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The use of intravenous immunoglobulin in pediatric rheumatology

Zastosowanie dożylnych preparatów immunoglobulin u dzieci z chorobami reumatycznymi

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Key words: rheumatic diseases in children, autoimmune diseases, IVIG.

Słowa kluczowe: choroby reumatyczne u dzieci, choroby autoimmunologiczne, IVIG.

Summary

Objectives: Intravenous immunoglobulin (IVIG) is applied in the treatment of primary immunodeficiency diseases, autoimmune disorders and inflammatory disorders. The mechanism of anti-inflammatory action of high-dose IVIG is diverse and dependent on the disease entity. The aim of this paper was to define the efficacy and safety of IVIG treatment of rheumatic diseases in children.

Material and methods: We performed a retrospective examination of the efficacy of IVIG therapy in pediatric rheumatology. All children were treated in the period 1.01.2009 to 31.12.2013 in the Pediatric Rheumatology Department and Pediatric Department in St. Louis Hospital in Kraków and in the Pediatric Rheumatology Department, Eleonory Reicher Institute of Rheumatology in Warsaw. During 5 years, 70 patients (27 male – 38.57%) received IVIG preparations, 16 of them in concordance with registration recommendations, the others on the basis of reliable published clinical reports. The mean age of children was 6 years, the mean weight was 23.5 kg, and the mean height was 106 cm.

Indications for IVIG therapy were: juvenile idiopathic arthritis (JIA), Kawasaki disease (KD), idiopathic thrombocytopenic purpura (ITP), juvenile dermatomyositis (JDM), systemic vasculitis (SV), juvenile lupus erythematosus diseminatus (JLED), scleroderma (SCLE). Statistical analysis was performed using Statistica software version 2.0.

Results: All patients experienced a beneficial effect of IVIG adjuvant therapy – clinical improvement and normalization of laboratory tests. There were no adverse effects of this therapy.

Streszczenie

Cel pracy: Dożylne preparaty immunoglobulin (*intravenous immunoglobulin* – IVIG) znajdują zastosowanie w leczeniu niedoborów odporności oraz chorób autoimmunizacyjnych i autozapalnych. Mechanizm przeciwzapalnego działania dużych dawek IVIG jest złożony i zróżnicowany zależnie od choroby podstawowej. Celem pracy było określenie skuteczności i bezpieczeństwa stosowania IVIG u dzieci z chorobami reumatycznymi.

Materiał i metody: Retrospektywnie oceniono skuteczność terapii wlewami immunoglobulin u dzieci z chorobami reumatycznymi. Dzieci były leczone w okresie 1.01.2009–31.12.2013 na Pododdziale Reumatologii Oddziału Dzieci Starszych i Oddziale Dzieci Młodszych Wojewódzkiego Specjalistycznego Szpitala Dziecięcego im. św. Ludwika w Krakowie oraz w Klinice i Poliklinice Reumatologii Wieku Rozwojowego Instytutu Reumatologii im. Eleonory Reicher w Warszawie. W ciągu 5 lat wlewy IVIG zastosowano u 70 pacjentów (27 chłopców – 38,57%), u 16 z nich – zgodnie z rejestracją i protokołem, u pozostałych na podstawie opisywanych w literaturze doświadczeń klinicznych, jako terapię uzupełniającą. Średni wiek dzieci wyniósł 6 lat, średnia masa ciała 23,5 kg, wzrost 106 cm.

Wskazaniami do podania IVIG były: młodzieńcze idiopatyczne zapalenie stawów, choroba Kawasaki, idiopatyczna plamica małopłytkowa, młodzieńcze zapalenie skórno-mięśniowe, układowe zapalenia naczyń, młodzieńczy toczeń rumieniowaty układowy, twardzina. Do obliczeń statystycznych zastosowano program Statistica.

Wyniki: U wszystkich badanych obserwowano korzystny efekt leczenia wlewami immunoglobulin, z poprawą kliniczną i norma-

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Conclusions: Autoimmune diseases in children are rare, characterized by diverse clinical course and still unclear pathogenesis. IVIG therapy can be used in pediatric rheumatology as an efficient medication of basic supplementary treatment. Drawing up uniform standards seems to be crucial for IVIG transfusions in pediatric rheumatology, when the results of primary treatment prove ineffective.

Wnioski: Choroby autoimmunizacyjne występują u dzieci rzadko. Charakteryzują się zróżnicowanym klinicznie przebiegiem i nieznaną patogenezą. Terapia IVIG może być zastosowana w leczeniu chorób reumatycznych u dzieci jako skuteczna terapia uzupełniająca leczenie podstawowe. Istotne wydaje się opracowanie jednolitych standardów terapii IVIG u dzieci z chorobami autoimmunizacyjnymi o ciężkim przebiegu, przy braku skuteczności leczenia podstawowego.

Introduction

IVIG therapy indications

Intravenous immunoglobulin (IVIG) preparations have been used in medicine since the 1950s. In 1952 Ogden Bruton was the first to administer – and achieved satisfactory results – subcutaneously IgG preparation to an 8-year-old boy with agammaglobulinemia [1]. For successive decades IgG preparations have been applied intramuscularly and since the 1980s also intravenously [2]. In 1981 Paul Imbach described a significant growth of the number of platelets in patients with immune thrombocytopenia, treated with IVIG due to immunodeficiencies. This observation was of key importance for making an attempt of IVIG therapy in a wide spectrum of autoimmune and inflammatory disorders [3]. Nowadays the US Food and Drug Administration (FDA) discerns two main indication groups of IVIG therapy. Immunoglobulins are used in primary and secondary immunodeficiencies associated with chronic lymphocytic leukemia, bone marrow transplantation, and human immunodeficiency virus (HIV) infection. Some autoimmune and chronic inflammatory diseases represent the second group of indications: idiopathic thrombocytopenic purpura (ITP), KD and chronic inflammatory demyelinating polyneuropathy [2, 4]. Furthermore, different countries state individual recommendations for administration of IVIG. In Poland IgG preparations may be recommended in the following disorders: Guillain-Barré syndrome, severe infections in addition to antibacterial and antiviral medications, to prevent infections in low-birth-weight preterm infants [5]. In clinical practice, based on reliable literature data, efficacious IgG therapy is also administered in numerous autoimmune diseases in adults and children. Applying IVIG in pediatric rheumatic disorders with severe course and poor response to a first-line therapy is of particular importance.

Characteristics of immunoglobulin preparations

Modern immunoglobulin preparations consist of impure polyclonal IgG with IgA and are derived from serum pools obtained from a plurality of human donors. Therapeutic IVIG is produced according to recommendations established by the World Health Organization. There is a low risk of infectious agent transmission during IVIG transfusion due to rigorous standards of production steps [6].

Immunoglobulin activity mechanism

Low-dose IgG (200–400 mg/kg every 3–4 weeks) administered to patients with immunodeficiency disorders as replacement therapy has pro-inflammatory properties and prevents recurrent infections [7]. In contrast, immunomodulatory and anti-inflammatory activity of high-dose IgG (1–2 g/kg given over 2 to 5 days) is used for the treatment of autoimmune diseases [7]. These anti-inflammatory mechanisms are derived and consist of the influence on function of the Fcγ receptor, immunocompetent cells, the complement cascade and the cytokine network [8, 9].

Adverse effects of immunoglobulin

Adverse events may occur following IVIG therapy, much like every treatment. The frequency of adverse events associated with the use of IVIG ranges from several to a dozen or so percent. They are usually classified as mild and do not require the termination of therapy [10, 11]. Risk factors of adverse effects are: initiation of treatment, delay since the last administration, infection, change of immunoglobulin preparation, rapid infusion rate [12], kidney failure, diabetes, obesity, and advanced age [13]. Severe reactions, mainly anaphylaxis, usually occur soon after infusion and are very rare. The most common adverse events develop 24–72 hours after the administration, and include fever, weakness, face reddening, headaches, nausea, vomiting, cough and rash. Preventive strategies for adverse events include administration of antihistamines, nonsteroidal anti-inflammatory drugs and glucocorticoids (CS) [14]. Children under 5 years of age may be particularly susceptible to excessive overload fluid volume and in this group the dose should be carefully calculated. Especially in children with KD the risk is high due to the impairment of cardiac function. Subcutaneous IgG preparations cause signifi-

cantly fewer adverse events; however, they are used as substitutive therapy in immunodeficiencies [13].

Aim of the study

The aim of this study was to examine the efficacy and safety of IVIG standard and off-label therapy in children with rheumatic diseases depending on indications for complementary treatment with immunoglobulin.

Material and methods

We performed a retrospective examination of efficacy of IVIG therapy in pediatric rheumatology. All children were treated between 1.01.2009 and 31.12.2013 in the Pediatric Rheumatology Department and Pediatric Department in St. Louis Hospital in Kraków and in the Pediatric Rheumatology Department, Eleonory Reicher Institute of Rheumatology in Warsaw.

During 5 years, 70 patients (27 male – 38.57%) received IVIG preparations, 16 of them in concordance with registration recommendations, the others on the basis of reliable published clinical reports. The mean age of children was 6 years, the mean weight was 23.5 kg, and the mean height was 106 cm.

The indications for use of immunoglobulin were: juvenile idiopathic arthritis (JIA), Kawasaki disease (KD), idiopathic thrombocytopenic purpura (ITP), juvenile dermatomyositis (JDM), systemic vasculitis (SV), juvenile lupus erythematosus diseminatus (JLED), scleroderma (SCLE).

Statistical analysis was performed using Statistica software version 2.0.

Results

During 5 years IVIG infusions were administered to 70 patients (27 male – 38.57%) with autoimmune disorders of severe course. The mean age of children was 6 years, the mean weight was 23.5 kg, and the mean height was 106 cm. The indications were KD, ITP, JIA, JDM, SV, JLED, and SCLE. The mean/median quantity of infusions was 2.32/1.0 (1.0–15.0). The mean/median combined dose was 2.63/1.74 g/kg (0.65–12.22), while the mean/median dose for a series of infusions was 1.38/1.27 g/kg (0.32–3.25); 40 patients required at least two administrations of IVIG.

The largest group of patients treated with immunoglobulin was children with JIA – 30 patients (43%). The mean/median quantity of infusions was 3.1/2.0 (1.0–9.0). The mean/median combined dose was 3.33/2.26 g/kg (0.71–7.8), while the mean/median dose for a series of infusions was 1.13/0.97 g/kg (0.7–2.65). IVIG therapy was well tolerated, and no significant sudden or late complications occurred. In most children, the results of treatment were satisfactory. Patients with KD constituted the second largest group – 14 patients (20%). Characteristics of all groups are presented in Table I. All patients out of this group received one IVIG infusion. The mean/median combined dose was 1.76/1.68 g/kg (0.96–3.25).

Kawasaki disease

Kawasaki disease (KD) is a systemic vasculitis of the small- and medium-sized arteries. It can affect coronary vessels leading to aneurysms and sudden cardiac death caused by ischemic heart disease. Efficacy of IVIG preparations in preventing developing coronary artery complications in children with KD is widely discussed and documented in the medical literature [15–19]. The efficiency of immunoglobulin infusions depends on the time since disease onset – initiating treatment within 10 days of the first symptoms is considered to be optimal [3]. IgG administration should be repeated in case of a non-satisfactory response to the first application [20]. According to the FDA, KD is a leading indication for high-dose IVIG therapy. The mechanism of IVIG activity in KD is presumably complex and involves: neutralization of bacterial superantigens, infectious agents, autoantibodies, inhibition of pro-inflammatory cytokine production, influence on function of Fcγ receptor and T cells [18]. During the 5-year study 14 children with complete KD were observed. On average the admission day was at 5.75 days of fever duration, the mean CRP value was 65.64 mg/l, OB 73.85 mm/h, and blood plate-

Table I. Demographic and clinical data of studied patients

Parameter *n*	Diagnosis		
	total	KD	JIA
	average (min–max)	average (min–max)	average (min–max)
age (years)	6.02 (0.31–17.49)	1.73 (0.31–4.64)	8.74 (1.48–17.12)
weight (kg)	23.5 (6.71–84.0)	11.15 (6.71–16.5)	30.28 (10.5–84.0)
height (cm)	106.37 (68.0–178.0)	83.07 (68.0–104.0)	117.87 (80.0–178.0)
gender		8 boys (57%)	12 boys (40%)

lets 573.07 thousand/µl. Coronary artery abnormalities peculiar to the acute phase of KD were observed in 9 patients (64%). Patients were, on average, administered high-dose immunoglobulin therapy on the ninth day of fever duration. We observed tolerance of IVIG treatment, quick clinical recovery and improvement in laboratory parameters described above in 12 patients and 2 children needed several consecutive doses.

Idiopathic thrombocytopenic purpura

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by bleeding risk because of increased platelet destruction. The most frequent bleeding manifestations are remittent epistaxis, and menorrhagia. Less common are severe life-threatening hemorrhages [19]. IVIG usage is approved by the FDA for ITP. Currently, the first-line treatment for ITP is CS therapy, and immunoglobulin preparations are usually administered to patients with significant bleeding risk or as a prevention before surgical interventions [3, 5, 21]. Although ITP was the first autoimmune disease with a solid recommendation for IVIG infusions, the mechanism of this therapy is still unclear. Acceleration of anti-platelet antibodies elimination, modulation of function of the Fc receptor and suppression of pro-inflammatory cytokine production are implicated [22, 23]. Two hospitalized children suffering from ITP required IVIG therapy due to severe thrombocytopenia and numerous mucocutaneous bleeding episodes. The course of transfusion was uncomplicated and fast platelet count normalization was obtained.

Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) is one of the most common autoimmune disorders among children. However, the diagnosis of juvenile idiopathic arthritis involves a heterogeneous group of clinical courses determined by onset signs. Diagnosis is based on two criteria: arthritis of at least 6 weeks duration and onset before the 16th year of life. The pathomechanism of JIA is still unknown. An increase of pro-inflammatory cytokine concentrations seems to play the most important role [24]. Recommendations of IVIG therapy of arthritis are based on case reports published in the 1990s [19]. IVIG administration is highly advised in patients with severe chronic JIA with a poor response to standard immunosuppressants and biologics [3, 25]. A total of 30 children suffering from JIA of very severe course needed immunoglobulin transfusion, and 20 of them received at least two infusions. The indication for this therapy among all patients was exacerbation of chronic disease – at the time of administration the average amount of leucocytes was 14.85 thousand/µl, CRP 50.2 mg/l, OB 61.12 mm/h. Six patients with JIA were treated because of macrophage activation syndrome – they showed signs of leukopenia, thrombocytopenia, anemia and liver damage. There were no important complications after IVIG administration.

Juvenile dermatomyositis

Juvenile dermatomyositis (JDM) is the most frequent childhood myopathy. It is characterized by symmetrical proximal muscle weakness and skin rash. Dermatomyositis is an autoimmune disease and it is probably caused by excessive activation of dendritic cells [26] and the complement cascade followed by hypercytokinemia [27]. There is solid clinical evidence indicating the efficacy of IVIG therapy in patients with a severe or atypical disease course if there is no satisfactory effect of combined therapy with methotrexate and glucocorticosteroids. Anti-inflammatory action of immunoglobulin creates an opportunity to achieve fast clinical improvement, and as a result, a decrease in CS doses [19, 20, 26–28]. In this study 7 patients with serious multiple organ manifestation of JDM were administered IVIG. The clinical outcome was positive and long-term. No severe adverse events were observed, as with the previous groups of patients.

Systemic vasculitis

Systemic vasculitis (SV) is a wide group of autoimmune diseases characterized by inflammation of blood vessels resulting in coagulation disorders and thromboembolic events. Childhood vasculitis is classified by the size of vessels [29]. The pathomechanism of vessel dysfunction in various types of SV seems to be complex and heterogeneous [30]. The first-line therapy is usually the use of glucocorticosteroids. IVIG can be helpful in severe cases [3]. Especially children with ANCA-associated SV obtain significant benefits from immunoglobulin therapy [19]. In this study 7 patients with SV received immunoglobulin infusions with expected improvement. They needed continuing therapy in order to maintain the effect. No significant complications were observed.

Juvenile systemic lupus erythematosus

Juvenile systemic lupus erythematosus (JSLE) is a multisystemic autoimmune disease characterized by diversity of symptoms, unpredictable course and varied types of autoantibodies in the blood. The drugs of choice are CS and immunosuppressants. Neurologic symptoms and thrombocytopenia comprise indications for IVIG therapy. The mechanism of action is similar to that in ITP. Additionally, immunoglobulins reduce formation

and deposition of the immune complex [31]. A total of 6 patients were treated with IVIG preparations: 3 of them because of serious thrombocytopenia, 1 with thrombocytopenia and hemolytic anemia, 1 with antiphospholipid syndrome, and 1 with chorea as a neurologic symptom of JSLE. The therapy was safe and beneficial. No recurrence of acute thrombocytopenic events or CNS effects were observed during the conventional therapy.

Scleroderma

The essence of SCLE is a chronic inflammation of collagen resulting in fibrosis of connective tissue, skin and internal organs. There is a disturbance in endothelial function and vascular reactivity due to the abnormal antibody in the blood. The method of treatment depends on the form (limited or diffused) and the clinical course of scleroderma [32]. Treatment with IVIG is helpful in an early phase of systemic vasculitis. The mechanism of action is the same as in JLED. The immunoglobulin infusions were administered to 2 children suffering from rapidly progressive SCLE. There was a perfect therapeutic response and no complications.

Differences in IVIG usage among particular disease entities

The treatment with immunoglobulin in Kawasaki disease and idiopathic thrombocytopenic purpura is usually short-term and is intended to prevent serious complications. It is expected to reduce the risk of coronary artery dysfunction leading to myocardial infarction in KD and life-threatening bleeding in ITP. On the other hand, in JDM, SV, JLED and SCLE of severe chronic course with a poor response to conventional therapy, it is a valuable medication of basic treatment and significant reduce of the threat of complications. In the case of systemic JIA, which is resistant to the standard therapy, IVIG infusions are used to achieve quick but short-term clinical improvement and laboratory parameters.

Summary

The decision of IVIG therapy initiation in pediatric rheumatology should be preceded by rigorous analysis of clinical condition, disease phase, response to conventional drugs, prognosis and recommendations based on solid clinical evidence. It is also very important to consider the potential benefit and risk of immunoglobulin usage. The patient should be properly prepared for the transfusion and possible adverse events should be monitored. Autoimmune diseases in children are rare, characterized by diverse clinical course and still unclear pathogenesis. There are no precise international treatment recommendations for these disorders. Beside CS, immunosuppressants and biologics, immunoglobulin is becoming a more and more important treatment option. The FDA approved KD and ITP for IVIG therapy. For all the other childhood rheumatic diseases, immunoglobulin preparations are used "off label" on the basis of double-blind randomized trials or case reports. In cases of severe atypical course with poor response to conventional medicines, IVIGs are a well-established and efficient therapeutic option. They improve the clinical condition and the quality of patients' lives. In addition, infusions of immunoglobulin are safe and well tolerated (Table II). The National Health Fund (Narodowy Fundusz Zdrowia – NFZ) has approved only those indications for immunoglobulin that are registered. These criteria are complied with by only a few childhood rheumatic disorders (mainly KD). The majority of recommendations mentioned above are not accepted by NFZ. It seems to be very significant to establish clear methods of treatment for JIA, JDM and JLED. Recommendations for IVIG transfusions in pediatric rheumatology should be widely discussed and updated on the national and global stage.

Table II. Efficacy and safety of IVIG therapy in pediatric rheumatic patients

Diagnosis	Number of patients	Percentage of patients	Clinical/laboratory indication for IVIG	Effect (good-moderate-poor)	Adverse events
JIA	30	43	clinical experience	good	no
KD	14	20	therapy protocol	good	no
JDM	9	13	clinical experience	good	no
SV	7	10	clinical experience	good	no
LED	6	8	clinical experience	good	no
SCLE	2	3	clinical experience	good	no
ITP	2	3	therapy protocol	good	no
	70	100			

The authors declare no conflict of interest.

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