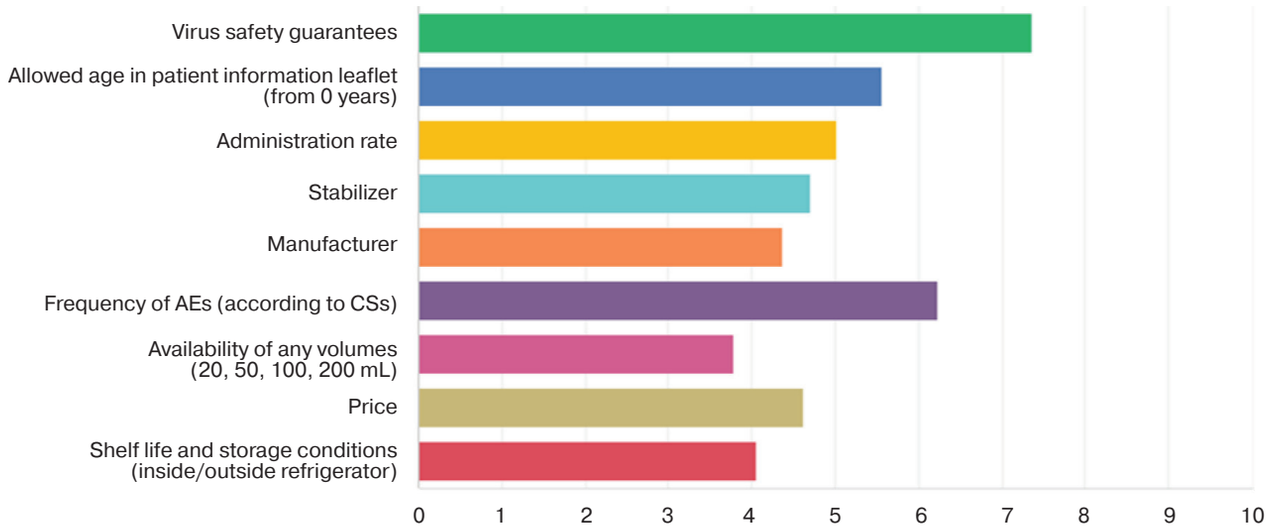

Figure1. The most important IVIG characteristics (the survey «Primary immunodeficiency. The usage of IVIG» of 86 RAACI members)

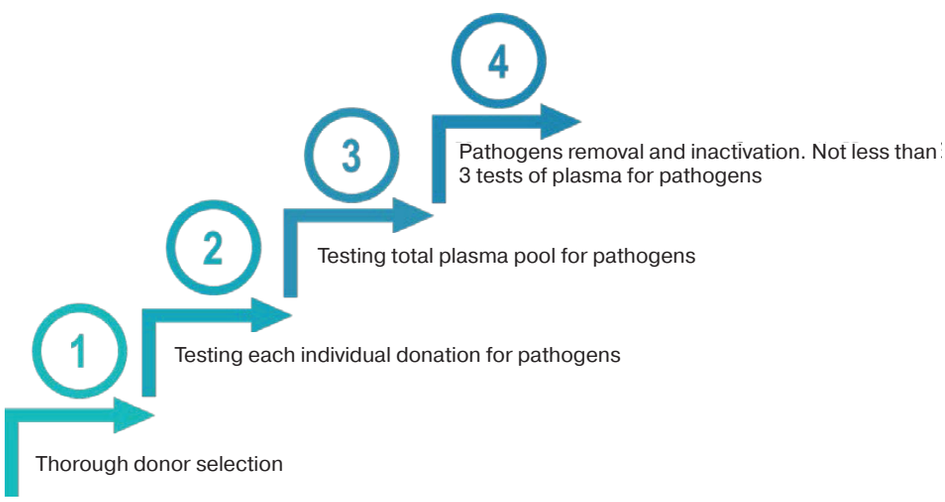

Figure 2. Steps of virus safety assurance in modern normal human immunoglobulins

their prescribing information [26, 28]. Use of such IVIG in patients with PID is undesirable since it may cause irreparable harm to patients' health [40].

Occurrence of new potential life-threatening virus infections (Zika virus, SARS, MERS, SARS-COV2) determine the need for plasma pool control taking into account new viruses to assure sufficient degree. Taking into account that these infections did not previously circulate in the population, there is no conviction that used inactivations agents allow effectively eliminate these pathogens from finished product. Octapharma has published an official statement that its products Octagam 5% and 10% do not contain the above viruses because used methods of virus inactivation and elimination (cold ethanol fractionation, treatment with solvent/detergent, inactivation at low pH (4.0)) allow controlling drugs safety regarding Zika virus, MERS SARS and SARS-COV2 [45–48].

Regarding the questions of IVIG tolerance, it should be noted that side effects that occur in the administration of IVIG products may be divided into common (as a common, not severe, caused mainly by impurities, dimers, technical errors of medicinal product administration) and severe. Those first include headache, joint/loin pain, increased body temperature, etc. Those second include acute renal failure, hemolysis, thromboembolic complications. Aseptic meningitis and anaphylaxis are very rare [49].

The formation of dimers and aggregates by immunoglobulin G molecules in storage is quite a serious problem all manufacturers of modern products face. As a rule, this is reversible events, however, aggravating with increase in IgG concentration in the solution, and it is associated with natural activity of immunoglobulin molecule. However, after intravenous administration, increased (>12%) number of dimers and aggregates of IgG molecule may cause adverse events such as headache, increased body temperature etc. Previous clinical trials demonstrated that lower content of dimers in IVIG promotes its better tolerance and rarer undesirable side

effects [18]. To prevent from this natural process, stabilizers: carbohydrates (dextrose, maltose and sorbitol) and amino acids (glycine and L-proline) are used in the manufacture of IVIG products. Only one stabilizer is used in manufacture of majority of products, several stabilizers are used in manufacture of two products (Immunovenin and Normal human immunoglobulin) (Table 2) [49, 50].

Table 2. IVIG stabilizers

Stabilizer	Product
Dextrose	• Sigardis [31] • Immunovenin [27] • Normal human immunoglobulin [28]
Sorbitol	• Flebogamma [33]
Maltose	• Flebogamma [33] • Octagam 10% [21] • I.G. Vena [25] • Immunovenin [27] • Sigardis-MT [32] • Gabreglobine-IgG [23] • Imbioglobulin [26]
Glycine	• Intratect [29] • Gamunex-C [24] • Immunovenin [27] • Normal human immunoglobulin [28]
L-proline	• Privigen [30]

The other side of using stabilizers is potential occurrence of side effects associated exactly with them [49].

The main concerns associated with IVIGs stabilized with carbohydrates, as a rule, were associated with ability to use in patients with diabetes mellitus. However, dextrose, maltose and sorbitol are metabolized in human body in a way that products containing them do not pose any threat to patients with this disease. Nevertheless, it is necessary to take into account that some not specific test systems may falsely identify maltose as glucose and give false data on increased glucose when such medicinal products are administered. Thus, glucose-specific test systems should be used to avoid unjustified prescription of insulin [21, 51]. Taking into account the ability of dextrose and sorbitol to metabolize to glucose, the use of products containing these stabilizers should be avoided in patients with hereditary fructose intolerance. Besides, in very rare cases, sorbitol itself may cause intolerance symptoms [51]. It should be also considered that maltose is manufactured by enzymatic treatment of corn; therefore, it is recommended to avoid using maltose-containing IVIG in patients with corn allergy [51].

Two amino acids are used as IVIG stabilizers: L-proline and glycine. Both substances demonstrate approximately same efficacy and safety parameters [52].

Individual approach is required when the product is chosen for patients from some special populations: patients older than 65 years of age, children, patients with renal failure, patients at risk of thromboembolism. Products with the lowest sodium content should be preferred. It is also important to pay attention to osmolarity which reflects total concentration of all dissolved particles (in the setting of IVIG these are carbohydrates and sodium). Its level should not be less than 240 mOsmol/kg, the use of products with osmolarity most close to that physiological (280–296 mOsmol/kg) is preferable. In these special patients population, products of choice are 10% normal human immunoglobulin solutions (since the administration thereof allows to reduce the volume of administered liquid) [49, 50].

The characteristics to be declared by a manufacturer in the prescribing information according to WHO is IgA level as well. At the same time, it is important that the level of IgA must be claimed. In case of many products marketed in the Russia, the prescribing information does not contain data on IgA level in the solution (Sigardis, Sigardis-MT, Normal human immunoglobulin, Immunovenin, Imbioglobulin, Gabriglobine-IgG). Therefore, it is not possible to make a conclusion of safety of these products in patients [49, 50].

Most serious side effects of IVIG are renal failure, hemolysis, thromboembolic complications. The reason for renal failure in IVIG administration is development of direct damaging effect on the renal tubules and secondary damage caused by hemolysis [53].

The products which may have direct damaging effect on the kidneys are sucrose-containing IVIGs. This is precisely why the manufacture of sucrose-containing IVIGs is gradually decreasing worldwide, and there is not a single product like that among IVIGs used in the Russian Federation [49].

Secondary impairment of the kidneys most commonly occurs due to hemolysis. At present, it is known that the reason for hemolysis is high level of anti-A and anti-B isoagglutinins in IVIG products [53]. The amount of isohemagglutinins is minimized in IVIG manufacture using fractionation by ethanol (e.g., Octagam). Therefore, this type of fractionation does not require additional control of donor population and is associated with minimum risk of hemolysis. If other method of protein fractionation is used, initial control of donations for isohemagglutinins is required and steps eliminating isohemagglutinins should be included in the process.

In 2013, the results of comparative safety study (based on retrospective analysis of publications) of different IVIG products with different stabilizers from in patients with pre-existing renal comorbidities was published. Four of eight studied products are authorized in the Russian Federation (Octagam, Privigen, Flebogamma, Gamunex). Octagam (and maltose stabilizer) demonstrated the greatest safety. The use of products stabilized with amino acids was associated with higher frequency of renal adverse events and with higher risk of hemolytic anemia (to a greater extent it was related to administration of medicinal products at high doses for the treatment of autoimmune diseases) [53]. Further, to decrease the risk of such complications, the companies which use amino

acids for IVIG solutions stabilization, started to perform more thorough control of donor population for isohemagglutinins. Some manufacturers developed additional special methods for decrease in isoagglutinins level in the finished product [54]. However, no new comparative studies were performed for this topic.

To decrease procoagulant activity of IVIG products and consequently to decrease the risk of clot formation, many manufacturers add additional steps to the manufacturing process. E.g., since 2011, manufacturing processes of Octagam and Octagam 10% include activated coagulation factor XI elimination step. Additionally, thrombin generation assay is performed for each product batch. This minimized the risk of thromboembolism in the setting of therapy with IVIG [55].

It should be noted that clot formation risk is more typical of high dose treatment regimen. Patients with risk factors (cardiovascular diseases, thromboembolic events in the past history, etc.) need adequate hydration and use of drugs with antiaggregant activities.

Therefore, when choosing IVIG product, it is necessary to take into account patient's age, presence of some rare hereditary diseases (corn allergy, fructose intolerance, hyperprolinemia) an a number of comorbid conditions (renal diseases, cardiovascular diseases) (Table 3).

Table 3. A personalized approach to choice-making of an immunoglobulin for the replacement therapy

Special patient populations	Recommendations
• Patients older than 65 years • Patients with renal diseases (or risk of them) • Patients with cardiovascular diseases • Patients with increased risk of thromboembolic events • Children	• I.V. 10% normal human immunoglobulin solutions are recommended (to reduce volume of administered liquid) • IVIG with high osmolarity are not recommended • IVIG with high sodium content are not recommended
Presence of anti-IgA antibodies	Content of IgA should be specified and should not exceed the label claim
Hereditary fructose intolerance	Sorbitol- and fructose-containing products are prohibited
Hyperprolinemia	Proline-containing products are prohibited
Corn allergy	Maltose-containing products are prohibited

Besides safety and efficacy of administration of normal human immunoglobulin products, the aspect of convenience of use is very important. Most IVIGs are infusion solutions and only Immunovenin is lyophilized powder. The need for additional manipulations while preparing the product for infusion is not only time expenditures but is also associated with technical errors which increase the risk of side effects [27].

An important quality parameter of IVIG is administration rate. Products with high purification degree have good tolerance which allows rapid administration of the product. High administration rate of IVIG is a practical advantage which allows, on one hand, to significantly reduce infusion time therefore saving both patient's and medical staff's time. So, the administration of full dose of Octagam 10% in a patient with body weight up to 60 kg may take not more than an hour [22, 30].

One of the first IVIG products meeting all listed requirements both worldwide and in Russia was Octagam 5% authorized in 1995 (10% product solution was authorized in 2011). There is large experience with Octagam in both patients with PID and SID at low therapeutic doses and patients requiring high dose treatment regimen. In 2014, the results of almost 20-year observation of this product efficacy in real clinical practice in patients with primary and secondary immunodeficiencies were published. The study included 363 patients with different forms of PID. The results demonstrated decrease in frequency of infectious diseases practically by 80%, severity of infectious diseases practically by 76.6%, period of infectious diseases by 73.6%, need for antibacterial therapy by 72.2% (Figure 3). The results made clear the significance of replacement therapy with IVIG in respect of treatment of patients. The value of the study is large patient sample (PIDs are orphan diseases, thus, studies on large sample are sporadic). Besides, importance is being increasingly attached to data obtained in real clinical practice, when not "ideal" patients but patients of all ages with comorbid conditions are evaluated, which is not always possible during clinical trials [55].

Besides efficacy, the product demonstrated good tolerance and safety. These results are especially important because this is a study of routine practice study, i.e. it included different patients from different countries, from different age groups, with different comorbidities [55].

Long-term experience with Octagam and Octagam 10% in the Russian Federation also resulted in high evaluation of efficacy/safety profile of these products according to allergist-immunologists (the survey was performed on independent platform for anonymous voting survey monkey and included 86 respondents of the members of RAACI prescribing therapy with IVIG) (Figures 4 a and b).

Thus, today there are wide opportunities for personified therapy with IVIG taking into account patient's

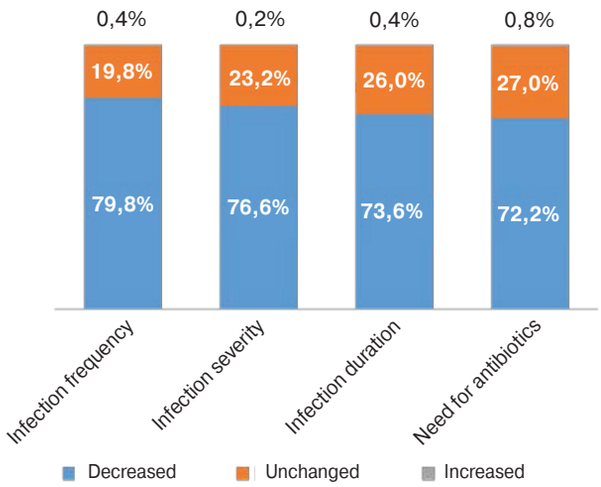

Figure 3. Control over infections in Patients with PID, receiving replacement therapy with Octagam 5% and Octagam 10%

needs and clinical particularities. Thorough analysis of comorbid conditions and patient's age may make therapy efficient and safe.

(List of references has been prepared according to international requirements; see https://pubmed.ncbi.nlm.nih.gov/).

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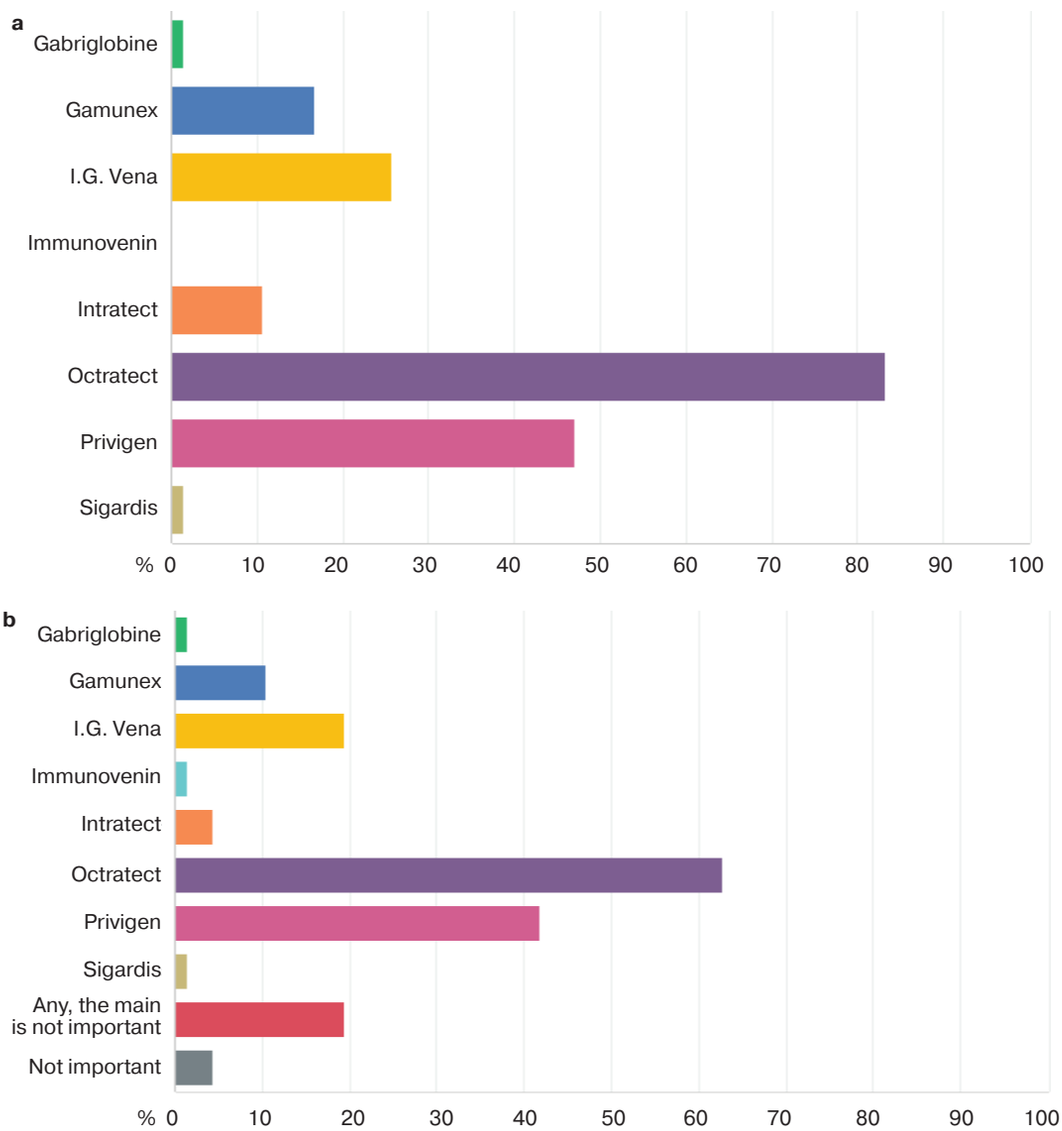

Figure 4. The results of "Primary immunodeficiency. The usage of IVIG" survey among the members of RAACI: a) How do you think, which product has the smallest number of side effects? b) What product would you chose if there is choice?

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