American Journal of Medicine and Medical Sciences 2019, 9(1): 1-6
DOI: 10.5923/j.ajmms.20190901.01

Study of the Effectiveness of the Use of the Drug Immunoglobulin for Intravenous Administration of "Octagam" as Part of a Complex Treatment of Hematological Diseases in Uzbekistan

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Abstract The aim of the study was to assess the tolerability, safety and efficacy of the use of the drug Octagam 5% and 10% in various hematological pathologies. The study in the control group involved conditionally healthy donors. Patients with hematological diagnoses were included in the main group, and in some of them they underwent a complex treatment with the use of the drug Octagam. The use of the drug "Octagam" showed its high clinical efficacy as a drug and allowed to reduce the time of hospitalization, the duration of infectious complications and the timing of their occurrence and the increase in the duration of remission of the main hematological disease.

Keywords Octagam, Hematological pathologies, Patients with hematological diagnoses, Clinical efficacy

1. Introduction

As is known, the immune system of hematological and oncohematological patients is in a depressed state. The exposure of this category of patients to various infectious complications is the subject of a study by various authors. Among the many infectious agents, viruses are of particular importance, among which a special place can be assigned to the parvovirus B19 (PV B19). It is known that parvovirus infection is often associated with the development of aplastic crises, hematological diseases, which are accompanied by inhibition of the hematopoietic and, in particular, erythroid germ, and also reveal an association with the development of hematological diseases [2].

The use of standard polychemotherapy in combination with antiviral therapy does not always help to achieve the desired effect. As is known, in individuals with hematologic and hematological diseases, there are often violations and imbalances in the immune system.

The use of immunoglobulins in conditions involving immunodeficiencies and immunodeficiencies is one of the effective methods of accompanying therapy in clinical practice [1]. Immunoglobulins for intravenous administration, with immunomodulating purpose, have been used since the 1980s [8]. At about the same time, the first publications appeared highlighting the use of intravenous immunoglobulins in hematology and oncohematology. In particular, J. Fehr (1982) proved the effectiveness of the use of high doses of intravenous immunoglobulins (IVIG) in immune thrombocytopenia (ITP) [4, 21].

As you know, each immunoglobulin preparation for intravenous administration has its own characteristics, its own range of advantages and disadvantages. At the same time, immunoglobulin preparations cannot be considered completely interchangeable. Each of them has its own spectrum of possibilities and its own peculiarities related to their purpose. Sometimes it is the right choice of an immunoglobulin drug that ensures the effectiveness and safety of the treatment of infectious viral complications [7, 18], including for hematological diseases [10].

It is known that immunoglobulins for intravenous administration, as a rule, are made from blood of at least 1 thousand donors, since only in this case a sufficient number of antibodies to the most diverse antigens will be contained in an immunoglobulin preparation. Drugs of this class have a complex multicomponent mechanism of action. Thus, the presence of opsonizing and neutralizing antibodies, causes the serum bactericidal activity, stimulates phagocytosis, neutralizes superantigens and toxins. Also, immunoglobulins are able to inhibit the development of autoimmune reactions, due to the presence of anti-idiotypic antibodies in their

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Published online at http://journal.sapub.org/ajmms

composition, and due to their ability to bind C3 and C4 complement components have the ability to affect the production and activity of various cytokines, including the widely studied tumor necrosis factor (TNF), interleukins-2 and - 6 (IL-2, IL-6) [9].

For preparations containing only immunoglobulins G-classes (IgG), in the absence of other classes of antibodies, such as immunoglobulins M и A (IgM and IgA), the content of which cannot exceed 2%, which helps to avoid unwanted adverse reactions, include Octapharma (Vienna, Austria).

One of the most well-known, widely used and well-recommended drugs is Octagam (Sandoglobulin®, Novartis, Switzerland or Octagam® 5% or Octapharma, Austria). "Octagam" is a sterile, well-purified, sucrose-free, and ready-to-use intravenous immunoglobulin preparation. Initially, Octagam was used to treat primary and secondary immunodeficiency states and immune thrombocytopenia [9] [17]. Currently, the literature describes the use of the drug “Octagam” for hematological and oncohematological diseases, which has become a common clinical practice [3, 13]. However, questions of the effectiveness of the use of certain hematological diseases may still remain open. Thus, the pharmacoeconomic analysis of individual studies proves the safety and efficacy of using Octagam in hematological diseases by reducing the costs of treating complications and relapses [3]. One of the reasons for the appointment of the drug "Octagam" are infectious processes, especially in the case of an unknown etiology or etiology process [11, 12].

According to the literature, the use of intravenous immunoglobulin preparations in hematology is recommended for partial red-cell aplasia, Diamond-Blackfen anemia, autoimmune hemolytic and aplastic anemia. Moreover, in case of idiopathic thrombocytopenic purpura (ITP), as well as various types of leukemia, and in patients after hematopoietic stem cell transplantation and other pathological conditions and syndromes associated with diseases of the blood system, it is recommended even as a first line therapy [6, 3].

2. Main Body

2.1. Purpose of the Study

Evaluation of tolerability, safety and efficacy of the drug Octagam 5% and 10% for various hematological pathologies.

2.2. Material and Methods of Investigation

The study involved a total of 210 conditionally healthy donors considered as a control group. In the main group, 701 patients were involved with a hematological diagnosis, of which 409 patients underwent complex treatment with the use of Octagam, which accounted for 58.3% of the total size of the group, which corresponded, on average, with minor deviations from the proportion of patients receiving therapy drug "Octagam" in each individual group.

88 patients were included in group III of patients with Anemia of Rapoport, 56 of whom received therapy with Octagam, and in group IV patients with partial red cell aplasia (PRCA) numbering 99 patients, 49 patients received therapy with Octagam. Among 113 patients with acute myeloid and monoblasts-myeloid leukemias (AML & AMML), Octagam was treated with 68 patients, and out of 104 patients with acute lymphoid leukemiya (ALL) who were involved in the study, 61 patients, and out of 68 patients with Lymphoma Burkitt, 64 patients and 101 patients with ITP, 64 patients, respectively. Therapy was carried out drug "Octagam". In general, among hematological patients in the II-VIII groups, the proportion of patients receiving Octagam was from 49.5% to 63.4%, respectively.

Patients were monitored for possible adverse reactions during and after complex treatment, including Octagam (table 1). The so-called adverse drug reactions (ADR) reactions could include nausea, the appearance of transient pain in the lumbar region, dizziness, itching. Also evaluated the severity of these reactions.

Table 1. Therapy regimen with the drug "Octagam"

Groups			With Octagam		Standart therapy	
№	Name	n=				
I	Donors	210	abs	%	abs	%
II	AA	128	70	54.69	58	45.3
III	Anaemiya Rappoport	88	56	63.64	32	36.4
IV	PRCA	99	49	49.49	50	50.5
V	AMML & AML	113	68	60.18	45	39.8
VI	ALL	104	61	58.65	43	41.3
VII	Burcitt’s Limphoma	68	41	60.29	27	39.7
VIII	ITP	101	64	63.37	37	36.6
Average (hemathological patients)		701	409	58.35	292	41.7

Also as indicators of the effectiveness of therapy supplemented with the introduction of the drug immunoglobulin for intravenous administration, the duration and severity of infectious complications, the frequency of recurrent infectious complications, the timing and duration of remission, and the frequency of relapse of the underlying disease were investigated. Also taken into account were the clinical signs arising from the use of Octagam: chills, shortness of breath, abdominal pain, nausea, headache, as well as changes in laboratory parameters, in which the concentrations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and bilirubin were investigated , urea and creatinine.

Also, as a marker of the state of parvovirus infection, a polymerase chain reaction (PCR) study was performed to identify the genome (DNA) of PV B19. Also for this purpose, in patients of the comparison groups, the content of PV19 IgM specific to PVM was studied by enzyme immunoassay.

2.3. Results and Discussion

Of the 104 patients with ALL who received polychemotherapy using the MB-2008 protocol, 76 patients were in the first stage of chemotherapy for PCT, 26 patients in this category received anti-relapse therapy, 69 were supportive, and in 28 patients with ALL, the protocol of PCT treatment was used (II protocol). At the same time, out of 113 patients with AML and AMML who received polychemotherapy using the AML-BFM-2004 protocols, 79 received the protocol for the first time, 63 were in the induction phase, 23 received anti-relapse therapy, 71 were supportive therapies, and 34 patients received the PCT treatment protocol.

A total of 21 events or so-called adverse drug reactions (ADR) were recorded, including: nausea (n = 11), the appearance of transient pain in the lumbar region (n = 8), dizziness (n = 4), which had moderate or moderate severity.

The number of patients with hematological diseases in whom the use of Octagam was ineffective was 3.0%, of which the proportion of patients with AA, Anemia Rapoport and PRCA was 2.9%, 1.8%, 2.0%, and patients with AML, ALL, Lymphoma Burkitt's and ITP – 4.4%, 3.3%, 4.9% and 1.6%, respectively. The number of complications was insignificant and the complications were not severe or moderately severe (table 2).

Table 2. The degree of effectiveness of therapy with and without the drug "Octagam"

Groups			No effect of therapy			
№	Name	n=	With Octagam		Standart therapy	
I	Donors	210	abs	%	abs	%
II	AA	128	2	2.86	11	19.0
III	Anemia Rapoport	88	1	1.79	6	18.8
IV	PRCA	99	1	2.04	9	18.0
V	AMML & AML	113	3	4.41	7	15.6
VI	ALL	104	2	3.28	7	16.3
VII	Burcitt's Limphoma	68	2	4.88	3	11.1
VIII	ITP	101	1	1.56	4	10.8
Average (hemathological patients)		701	12	2.93	47	16.1

The use of Octagam with AA, Anemia Rappoport and PRCA showed that the incidence of infectious complications and their severity, including viral etiology, was higher among patients who had specific immunosuppressive treatment and did not receive intravenous immunoglobulins, unlike treated drug "Octagam". The results of the PCR analysis of the PV B19 DNA detected in this study can serve as confirmation of the clinical data.

Among patients with AA who received Octagam as an adjuvant therapy, the number of people with a positive parvovirus DNA was 11.4%, while among patients not treated with IVIG, the detection rate of the B19 PV genome was 19.0%, which was 1.7 times more. The rates of parvovirus DNA in the blood of patients with Anemia of Rapoport who received and did not receive Octagam were 5.4% and 18.8%, respectively, which was almost 3.5 times higher among patients in the second subgroup. In this case, the serological marker of acute-phase parvovirus infection among patients with AA who were not administered IVIG was found among 5.2% of those examined, which was 1.8 times more than in patients with AA who underwent therapy with Octagam. PV B19 IgM was detected in 2.9% of cases.

So, in patients with PRCA who received the drug Octagam, the parvovirus genome was detected among 12.2% of the examined, and the number of individuals positive for the PV B19 genome who were not intravenously administered with immunoglobulin preparations was 18.0%, which was 1.5 times more and the frequency of detection of IgM to PV B19 was among patients who were injected with Octagus and not receiving IVIG – 4.1 and 6.0%, respectively, or 1.5 more often among patients of the second subgroup.

The use of the drug "Octagam" in acute lymphoblastic leukemia (ALL) has shown the effectiveness and safety of its use in the complex treatment of this pathology [20]. Since the prevalence of ALL is higher in children and adolescents, it is the representatives of these age categories that made up the majority of the recipients who received the Octagam drug. Previously obtained clinical and laboratory data testified to the depressed state of immunity before the start of treatment.

Patients who received polychemotherapy treatment for ALL had a greater number of episodes of infectious complications of bacterial, fungal or viral etiology, in contrast to the subgroup of patients who received injections of the drug Octagam. This was reflected, including the ability to delay antibacterial, antifungal and / or antiviral supportive treatment in patients receiving Octagam. The time range between the onset of specific PCT and supportive anti-infective therapy was less in patients with ALL who did not receive Octagam. The recurrence rate of the underlying disease in patients with ALL who did not receive IVIG was insignificant, but still 1.2 more often, and the duration of remission is also insignificant, 1.1 times, but shorter than in patients treated with Octagam. The frequency of infectious complications was higher than in patients who did not receive Octagam.

So, in patients with ALL who underwent PCT and who did not receive Octagam, the frequency of detection of PV19-specific IgM by the ELISA method and the parvovirus genome was higher than among those patients who were injected with Octagam. So, if patients who received Octagam DNA PV B19 were detected in 8.2% of cases, in patients with this diagnosis, the parvovirus did not receive an IVIG gene, it was detected in 16.3% of cases, which was 2.0 times more often (table 3).

In many ways, all of the above can be attributed to the results of a comparative study of patients with AML and AMML who received and did not take Octagam. In patients with AML and AMML who received Octagam with the PV B19 genome, it was detected in 5.9% of cases, and in the subgroup with this diagnosis, where the immunoglobulin preparation was not used for intravenous administration,

already in 15.6% of cases, which was higher 2.6 times.

Table 3. The frequency of occurrence of IgM-positive patients in groups with standard therapy and with the drug "Octagam"

Groups			With Octagam			Standart therapy		
№	Name	n=	abs	IgM+	%	abs	IgM+	%
I	Donors	210		3	1,4			
II	AA	128	70	2	2,86	58	3	5,17
III	Anemia Rapoport	88	56	1	1,79	32	1	3,13
IV	PRCA	99	49	2	4,08	50	4	6.00
V	AMML & AML	113	68	2	2,94	45	2	4,44
VI	ALL	104	61	1	1,64	43	2	4,65
VII	Burcitt's Limphoma	68	41	1	2,44	27	2	7,41
VIII	ITP	101	64	2	3,13	37	2	5,40
Average (hemathological patients)		701	5,4	11	2,69	292	16	5,48

As it is known in immune thrombocytopenia (ITP), platelet count can be reduced to critically low values that pose a threat to the life and health of the patient. Such a relatively safe concentration of platelets, at which a more or less normal quality of life of the patient is observed, without frequent spontaneous hemorrhages, is the level from 50.0 to 109 and above [6] (table 4).

Table 4. The difference in the effectiveness of treatment between patients with immune thrombocytopenia (ITP) treated with standard therapy and with the addition of the drug Octagam

Groups		1 day		1 week		2 week	
Name	n	abs	%	abs	%	abs	%
Detection rate of patients with bleeding							
Standart therapy	37	19	51.4	24	64.9	18	48.6
With Octagam	64	21	32.8	20	31.3	9	14.1
The difference	%	18.5		33.6		34.6	
detection rate of patients with low platelet count							
Standart therapy	37	26	70.3	19	51.4	16	61.54
With Octagam	64	40	62.5	22	34.4	8	12.5
The difference	%	7.8		17		49.04	

Treatment of autoimmune thrombocytopenia was effective in patients with ITP in group VIII, which was consistent with the results of other authors [15, 19]. As is known, compared with other methods of therapy, the use of intravenous immunoglobulins (IVIG), in particular the drug Octagam in ITP is a safe, cost-effective, relatively readily available method of treatment, and also effective in refractory to conventional therapy, during ITP the opinion of the authors testifies to it as the most preferred choice of treatment for this nosology [14, 16].

So, in patients with ITP who received therapy with Octagam, an increase in the number of platelets in the peripheral blood was observed when performing a general blood test, which correlated with a decrease in the number of bleeding both in the first 24 hours after treatment and during the first week after the start of treatment. Thus, out of 37 patients with ITP who did not receive intravenous immunoglobulins as part of therapy, 24 had bleeding during the first week, which was 64.9%, and during the first days after taking it, only 19, which was 51.4%. At the same time, out of 64 patients with ITP who received Octagam, bleeding during the first week and first day occurred, respectively, in 31.3% and 32.8%, which was less than in the group of patients who did not receive Octagam. 33.6% and 18.5% respectively. During the second week, 18 patients who received traditional therapy experienced bleeding, which was 48.6%, which was 34.6% lower than in 9 (14.1%) patients who received therapy with Octagam.

At the same time, there was a decrease in the number of bleeding episodes among individuals who received therapy with Octagam. If there were no significant differences in the number of bleeding episodes between groups of patients with ITP who received various types of therapy on the first day, despite the fact that one patient treated with octagam had an insignificant, but still fewer cases of bleeding weeks, the number of bleeding among patients who received therapy with Octagam was 18% less compared to individuals treated without the use of intravenous immunoglobulins, and during the 2nd week the number of bleeding in those who were injected with Octagam were 26.9% less than those treated without it.

At the same time, the time to achieve the maximum platelet count decreased from an average of 12 days in people who received traditional therapy to 7 days while taking the Octagam drug, which was an average of 41.7% less. At the same time, the number of platelets after a week of treatment with traditional therapy averaged 76.5 x 109 in l of blood, and in individuals after taking the drug intravenous immunoglobulin during this period increased to an average of 117.6 x 109 in l of blood, which was more by 34.9%. After 2 weeks of comparative therapy, it was found that in patients receiving therapy with Octagam the number of platelets increased from 117.6 to 149.5 x 109 in l of blood or by 21.3%, while in patients who did not take the preparation of intravenous immunoglobulin c by 76.5 to 113.9, i.e. only 32.8%. Thus, as a result of taking Octagam with ITP, the number of platelets after 2 weeks of therapy was higher by 23.8%, which confirms the effectiveness of its use in this pathology.

The number of patients whose platelet count was less than the maximum permissible concentration of 50 x 109 in l by the end of the first day in the group of patients receiving traditional therapy was 26 patients, which was 70.3%, and among those who received therapy with Octagam 40 patients or 62, 5%, which was 7.8% less, and by the end of the first week: among patients who did not receive therapy with intravenous immunoglobulins, the number of such patients

dropped to 19 or 51.4%, which was higher than among those who received "Octagas", by 17%, among which the number of patient data 22 persons or 34.4%, respectively. By the end of the second week of ITP treatment, these figures were 16 (62.0%) - among patients treated with traditional therapy, which was 49% higher than among patients receiving Octagam, among whom 8 individuals or 13% of patients had platelet numbers below maximum permissible values.

Thus, regular use of the drug IgG Octagam (Austria, Vienna) in hematological patients generally resulted in a decrease in infectious complications, reduced hospital stay, there was a tendency for an earlier onset of remission and an increase in its duration, and among patients with identified PV B19 markers, especially with a manifest flow pattern, these differences were more pronounced than in patients in whom these markers were not detected.

It should be noted that in the course of therapy with Octagam there were no serious complications. The frequency of such complications as nausea, headache, skin redness was insignificant (did not exceed 3.5%), which is consistent with data from other researchers. In general, world experience confirms the high effectiveness of IVIG and, in particular, Octagam, both as a treatment and prevention of the occurrence of infectious complications in hematological pathologies, and as an etiotropic treatment of hematological nosologies themselves, as for example in the case of ITP [5].

In conclusion, I would like to emphasize the need for continuous monitoring of the condition of patients with hematological pathology, who are undergoing therapy with Octagam. Thus, the result of the research was the elaborated criteria for monitoring the quality of the treatment of IVIG and the Octagam preparation in particular:

- routine research of the level of total IgG (at least 1 time per week);
- a study to identify a specific immune response to PV B19 before and after the treatment with Octagam
- diagnosis and detection of PV B19 by PCR in the blood serum of hematological patients;
- it is possible to conduct screening studies for the presence of auto / alloimmune complications of IVIG therapy, if necessary [4].

3. Conclusions

The use of the immunoglobulin preparation for intravenous administration of Octagam showed good tolerability, without the presence of serious side effects and an extremely small number of drug reactions of mild, moderate and moderate severity.

The use of the drug "Octagam" showed its high clinical efficacy as a drug that allowed to reduce the time of hospitalization, the duration of infectious complications and the main hematological disease, the timing of the onset and the increase in the duration of remission.

ACKNOWLEDGEMENTS

The author thanks the scientific adviser and the head of the Department of Molecular Medicine and Cell Technologies of, Scientific Research Institute of Hematology and Blood Transfusion of the Ministry of Health of the Republic of Uzbekistan Hamid Yakubovich Karimov for assistance in the management and organization of the conducted studies.

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