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Retrospective Evaluation of Intravenous Immunoglobulin Use in Adult Hematology Practice

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Abstract Intravenous immunoglobulin (IVIGs) preparations, which are used in the treatment of many immune-based diseases, also have an important place in hematology practice. It is an important treatment option with many different immunoregulatory roles. There is a limitation of its use on adult patients due to the lack of retrospective data. In our study, the retrospective usage indications, responses and rates of IVIG preparations evaluated in our Hematology Clinic and used in various indications between January 2010 and January 2020 were attempted to be put forth. Our targets for treatment responses were as follows: For immune thrombocytopenia, the platelet count target was 30000 x 10^3/µL and above; no hospitalization need for secondary hypogammaglobulinemia; no replacement need for hemolytic anemia after IVIG and a hemoglobin level above 8 g/dl. When 166 patients were examined in total, 66 were diagnosed with immune thrombocytopenic purpura (ITP) (39.8%) and 19 chronic lymphocytic leukemia (CLL) (11.4%). There were emergency indications for all patients with thrombocytopenia before getting a primary diagnosis. The number of patients who used IVIG before getting a primary diagnosis was 79 (47.6%), 41 of whom (51.9%) were diagnosed with immune thrombocytopenic purpura in follow up. The expected response was 36.1% with 60 patients within the entire patient group. With further examination performed after emergency usage, the diagnoses received by the patients were revealed. The response was 58.5% with 24 patients in whom IVIG was used under emergency conditions and deep thrombocytopenia before getting a primary diagnosis and were diagnosed with ITP after further examinations.

Keywords: *IVIG, Immunoregulatory, Immunocomplexes, Immune Thrombocytopenic Purpura, Malignancies, Alloimmunisation, Off-Label Usage*

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1. Introduction

Intravenous immunoglobulin preparations (IVIGs) have been used for many years in the treatment of many diseases. It finds itself a place within multiple indications especially due to its effects on the immune system. The first-use purpose of IVIGs, which was first used in the United States in 1981 with the approval of the FDA, was replacement therapy and has been used in different indications with the detection of anti-inflammatory and immunomodulatory effects over time. [1]

The mechanism of action lies in binding with the Fc receptors of the phagocytic system or preventing the immunocomplexes from binding with these Fc receptors. In this way, proinflammatory mediator and cytokine release of macrophages are prevented. It is known to have regulatory effects not only on the mononuclear system, but also on T and B cells. The main effect on the B cell occurs with using different mechanisms. It suppresses antibody release of B cells, neutralizes auto-antibodies that play a role in many diseases. It inhibits B cell proliferation and accelerates the catabolism of pathological immune complexes.

It has also been found to have effects on T cells that inhibit proliferation and activation. In addition, dendritic cells, which are known to have a very strong effect on antigen presentation, are inhibited through the use in especially higher doses.

It inhibits the release of many proinflammatory cytokines such as IL-4, IL-5 and TNF-alpha. It prevents complement system activation with C3b and C4b inhibition.

With the emergence of these inflammatory effects, IVIGs, which are included in many indications, are also preferred in patients with hematologic benign or malignant diagnoses at different doses and usage frequencies. Although it is seen that the most common indication in the literature and daily practice is immune thrombocytopenic purpura and its emergency treatment, it is obvious that the frequency of use in different situations is increasing. In our study, we analyzed the use of IVIGs in our clinic retrospectively and obtained descriptive data.

2. Method

Indications of retrospective usage, responses and rates of intravenous immunoglobulin preparations are evaluated in the Hematology Clinic of our hospital and usage with various indications between January 2010 and January 2020 were attempted to be put forth. The patient data in the study were accessed and analyzed through the hospital information processing system after the approval of the hospital ethics committee.

When the responses were evaluated, the target values were handled and the response status was revealed. Our targets for treatment responses were as follows: For immune thrombocytopenia, the platelet count target was 30000 x 10^3/μL and above; no hospitalization need for secondary hypogammaglobulinemia; no replacement need for hemolytic anemia after IVIG and a hemoglobin level above 8 g/dl.

3. Clinical Features and Results

Between January 2010 and January 2020, the number of patients using IVIGs was 166. Of these patients, 71 were female (42.8%) and 95 were male (57.2%). Indications for IVIGs were listed as follows. Immune thrombocytopenic purpura (ITP), chronic lymphocytic leukemia (CLL), autoimmune hemolytic anemia (AIHA), myelodysplastic syndrome (MDS), aplastic anemia (AA), combined variable immunodeficiency syndrome (CVID), acute myeloid leukemia (AML) acute lymphoblastic leukemia (ALL), Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), multiple myeloma (MM), myelofibrosis, Waldenström macroglobulinemia (WM), hairy cell leukemia (HCL), pure red cell aplasia (PRCA), acquired immunodeficiency syndrome (AIDS), systemic lupus erythematosus (SLE), Castleman Disease, sickle cell anemia and lung cancer. The wide range of diseases in our study is explained as follows: Patients who applied to the emergency department or hematology outpatient clinic with thrombocytopenia and who were treated as immune thrombocytopenic purpura at first and who took IVIG together with glucocorticosteroids according to the emergency treatment plan received different diagnoses after their advanced examinations. Therefore, patients were divided into two groups: Those who were diagnosed before or after using IVIGs.

It is underlined that an approval has been obtained at the point of using IVIGs in indications not included in the health safety system and health practice notification.

It is important to note that different doses of glucocorticosteroids have been used together in all cases of thrombocytopenia, which are thought to be of immune origin. Patients with the diagnosis of ITP were refractory cases under different doses of glucocorticoids; also it was observed that similarly different doses of glucocorticoids were used together with IVIG. Except for steroids, there was no patient diagnosed with ITP who received another type of immunosuppressive. For an autoimmune hemolytic anemia patient, methylprednisolone was used in doses that were tried to be reduced starting from 1 mg/kg for 2 months. Afterwards, weekly rituximab treatment was started due to recurrence; but there was no response.

Table 1. Disease and Gender Distribution

	TOTAL	%	FEMALE	%	MALE	%
	166	100,0	71	42,8	95	57,2
ITP	66	39,8	33	50,0	33	50,0
CLL	19	11,4	3	15,8	16	84,2
AIHA	1	0,6	0	0,0	1	100,0
MDS	8	4,8	2	25,0	6	75,0
AA	5	3,0	3	60,0	2	40,0
CVID	3	1,8	1	33,3	2	66,7
AML	11	6,6	7	63,6	4	36,4
ALL	8	4,8	2	25,0	6	75,0
HL	4	2,4	2	50,0	2	50,0
NHL	14	8,4	8	57,1	5	35,7
MM	14	8,4	2	14,3	12	85,7
LUNG CA.	1	0,6	0	0,0	1	100,0
MYELOFIBROSIS	1	0,6	1	100,0	0	0,0
WM	1	0,6	0	0,0	1	100,0
HCL	1	0,6	1	100,0	0	0,0
PRCA	2	1,2	2	100,0	0	0,0
AIDS	3	1,8	1	33,3	2	66,7
SLE	1	0,6	1	100,0	0	0,0
CASTLEMAN	1	0,6	0	0,0	1	100,0
SICKLE CELL ANEMIA	2	1,2	1	50,0	1	50,0

Table 2. IVIG Usage Before Getting Primary Diagnosis

	TOTAL	%	FEMALE	%	MALE	%
	79	47,6	36	45,6	41	51,9
ITP	41	51,9	21	51,2	19	46,3
CLL	2	2,5	0	0,0	2	100,0
AIHA	0	0,0	0	0,0	0	0,0
MDS	7	8,9	2	28,6	5	71,4
AA	5	6,3	3	60,0	2	40,0
CVID	0	0,0	0	0,0	0	0,0
AML	7	8,9	5	71,4	2	28,6
ALL	7	8,9	1	14,3	6	85,7
HL	0	0,0	0	0,0	0	0,0
NHL	7	8,9	3	42,9	4	57,1
MM	0	0,0	0	0,0	0	0,0
LUNG CA.	1	1,3	0	0,0	1	100,0
MYELOFIBROSIS	1	1,3	1	100,0	0	0,0
WM	0	0,0	0	0,0	0	0,0
HCL	0	0,0	0	0,0	0	0,0
PRCA	0	0,0	0	0,0	0	0,0
AIDS	1	1,3	1	100,0	0	0,0
SLE	0	0,0	0	0,0	0	0,0
CASTLEMAN	0	0,0	0	0,0	0	0,0
SICKLE CELL ANEMIA	0	0,0	0	0,0	0	0,0

66 of 166 patients were diagnosed with ITP (39.8%), 19 CLL (11.4%), 1 autoimmune hemolytic anemia (0.6%), 8 MDS (4.8%), 5 aplastic anemia (3%), 3 CVID (1.8%), 11 AML (6.6%), 8 ALL (4.8%), 4 Hodgkin lymphoma (2.4%), 14 non-Hodgkin lymphoma (8.4%), 14 multiple myeloma (8.4%), 1 myelofibrosis (0.6%), 1 Waldenström macroglobulinemia (0.6%), 1 hairy cell leukemia (0.6%), 2 PRCA (1.2%), 3 AIDS (1.8%), 1 SLE (0.6%), 1 Castleman Disease, 2 sickle cell anemia (1.2%) and 1 lung cancer. Disease and gender distribution of the patients are given in Table 1. We should emphasize that all patients for whom IVIGs were used before getting primary diagnosis were thrombocytopenic. This usage was indicated in emergency conditions and emergency treatment. In this context, we see that the number of patients who were used IVIG before getting a primary diagnosis was 79 (47.6%) and 41 of whom (51.9%) were diagnosed with immune thrombocytopenic purpura. In the remaining distribution, 2 patients were diagnosed with KLL (2.5%), 7 patients with MDS (8.9%), 5 patients with aplastic anemia (6.3%), 7 patients with AML (8.9%), 7 patients with ALL (8.9%), 7 patients with NHL (8.9%), 1 patient with lung cancer (1.3%), 1 patient was myelofibrosis (1.3%), and 1 patient was diagnosed with AIDS (1.3%). Patients and their clinical-gender distributions are given in Table 2.

When we look at the usage in patients which have a primary diagnosis before getting IVIG therapy; out of 87 patients (52.4%), 25 patients were diagnosed with ITP (28.7%), 7 patients with KLL (19.5%), 1 with autoimmune hemolytic anemia (1.1%), 1 with myelodysplastic syndrome (1.1%), 3 CVID (3.4%), 4 with AML (4.6%), 1 (1.1%), 4 with Hodgkin lymphoma (4.6%), 7 with non-Hodgkin lymphoma (8%), 14 with multiple myeloma, 1 with Waldenström macroglobulinemia (1.1%), 1 with hairy cell leukemia (1.1%), 2 with PRCA (2.3%), 2 with AIDS (2.3%), 1with SLE (1.1%), 1 with Castleman Disease (1.1%) and 2 was diagnosed with sickle cell anemia (2.3%). Besides primary disease, the indications for IVIG use are given in Table 3. Immun thrombocytopenia is targeted in all cases diagnosed with ITP. It was used in the treatment of immune thrombocytopenia (23.5%) in 4 of 17 patients with CLL, secondary hypogammaglobulinemia in 11 (64.7%) and autoimmune hemolytic anemia in 2 (11.8%). It can be said that these rates are in line with the literature. Although different figures are mentioned in various publications, CLL-related autoimmune-origin cytopenia is reported on average around 20-25%. (6) In MDS, AML, ALL, AIDS and Waldenström patients with thrombocytopenia, IVIGs have been used off-label with the approval of the ministry of health in the treatment of secondary to immune-origin, resistant or alloimmunization. It has been observed that 5 (8%) of the 7 patients diagnosed with non-Hodgkin lymphoma have been administered IVIG therapy; it was used for the treatment of immune-induced thrombocytopenia in 5 (71.4%) and in 2 (28.6%) for the treatment of secondary hypogammaglobulinemia and secondary immunodeficiency.

Of the 14 patients (16.1%) diagnosed with multiple myeloma, 5 (35.7%) had IVIG therapy for the treatment of alloimmune thrombocytopenia and 9 (64.3%) for secondary hypogammaglobulinemia (Table 3).

The patients and their distributions were evaluated according to the targets determined for the response. The expected response was 36.1% with 60 patients within the entire patient group. In 108 patients, the target response could not be obtained (63.9%). In the ITP patient group, the response was 56.1% out of a total of 37 patients; 8 patients in CLL (42.1%), 1 patient in autoimmune hemolytic anemia (100%), 3 patients in CVID (100%), 1 patient in ALL (12.5%), 1 patient in HL (25%), It resulted in 5 patients (35.7%) in MM, 1 patient in HCL (100%), 2 patients in PRCA (100%), 1 patient in AIDS (33.3%). In patients with primary diagnosis of MDS, AA, AML, NHL, WM, sickle cell anemia and Castleman Disease, the target response could not be obtained with various indications (Table 4).

The response was 58.5% with 24 patients in patients who were not diagnosed with any disease subgroup before getting IVIGs, were diagnosed with ITP with urgent and deep thrombocytopenia after IVIG usage. No response was obtained in other patients (Table 5).

Table 3. IVIG Usage Indications with Primary Diagnoses

	TOTAL	%	THROMB*	%	SC. HY.**	%	HA	%	OTHERS	%
	87	52,4	54	62,1	26	29,9	4	4,6	3	3,4
ITP	25	28,7	25	100,0	0	0,0	0	0,0	0	0,0
CLL	17	19,5	4	23,5	11	64,7	2	11,8	0	0,0
AIHA	1	1,1	0	0,0	0	0,0	1	100,0	0	0,0
MDS	1	1,1	1	100,0	0	0,0	0	0,0	0	0,0
CVID	3	3,4	3	100,0	0	0,0	0	0,0	0	0,0
AML	4	4,6	4	100,0	0	0,0	0	0,0	0	0,0
ALL	1	1,1	1	100,0	0	0,0	0	0,0	0	0,0
HL	4	4,6	3	75,0	1	25,0	0	0,0	0	0,0
NHL	7	8,0	5	71,4	2	28,6	0	0,0	0	0,0
MM	14	16,1	5	35,7	9	64,3	0	0,0	0	0,0
WM	1	1,1	1	100,0	0	0,0	0	0,0	0	0,0
HCL	1	1,1	0	0,0	1	100,0	0	0,0	0	0,0
PRCA	2	2,3	0	0,0	0	0,0	0	0,0	2	100,0
AIDS	2	2,3	2	100,0	0	0,0	0	0,0	0	0,0
SLE	1	1,1	0	0,0	0	0,0	1	100,0	0	0,0
CASTLEMAN	1	1,1	0	0,0	0	0,0	0	0,0	1	100,0
SICKLE CELL ANEMIA	2	2,3	0	0,0	2	100,0	0	0,0	0	0,0

*Thrombocytopenia
**Secondary Hypogammaglobulinemia

Table 4. Responses in Total

	YES	**%**	**NO**	**%**
	60	36,1	106	63,9
ITP	37	56,1	29	43,9
CLL	8	42,1	11	57,9
AIHA	1	100,0	0	0,0
MDS	0	0,0	8	100,0
AA	0	0,0	5	100,0
CVID	3	100,0	0	0,0
AML	0	0,0	11	100,0
ALL	1	12,5	7	87,5
HL	1	25,0	3	75,0
NHL	0	0,0	14	100,0
MM	5	35,7	9	64,3
LUNG CA.	0	0,0	1	100,0
MYELOFIBROSIS	0	0,0	1	100,0
WM	0	0,0	1	100,0
HCL	1	100,0	0	0,0
PRCA	2	100,0	0	0,0
AIDS	1	33,3	2	66,7
SLE	0	0,0	1	100,0
CASTLEMAN	0	0,0	1	100,0
SICKLE CELL ANEMIA	0	0,0	2	100,0

Table 5. Responses- Before Getting Primary Diagnosis

	YES	**%**	**NO**	**%**
	24	30,4	55	69,6
ITP	24	58,5	17	41,5
CLL	0	0,0	2	100,0
AIHA	0	0,0	0	100,0
MDS	0	0,0	7	100,0
AA	0	0,0	5	100,0
CVID	0	0,0	0	100,0
AML	0	0,0	7	100,0
ALL	0	0,0	7	100,0
HL	0	0,0	0	100,0
NHL	0	0,0	7	100,0
MM	0	0,0	0	100,0
LUNG CA.	0	0,0	1	100,0
MYELOFIBROSIS	0	0,0	1	100,0
WM	0	0,0	0	100,0
HCL	0	0,0	0	100,0
PRCA	0	0,0	0	100,0
AIDS	0	0,0	1	100,0
SLE	0	0,0	0	100,0
CASTLEMAN	0	0,0	0	100,0
SICKLE CELL ANEMIA	0	0,0	0	100,0

Table 6. Responses- with Primary Diagnoses

	YES	%	NO	%
	36	41,4	51	58,6
ITP	13	52,0	12	48,0
CLL	8	47,1	9	52,9
AIHA	0	0,0	1	100,0
MDS	0	0,0	1	100,0
CVID	3	100,0	0	0,0
AML	0	0,0	4	100,0
ALL	1	100,0	0	0,0
HL	1	25,0	3	75,0
NHL	0	0,0	7	100,0
MM	5	35,7	9	64,3
WM	1	100,0	0	0,0
HCL	1	100,0	0	0,0
PRCA	1	50,0	1	50,0
AIDS	1	50,0	1	50,0
SLE	0	0,0	1	100,0
CASTLEMAN	0	0,0	1	100,0
SICKLE CELL ANEMIA	1	50,0	1	50,0

Table 7. Usage for Prophylaxis

	TOTAL	%	FEMALE	%	MALE	%
	21	12,7	7	33,3	13	61,9
MM	6	28,6	2	33,3	4	66,7
NHL	3	14,3	1	33,3	2	66,7
HL	1	4,8	1	100,0	0	0,0
CVID	3	14,3	2	66,7	1	33,3
CLL	6	28,6	2	33,3	4	66,7
SICKLE CELL ANEMIA	2	9,5	1	50,0	1	50,0

In patients who were diagnosed with a primary disease prior to the usage of IVIGs; considering the various indications, usage and responses mentioned previously: 52% with 13 patients in ITP, 47.1% with 8 patients in CLL, 100% with 3 patients in CVID, and 100% with 1 patient in ALL, 25% with 1 patient in Hodgkin lymphoma, 35.7% with 5 patients in multiple myeloma, 100% with 1 patient in Waldenström macroglobulinemia and HCL, 50% with 1 patient in PRCA, sickle cell anemia and AIDS (Table 6).

Table 7 shows the patients used for prophylaxis. The distribution of patients who are preferred for the treatment of secondary hypogammaglobulinemia and secondary immunodeficiency can be seen. Out of 21 patients, 6 were diagnosed with multiple myeloma (28.6%), 6 with KLL (28.6%), 3 with non-Hodgkin lymphoma (14.3%), 1 with Hodgkin lymphoma (4.8%), 3 with CVID (% 14.3) and 2 of them were diagnosed with sickle cell anemia (9.5%). Two patients with sickle cell anemia were otosplenectomized; it should be noted that they received treatment with the indication of secondary hypogammaglobulinemia.

4. Discussion

IVIG products appear with a wide range of indications in our clinical practice. Our study contributes to the literature retrospectively by revealing the data of our hematology clinic patients.

There are basic restrictions in the presentation of study data and these restrictions are an obstacle to the statistical evaluation of the answers. The most important is the problems experienced in the standardization of IVIG products used for treatment. It was predicted that the statistical comparison of patients and responses would not be considered optimal because the products were not identical in terms of content. Prospective randomized double-blind controlled studies are required to clearly demonstrate its effectiveness, but it does not seem possible due to differences in content standardization, the amount and duration of dose per kilo used.

Important data have been revealed for the use of IVIG preparations in adult practice. Especially in the patient group before primary diagnosis, it is important to reveal the experience and to observe the responses carefully in terms of emergency approach to thrombocytopenia. It contains important data in terms of treatment and approach. In the literature, data on similar clinical conditions, emergency situations and their primary diagnoses are limited. Another important limitation in our study is that glucocorticosteroids were used in different doses and types in addition to IVIG for patients who used IVIG for immuntrombocytopenia, and therefore it is not possible to statistically evaluate the emergency IVIG response on an individual basis.

Many hematologic diseases and alloimmunization have been reported in the literature. [1,2,3] In particular, hemolysis and thrombocytopenia, which lead to frequent alloimmune-based frequent replacement needs, are clinically very important. Although different rates are reported in the literature, we see that alloimmunization-targeted IVIG

use is only against thrombocytopenia in our patient group. Treatment success in these cases also results in a low rate similar to the literature. [4,5,6]

Especially in the MDS group, there are studies with a wide array of alloimmunization ranging from15% to 59%. [7,8,9,10] However, it is necessary to stat that there are serious restrictions on treatment and outcomes in these study groups; optimization of the results is seen as the biggest problem.

In our hematology practice, IVIG can be used in cases of immunodeficiency, often secondary to malignant hematological diseases or immunochemotherapies. In addition, immunosuppressive agents, malnutrition and aging cause the development of secondary immunodeficiency. Life-threatening infections may develop. Especially in patients with B cell lymphoproliferative diseases, with advanced stages of the disease or more, secondary immunodeficiency develops. The use of Rituximab or Ibrutinib often leads to this result. CAR-T cell treatments, which are the current treatment options, can cause secondary immunodeficiency. In the absence of neutropenia, the presence of an infection clinic affecting the patient's 2 or more organs suggests the possibility of secondary immunodeficiency. In hematologic malignancies, it is recommended to be given subcutaneously or intravenously for 1 or 2 years and every 3-6 weeks, 200-400mg/kg/day. Baseline serum quantitative immunoglobulin values at diagnosis and after treatment are recommended to be measured [11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27].

5. Conclusion

IVIG products stand out with a wide range of effective usages and are frequently preferred. Our study contributes to the literature retrospectively with revealing our patients' data. Content standardization, disease distributions and different doses of glucocorticosteroids used beside IVIGs in our study restricted the statistical evaluation retrospectively. It is important in terms of transferring experience and revealing data.

Competing Interests

The authors declare that they have no financial or non-financial competing interests.

Ethics Statement

The study was carried out with the approval of Istanbul Training and Research Hospital Ethics Committee. (10.01.2020, approval number: 996).

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Disclosure Statement

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Author Contributions

I.S. and O.Y. conceived of the presented idea. I.S. developed the theory and performed the computations. I.S. and F.Y. collected the data. I.S. wrote and a developed the final manuscript.

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