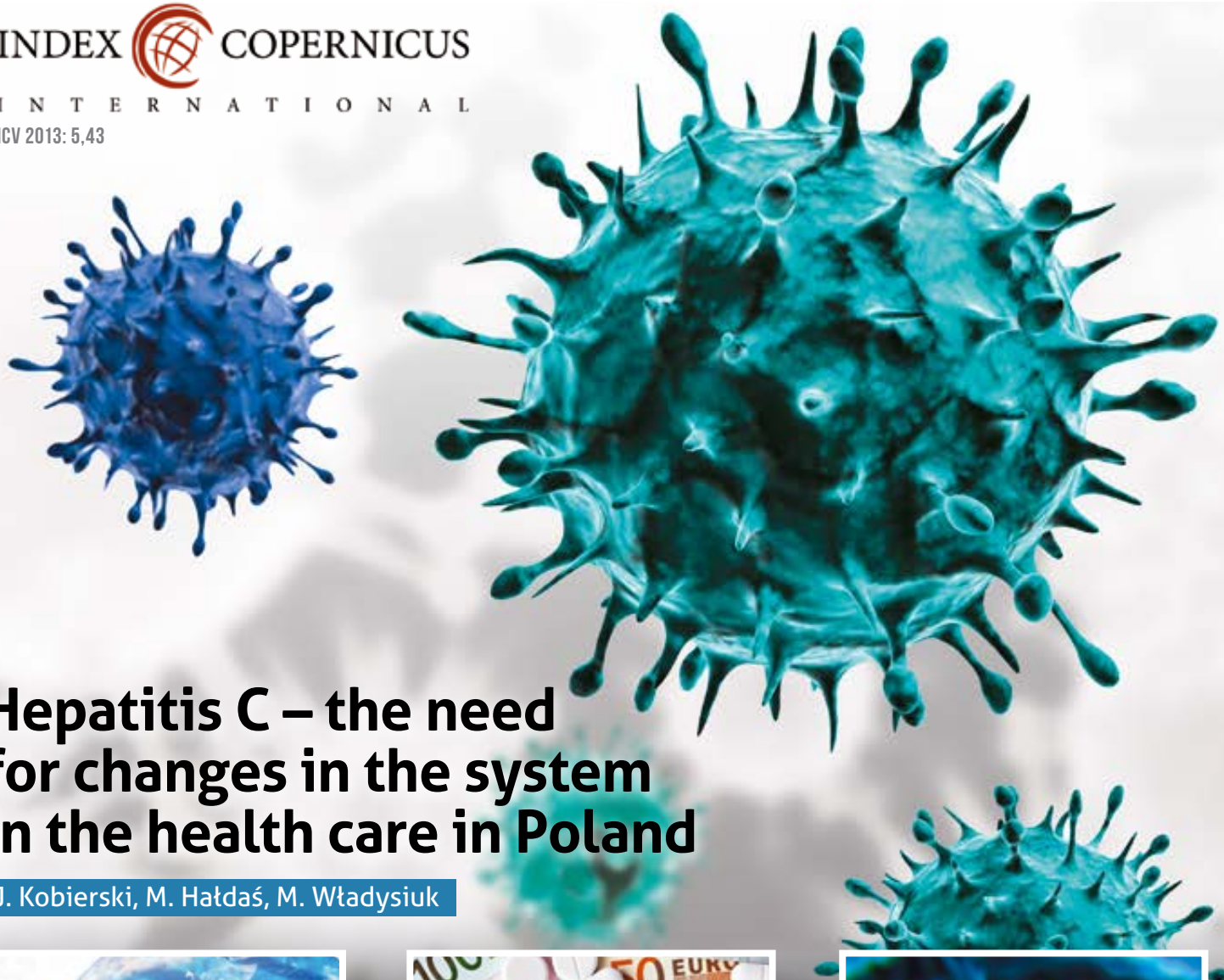
#02/2014
ISSN 2299-1247

MEDICINE & PHARMACOECONOMICS JOURNAL

WWW.JHPOR.COM

JHPOR | Journal of Health Policy & Outcomes Research

INDEX COPERNICUS
INTERNATIONAL
ICV 2013: 5,43



Hepatitis C – the need for changes in the system in the health care in Poland

J. Kobierski, M. Hałdaś, M. Władysiuk

Patients Registries - the role of the health system, new trends and hopes for Polish patients - 2nd JHPOR conference, Warsaw March 19th 2015

A. Fałek et al

Polish Experience in Financial Management of Medicines Market by Public Payer

T.Płusa

Ebola viral hemorrhagic fever

JHPOR | Journal of Health Policy & Outcomes Research

Current treatment options with immunoglobulin G for adult patients with primary immunodeficiency disease in Poland

E.Więsik-Szewczyk, Department of Immunology and Clinical Allergology, Military Institute of Medicine in Warsaw, Central Clinical Hospital of the Ministry of National Defense
K. Jahnz-Różyk, Department of Immunology and Clinical Allergology, Military Institute of Medicine in Warsaw, Central Clinical Hospital of the Ministry of National Defense
A.Kucharczyk, Department of Immunology and Clinical Allergology, Military Institute of Medicine in Warsaw, Central Clinical Hospital of the Ministry of National Defense

Keywords:
IgG, adults, drug program, IVIG, primary immunodeficiency, SCIG

DOI: 10.7365/JHPOR.2014.2.5
JHPOR, 2014, 2, 42-49

ABSTRACT

Polyclonal immunoglobulin G life-long replacement is a corner stone therapy in patients with primary antibodies deficiency. The evidence of safety and effectiveness of IgG in PAD are strongly documented for reduction and protection for serious infections. There are still limited data for deletion from long term complications as progression of chronic lung diseases, bronchiectasis and damage. Nowadays accelerated progress in IgG products modulation and ways of administration allows for adjustment of this chronic treatment for patients needs and preferences, improving the patients' compliances and quality of life. Intra venous immunoglobulin therapy has been used for many years. There are worldwide accumulating experiences with subcutaneous therapy. The latter can be given by infusion delivery pump, via rapid push or facilitated by pre-infusion of recombinant human hyaluronidase (rHuPH20). The immunoglobulin G life-long replacement is an expensive procedure. In the past in Poland replacement immunoglobulin therapy was provided mainly by pediatricians resulting in a gap with high quality care for adult patients. Awareness of problem of primary immunodeficiency in adult patients provokes the rise of centers which take care of adult patients. To improve the access for immunoglobulin therapy in Poland, a drug program has been introduced for adult patients with primary immunodeficiency. This review paper presents aspects of current immunoglobulin therapy in primary immunodeficiency complying resolutions proposed in Polish health care system.

INTRODUCTION

Polyclonal immune globulin products contain mainly immunoglobulins G (IgG) purified from pooled human plasma. In the 1950s, first passive, intramuscular administration of human immunoglobulins for patient with agammaglobulinemia gave a spectacular reduction in the frequency of sepsis and severe bacterial infections[1]. Nowadays patients with primary antibody deficiencies (PAD) require a systematic, life-long immunoglobulin G (IgG) replacement[2-5]. Continuous progress in ways of production, purification of Ig products and advances in the mode of immune globulin administration, give now possibility to tailor the chronic treatment to patients and provider needs and preferences. Both intravenous (IVIG) and subcutaneous (SCIG) IgG are effective and safe. In the past in Poland, due to lack of referral centers dedicated for care of adult patients with PAD, availability of SCIG was especially limited. With the growing knowledge about primary immune deficiencies (PID) in adults and awareness of the problem among physicians and pediatricians, who transfer patients to adults care centers, the new sites providing IgG treatment have been established. Moreover due to implementation of the new therapeutic program for adults' patients with PAD, the standard of care for adults can be improved.

INDICATIONS

Immune globulin G replacement therapy is a cornerstone of treatment for variety of PIDs. The prevalence and incidence of PIDs remain unclear. In the paper published in 2013 upper estimates suggest that six million people may be living with a PID worldwide. In Europe upper estimate was 638,000 cases, and 15,052 cases are currently registered (2.27 %)[6]. Not all PIDs are equally clinically significant and require IgG substitution. In this paper we mainly consider PIDs with antibody deficiency occurring in adult patients who have been transferred from pediatrics centers or diagnosed in adulthood. The main indication from this point of view is common variable immune deficiency (CVID). It is a complex immune disorder characterized by the impaired B cell peripheral differentiation leading to hipogammaglobulinemia. The disorder involve wide spectrum of symptoms, with majority of subjects affected by recurrent serious infections. The course of disease if untreated deteriorates with age, leading to pulmonary chronic lung disease and irreversible damage. It has to be point out that CVID is a systemic disease with profound immune system deregulation. In 30% of patients with immunodeficiency paradoxically co-exist autoimmune complications and sometimes granulomatous inflammation[7-9]. Moreover patients with CVID are at higher risk of malignancy, mainly but not only lymphoma[10]. To qualify as having CVID, patients have to present with hipogammaglobulinemia (significant reduction in >2 isotypes of serum immunoglobulin (less than 50% lower limit of normal and not simply borderline values)) and defective antibody production. In addition, flow cytometry analysis in CVID should show abnormalities in B cells, such as alterations in memory B cells or isotype switched B cells. Abnormal flow cytometry data are particularly important to confirm a questionable diagnosis[11,12].

Other B cell immune deficiencies for which IgG are indicated includes agammaglobulinemia with classical X-linked (XLA or Brutton's agammaglobulinemia) or autosomal recessive pattern. Hyper IgM syndrome including defects of the CD40 ligand and rare forms caused by defects in enzyme required for the immunoglobulin class switching also lead to IgG deficiency, and are indications for Ig supplementation.

Other immune deficiencies with defects of antibody production include Wiscott-Aldrich syndrome, some cases of DiGeorge syndrome, and patients with sub-class deficiency. In this cases IgG replacement can be indicated despite normal IgG level.

The main issue in patients' treatment is to properly establish diagnosis and verify indication for treatment by clinical immunologist. Replacement Ig therapy should not be given in case of a clinical picture that generally includes borderline immunoglobulin levels, a history of poorly documented pulmonary infections in which etiology is not defined, and a preponderance of chronic rhinosinusitis (often in atopic patients), and chronic fatigue as leading common complaint. According

to some experts' opinion, because the decision to treat or not to treat such patients long-term with immunoglobulin replacement rests on non-functional laboratory assessments, subjects with normal B-cell immunity are often being treated unnecessarily[11].

AIMS OF IGG THERAPY

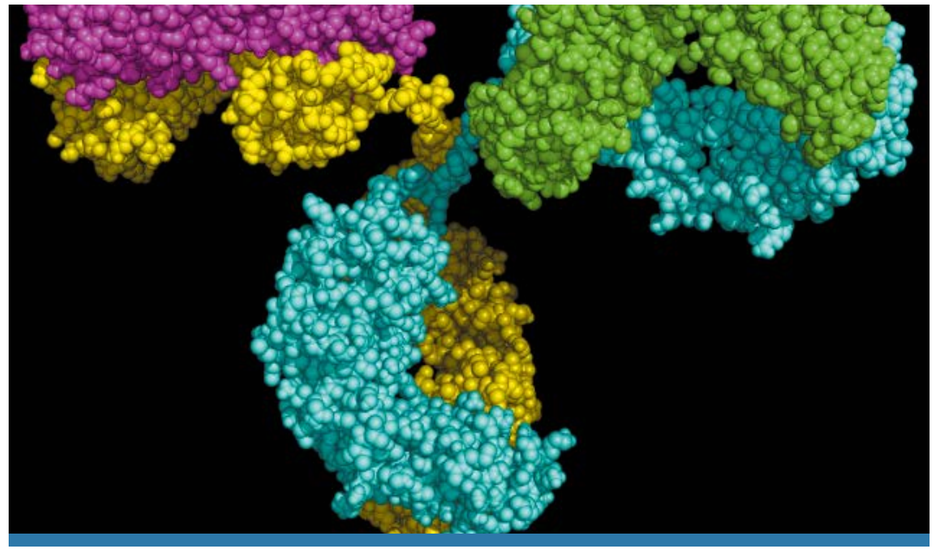
IgG replacement therapy reduces the number and severity of infections, decreases antibiotics use and hospitalizations[13]. The main efficacy end-points in clinical studies of IVIg treatment in PAD are measurement of the rate of serious bacterial infections during regularly repeated administration of the investigational IGIV product in adult and pediatric subjects for 12 months (to avoid seasonal biases) and comparison of the observed infection rate to a relevant historical standard or to a concurrent control group. Secondary endpoints normally include trough total IgG and specific antibody levels, all infections of any kind/seriousness, non-serious infections (total and by category, including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, acute bronchitis, infectious diarrhea, etc.), time to resolution of infections, antibiotic treatment (oral, parenteral, oral plus parenteral, prophylactic, and therapeutic), hospitalizations due to infection, episodes of fever, days lost from school and/or work due to infections and their treatment, and additional quality of life measures[14]. The effect of IgG replacement in subjects with hipogammaglobulinemia was so impressive immediately after treatment introduction that placebo-controlled studies have not been performed and are prohibited in PAD. In an retrospective study forty-two (84%) of the 50 patients with CVID had pneumonia at least once before receiving immunoglobulin treatment, and 11 of 42 of these patients had multiple episodes. After treatment with IgG over a mean period of 6.6 +/- 5.2 years (range, <1-20 years), the number of patients experiencing pneumonia significantly decreased to 11 (22%) of 50. In most cases these patients had pneumonia in the first year of immunoglobulin treatment[15]. It is supposed that IgG replacement can slow the progression of chronic lung diseases, although it not have been firmly proven. A prospective study was conducted in 24 adult patients consecutively diagnosed with CVID, with no previous intravenous immunoglobulin (IVIG) treatment. IVIG dose, total serum IgG level, bacterial infection rate, pulmonary function tests (PFTs) and high resolution computed tomography (HRCT) of the thorax were monitored over 2 years. Moreover, outcome data were determined by measurement of chronic pulmonary disease (CPD). IVIG dose variability (205-372 mg/kg/21 days) to obtain the required serum IgG levels was determined. Patients with CPD needed higher doses than those without CPD (p=0.045). A significant reduction in severe and mild infections/patient-year was observed during treatment. Overall, there were no changes in PFTs and HRCT scores in patients without CPD, but both improved in patients with CPD. An increase of over 15% in overall HRCT score was detected in two patients without evidence of impairment in either clinical status or PFT values[16].

Immune globulin therapy has its limitations. It is not effective in the protection from chronic or recurrent sinusitis and does not influence autoimmune phenomena observed in PID patients[17]. Paradoxically granulomatous inflammation or co-existing benign lymphoproliferation have to be treated with immunosuppressive medications. There is no sufficient data for benefits of IgG on the risk and incidences of malignancy in PID.

The matter of debate is the relationship of the dose, trough IgG level and outcome in PAD. According to FDA recommendation for efficacy more data are needed to better understand the quantitative relationships among trough total and pathogen-specific plasma IgG levels and serious infection risk. It is suggested to initiate exploratory analyses of clinical trial data to evaluate the relationship of both serious and nonserious infections to the pharmacokinetic parameters, the total IgG levels, the levels of the various subclasses of IgG and, if possible, the levels of selected specific antibodies such as anti-pneumococcal capsular polysaccharide and anti-Haemophilus influenzae antibodies. The serum IgG level that rises up to 500 mg/dl is commonly acceptable target for the beginning of replacement therapy. However in the healthy population there is a wide range of IgG level that protects from infection. Moreover the impact of trough IgG level on pneumonia incidence was described. In the meta-analysis including seventeen studies with 676 total patients and 2,127 patient-years of follow-up, pneumonia incidence declined by 27% with each 100mg/dL increment in trough IgG (incidence rate ratio, 0.726; 95% confidence interval, 0.658-0.801). Pneumonia incidence with maintenance of 500 mg/dL IgG trough levels (0.113 cases per patient-year) was 5-fold greater that with IgG level of 1000 mg/dL (0.023 cases per patient-year) [18]. In clinical practice it seems to be reasonable to accept as a goal of therapy a "biological" IgG level, individualized for each patient. This is the level obtained by charting patient's infections against IgG levels over time, with addition of change in clinical status and co-morbidites[19]. The concept of targeting individual level is supported by data from 22 years long observation of the cohort of CVID patients. Data were collected prospectively from a cohort of 90 patients with confirmed CVIDs from 1 center. Immunoglobulin doses had been adjusted in accordance with infections rather than to achieve a particular trough IgG level. Doses to achieve infection-free periods were determined and achieved trough levels analyzed. A smaller group of patients with X-linked agammaglobulinemia was analyzed for comparison. Patients with a CVID had a range of trough IgG levels that prevented breakthrough bacterial infections (5-17 g/L); viral and fungal infections were rare. Doses of replacement immunoglobulin to prevent infections ranged from 0.2 to 1.2 g/kg/mo. Patients with proven bronchiectasis or particular clinical phenotypes required higher Ig replacement doses. Patients with X-linked agammaglobulinemia showed a similar range of IgG levels to stay infection-free (8-13 g/L)[20]. This individualized attitude is possible according to rules of Polish Therapeutic Program, as it defines only the minimal target IgG level.

MODES OF ADMINISTRATION

IVIG therapy has been used from many years. For years, experience with SCIG therapy has been accumulating. The latter in Poland was limited mainly to pediatrics population due to already mentioned limitations in regulations of health care system. The diversity in SCIG usage is observed not only in Poland, but also among other European countries. Both types of IgG replacement are equally effective and have their own advantages and disadvantages. It is crucial to implement therapy according to patients' needs and preferences leading to improvement in quality of life. A standard initial dose of IVIG for the treatment of PAD patients is 400 mg/kg (range of 300-500 mg/kg) every three or four weeks. Longer



intervals between doses are not recommended even on maintaining therapy. In Poland, to authors' knowledge, IVIG is a inpatient procedure; the home IVIG therapy, although possibly more cost effective, is not provided. Standard starting doses for SCIG are 100 to 150 mg/kg per week. SCIG therapy can be given by infusion delivery pump, via rapid push or facilitated (IGHy) by preinfusion of recombinant human hyaluronidase (rHuPH20)[21-23]. Neither IGHy nor rapid-push SCIG is yet available in Polish Therapeutic Program (as of January 2015).

The advances in therapy allow to limit sites injections, increase the infusion rate and volume, with preserved safety of treatment. Routinely SCIG once-weekly administration is the most common, although regimens ranging from daily to bi-weekly have been used. Recently approved in Europe and United States for use in adults recombinant human hyaluronidase-facilitated subcutaneous IgG (IGHY) allowed administration every 3 or 4 weeks, similarly to IVIG, using one site (median, 1.09/month), with a mean volume of 292.2 mL. The bioavailability of IGHy measured by area under the concentration versus time curve was 93.3% of IGIV, which is pharmacokinetically equivalent. Systemic reactions were less frequent with IGHy than with IGIV (8.3% vs 25.0% of infusions). Local reactions to IGHy were generally mild to moderate, with a rate of 0.203 per infusion [23]. (wasserman) IGHy seems to be attractive from physicians' and patients' point of view. The extent to which IgHy will be used in future will depend on further real life experiences, long term observation and cost-benefit ratio[22].

IGG THERAPY AND COST ASPECTS

IgG life-long replacement therapy is a highly expensive procedure. The main cost related to IgG therapy is the gamma globulin itself. All form of preparations are expensive. According to the Clinical Immunology Committee of the International Union of Immunological Societies and the World Health Organization for manufacturing IVIG it should be extracted from a pool of at least 1000 donors. It should contain minimal IgA and the biochemical modification of IgG molecules should be as little as possible. The preparation should be free from preservatives or stabilizers that might accumulate in vivo[24]. In some European countries and Canada SCIG seems to be less expensive then IVIG[25]. In Canada in 3 year perspective the cost reduction on rapid –push therapy was mainly due to smaller use of hospital personnel. If 75% of patients switched to SCIG, the reduced costs reached $1·962 million or 56% of total budget[26]. A cost-analysis performed to determine whether SCIG is cost-effective compared with IVIG from a French social insurance perspective revealed that direct medical costs ranged from 19 484 euro for home-based IVIG to 25 583 euro for hospital-based IVIG, with home-based SCIG in between at 24 952 euro per year, calculated through a simulation testing different hypothesis on costs drivers. However, costs estimated on the basis of field data collected by a questionnaire completed by a population of patients suffering from agammaglobulinaemia and hyper-IgM syndrome were found to be different, with significantly higher costs for IVIG. This result was explained mainly by a higher immunoglobulin mean dose prescribed for IVIG. While the theoretical model showed very little difference between SCIG and hospital-based IVIG costs, according to authors SCIG appears to be 25% less expensive with field data because of lower doses used in SCIG patients[27]. Economic aspects of SCIG treatment in comparison with previous IVIG therapy were analyzed in phase III pivotal study of IgPro20, an L-proline-stabilized 20% human SCIG in Japan. Switching from IVIG to SCIG reduced markedly productivity loss and hospital-related absenteeism[28].

According to IPOPI survey half of IV recipients would prefer SCIG. SCIG is perceived to perform better on a number of aspects relating to quality of life (convenience, allowing independence and personal freedom) in the survey sample. From patients' perspective the time spent for SC infusion is not perceived as the lost from other activities. Moreover the time required for transportation to the hospital is regained by the patient[29]. One of the aims of new drug program "Treatment of primary immunodeficiency in adult patients" in Poland is improvement of patients' quality of life.

POLISH THERAPEUTIC PROGRAM FOR ADULT PATIENTS WITH PID

Drug program "Treatment of primary immunodeficiency in adult patients" has been introduced to the Polish health system in 2015. As part of this program following disease entities will be treated with immunoglobulin, according to the ICD-10 code:

- D.80.0 Hereditary hipogammaglobulinaemia
- D.80.1 Non-family hipogammaglobulinaemia
- D.80.3 Selective deficiency of immunoglobulin G subclasses (IgG)
- D.80.4 Immunodeficiency with increased levels of IgM
- D.80.5 Deficiency of serum immunoglobulin antibodies similar to normal or hypergammaglobulinemia
- D.80.8 Other immunodeficiencies with defect prevalence of antibodies
- D.80.9 Unspecified immunodeficiency with predominant antibody defect
- D.81.9 Determined combined immunodeficiency
- D.82.0 Wiskott Aldrich syndrome
- D.82.1 Di George syndrome
- D.82.3 Deficiency response to infection with EB virus
- D.82.8 Deficiency associated with other serious defects
- D.82.9 Indefinite immunodeficiency associated with severe defects
- D.83.0 Common variable immunodeficiency with a predominance of dysfunction or the number of B cells
- D.83.1 Common variable immunodeficiency disorders predominantly related immunoregulatory T cells
- D.83.8 Other common immunodeficiency
- D.83.9 Indefinite common immunodeficiency
- D.89.9 Determined disorders involving the immune mechanism

THE AIM OF THE ANALYSIS WAS TO DETECT ALL SUBSTANTIAL DIFFERENCES BETWEEN THE RESULTS OF QUESTIONNAIRES GATHERED FROM DIFFERENT CENTERS/ COUNTRIES AND TO DETECT ASSOCIATIONS BETWEEN PARTICULAR QUESTIONS.

Drug Program is a guaranteed benefit. The program is done with the use of innovative, expensive active ingredients. Treatment is carried out in selected diseases and includes strictly defined group of patients. The content of each drug program is published as an annex to the notice of the Minister of Health on the list of the Reimbursement of Drugs, Food Products for Special Dietary Purposes and Medical Devices (www.mz.gov.pl)[30]. Description of the program include: patient eligibility for the treatment, exclusion and inclusion criteria of the program, drug regimen, method administration, a list of diagnostic tests performed at the patient's eligibility for the program and necessary to monitor treatment. Eligible patients for drug programs are treated free of charge.

Immunoglobulins are administered intravenously in a hospital or subcutaneously at home. Immunoglobulins home therapy must be initiated in the hospital where the patient is educated in the principles of the home treatment.

The patient is eligible for the program by the Coordinating Team established by the President of the National Health Fund.

Primary immunodeficiencies in adults are rare diseases, and records for this group of patients has not been carried out. Therefore, currently the number of patients remains unknown.

CONCLUSIONS

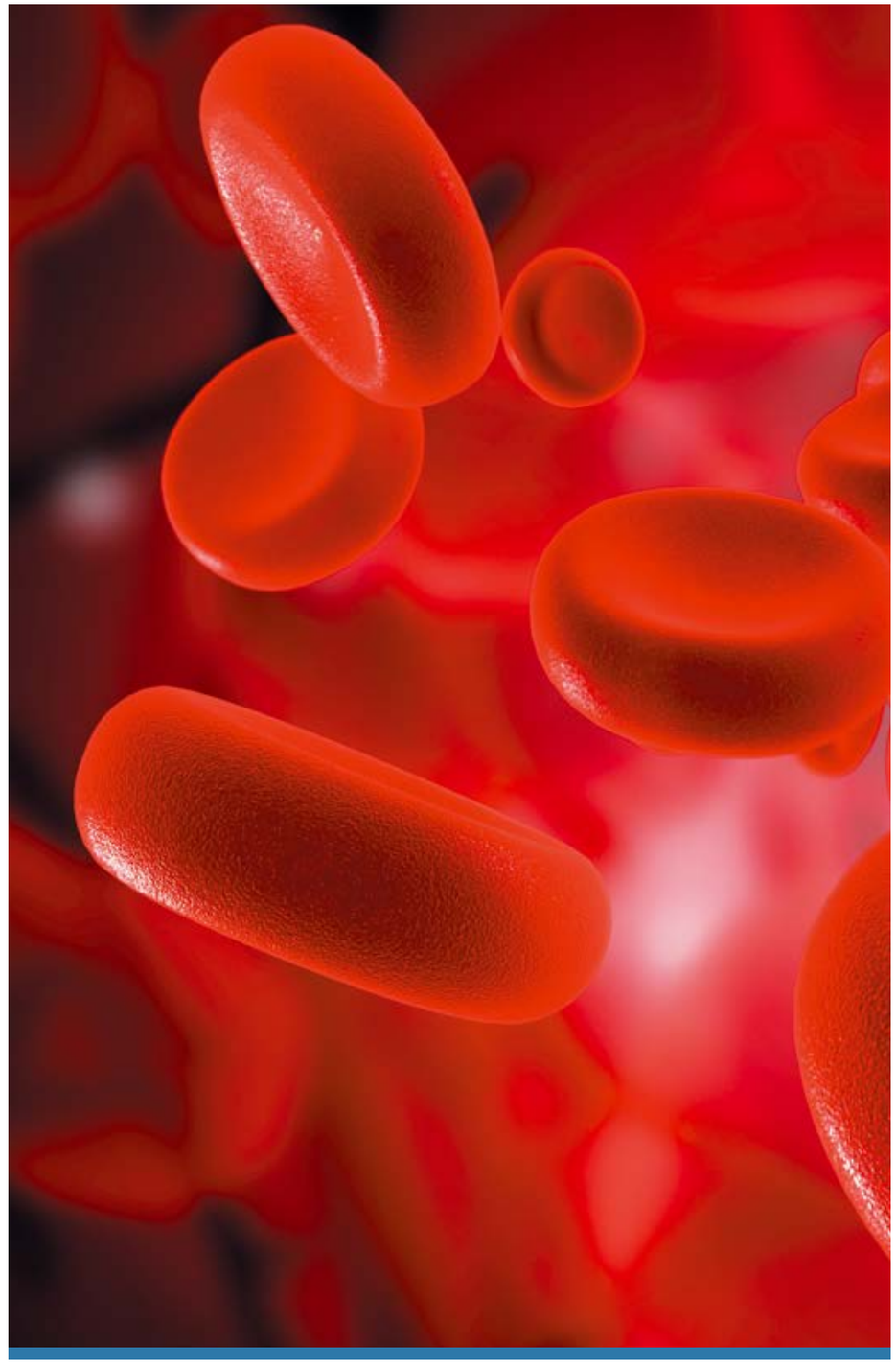
The IgG life-long replacement in PAD is an expensive therapy with proven safety and efficacy. The main issue is a well performed diagnosis leading to therapeutic proposals which should be reviewed by the clinical immunologist. It is now possible to tailor the Ig administration route, infusion technique and treatment regime according to patient needs and preferences. It can be supposed that introduction of drug program "Treatment of primary immunodeficiency in adult patients" will help to improve the care of PAD in adults, and to regain data of needs for IgG supplemental therapy in Poland.

Disclosers

EWS received traveler grants from Kendrion, CLS Behring and participated in Advisory Board Meeting for Baxter. ■

REFERENCES:

1. Bruton OC.: Agammaglobulinemia. Pediatrics 1952; 9: 722-728
2. Yong PL., Boyle J., Ballow M., et al.: Use of intravenous immunoglobulin and adjunctive therapies in the treatment of primary immunodeficiencies: A working group report of and study by the Primary Immunodeficiency Committee of the American Academy of Allergy Asthma and Immunology. Clin. Immunol. 2010; 135: 255-263
3. Roifman CM., Berger M., Notarangelo LD.: Management of primary antibody deficiency with replacement therapy: summary of guidelines. Immunol. Allergy. Clin. North. Am. 2008; 28: 875-876
4. Available from: http://www.ivig.nhs.uk/documents/dh; [Accessed: 28.01.2015]
5. Jolles S., Orange JS., Gardulf A., et al.: Current treatment options with immunoglobulin G for the individualization of care in patients with primary immunodeficiency disease. Clin. Exp. Immunol. 2015; 179:146-160
6. Bousfiha AA., Jeddane L., Ailal F., et al.: Primary immunodeficiency diseases worldwide: more common than generally thought. J. Clin. Immunol. 2013; 33: 1-7
7. Resnick ES., Moshier EL., Godbold JH., Cunningham-Rundles C.: Morbidity and mortality in common variable immune deficiency over 4 decades. Blood 2012; 119: 1650-1657
8. Chapel H., Lucas M., Lee M., et al.: Common variable immunodeficiency disorders: division into distinct clinical phenotypes. Blood 2008; 112: 277-286
9. Quinti I., Soresina A., Spadaro G., et al.: Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. J Clin Immunol 2007; 27: 308-316
10. Quinti I., Agostini C., Tabolli S. et al.: Malignancies are the major cause of death in patients with adult onset common variable immunodeficiency. Blood. 2012; 120: 1953-1954
11. Gelfand EW., Ochs HD., Shearer WT.: Controversies in IgG replacement therapy in patients with antibody deficiency diseases. J. Allergy. Clin. Immunol. 2013; 131: 1001-1005
12. Piątosa B.: Flow cytometry as a reliable tool in diagnostics – review of basic principles, standard procedures and tests in diagnostics of primary immunodeficiencies. Central Eur. J. Immunol. 2007; 32, 247-257
13. Gathmann B., Mahlaoui N., CEREDIH., et al.: Clinical picture and treatment of 2212 patients with common variable immunodeficiency. J. Allergy. Clin. Immunol. 2014; 134: 116-126
14. Available from: http://www.fda.gov/downloads/Biologics Blood Vaccines /Guidance Compliance RegulatoryInformation/ Guidances/Blood/ucm078526.pdf; [Accessed: 30.01.2015]
15. Busse PJ., Razvi S., Cunningham-Rundles C.: Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency. J. Allergy. Clin. Immunol. 2002; 109: 1001-1004
16. de Gracia J., Vendrell M., Alvarez A., et al.: Immunoglobulin therapy to control lung damage in patients with common variable immunodeficiency. Int. Immunopharmacol. 2004; 4: 745-753
17. Baumann U., Miescher S., Vonarburg C.: Immunoglobulin replacement therapy in antibody deficiency syndromes: are we really doing enough? Clin. Exp. Immunol. 2014; 178: 83-85S
18. Orange JS., Grossman WJ., Navickis RJ., Wilkes MM.: Impact of trough IgG on pneumonia incidence in primary immunodeficiency: A meta-analysis of clinical studies. Clin. Immunol. 2010; 137: 21-30
19. Bonagura VR.: Dose and outcomes in primary immunodeficiency disorders. Clin. Exp. Immunol. 2014; 178:7-9S
20. Lucas M., Lee M., Lortan J., Lopez-Granados E., Misbah S., Chapel H.: Infection outcomes in patients with common variable immunodeficiency disorders: relationship to immunoglobulin therapy over 22 years. J. Allergy. Clin. Immunol. 2010; 125: 1354-1360
21. Shapiro RS.: Subcutaneous immunoglobulin therapy given by subcutaneous rapid push vs infusion pump: a retrospective analysis. Ann Allergy Asthma Immunol. 2013; 111:51-55
22. Wasserman RL.: Overview of recombinant human hyaluronidasefacilitated subcutaneous infusion of IgG in primary immunodeficiencies. Immunotherapy 2014; 6: 553–567
23. Wasserman RL., Melamed I., Stein MR., et al.: Recombinant human hyaluronidase-facilitated subcutaneous infusion of human immunoglobulins for primary immunodeficiency. J. Allergy. Clin. Immunol 2012; 130: 951–7 e11
24. IUIS/WHO notice. Appropriate uses of human immunoglobulin in clinical practice. Clin Exp Immunol. 1983; 52: 417–422
25. Hogy B., Keinecke HO., Borte M.: Pharmacoeconomic evaluation of immunoglobulin treatment in patients with antibody deficiencies from the perspective of the German statutory health insurance. Eur. J. Health. Econ. 2005; 6: 24-29
26. Martin A., Lavoie L., Goetghebeur M., Schellenberg R.: Economic benefits of subcutaneous rapid push versus intravenous immunoglobulin infusion therapy in adult patients with primary immune deficiency. Transfus. Med. 2013; 23: 55-60
27. Beauté J., Levy P., Millet V., et al.: Economic evaluation of immunoglobulin replacement in patients with primary antibody deficiencies. Clin. Exp. Immunol. 2010; 160: 240-245
28. Igarashi A., Kanegane H., Kobayashi M., Miyawaki T., Tsutani K.: Cost-minimization analysis of IgPro20, a subcutaneous immunoglobulin, in Japanese patients with primary immunodeficiency. Clin Ther. 2014; 36:1616-1624
29. IPOPI PID Patient Needs & Outlooks Survey; Available from: http://www.ipopi.org/uploads/IPOPI%20PID%20Patient%20Survey%20-%20Shortened%20Report%20-%20030812_Final%20IPOPI%20format.pdf; [Accesssed: 31.01.2015]
30. Available from: www.mz.gov.pl; [Accessed:31.01.2015]



JHPOR | Journal of Health Policy & Outcomes Research

#02/2014
ISSN 2299-1247

WWW.JHPOR.COM