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Neutropenia following intravenous immunoglobulin therapy in adult patients with immune thrombocytopenic purpura

A single center experience and literature review

Sang-Bo Oh, MD[a], Ho-Jin Shin, MD, PhD[b,*]

Abstract

The purpose of this study was to evaluate neutropenia following intravenous immunoglobulin (IVIG) therapy in adults with immune thrombocytopenic purpura (ITP).

Our analysis included 88 patients with ITP, who received IVIG from January 2006 to March 2016, at Pusan National University Hospital in Korea. Their white blood cell (WBC) count and absolute neutrophil count (ANC) before and after IVIG treatment were analyzed.

Of 88 patients, 24 patients (27.3%) were male, and 64 patients (72.7%) were female. Neutropenia developed in 8 patients (18.7%) after IVIG treatment. In patients with a decrease in WBC count and ANC compared to baseline, median WBC count decreased from 6280/μL to 4530/μL after IVIG therapy, and median ANC decreased from 3840/μL to 2840/μL after IVIG therapy. The neutropenia induced by IVIG had resolved spontaneously after several days, and the mean recovery time was 8.72 days after the completion of the IVIG treatment. During the neutropenic episodes, only one patient developed neutropenic fever, which subsided soon without any treatment.

The results of this study suggest that IVIG may cause neutropenia commonly in adults with ITP, and it seems to be transient and self-limited. This study is meaningful as the first report that not only pediatric ITP patients may develop neutropenia post IVIG administration, but also adult patients suffering ITP.

Abbreviations: ANC = absolute neutrophil count, IRB = Institutional Review Board, ITP = immune thrombocytopenic purpura, IVIG = intravenous immunoglobulin, WBC = white blood cell.

Keywords: immune thrombocytopenic purpura, intravenous immunoglobulin, neutropenia

1. Introduction

Immune thrombocytopenic purpura (ITP) is an autoimmune disease in which anti-platelet antibodies accelerate the destruction of platelets.[1] In addition, platelet production can be impaired because anti-platelet antibodies can also damage megakaryocytes.[2,3] Typically, ITP is chronic in adults and is usually acute and self-limited in children. The signs and symptoms of ITP vary widely: some patients have no symptoms or have minimal bruising, whereas others experience severe bleeding such as intracranial hemorrhage. ITP is suspected in patients with isolated thrombocytopenia. Because manifestations of ITP are nonspecific, other causes of isolated thrombocytopenia (drugs, alcohol, lympho-proliferative disorders, other autoimmune diseases, and viral infections) need to be excluded by clinical evaluation and appropriate testing.[4] Traditional therapies such as steroid therapy, intravenous immunoglobulin (IVIG) therapy, and splenectomy generally reduce the peripheral destruction of platelets. However, they may cause significant side effects. In particular, it has been recently reported that neutropenia sometimes develops in children as an adverse effect after IVIG administration.[5–7] On the other hand, there is no previous report on neutropenia developing as a complication of IVIG therapy in adult patients with ITP. The aim of this study was to further investigate the incidence and course of neutropenia following IVIG therapy in adults with ITP.

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required. This article does not contain any studies with animals performed by any of the authors.

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[a] *Division of Hematology-Oncology, Department of Internal Medicine, School of Medicine, Medical Research Institute, Pusan National University Yangsan Hospital, Yangsan,* [b] *Division of Hematology-Oncology, Department of Internal Medicine, School of Medicine, Medical Research Institute, Pusan National University Hospital, Busan, Republic of Korea.*

[*] *Correspondence: Ho-Jin Shin, Division of Hematology-Oncology, Department of Internal Medicine, School of Medicine, Pusan National University Hospital, 179 Gudeok-Ro, Seo-Gu, Busan, Republic of Korea (e-mail: hojinja@hanmail.net).*

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2. Materials and methods

We performed a retrospective chart review of 88 ITP patients who had received IVIG to manage severe thrombocytopenia between January 2006 and March 2016 at Pusan National University Hospital in Korea. Inclusion criteria were the following: age ≥ 18 years, ITP diagnosis according to the American Society of Hematology guidelines (platelet count of less than 100×10^9/L in the absence of other causes or disorders that may be associated with thrombocytopenia).[8] Exclusion criteria included other diseases known to be associated with ITP, such as human immunodeficiency virus or hepatitis C virus infection, lympho-proliferative disorders, thyroid or liver disease, and definite systemic lupus erythematosus. Patients included in this study had a complete and differential blood count performed before and after the IVIG treatment. Patients were treated according to a standard protocol, consisting of IVIG administration (1 g/kg per day for 2 days).

All statistical analyses were performed using the SPSS software, version 18.0 (SPSS Inc., Chicago, IL). Measurement data are expressed by the median and the range, and the count data is represented by the number of cases and the percentages. Continuous variables were compared using Wilcoxon signed rank test and categorical variables were compared using Chi-square test, with a value of $P < .05$ was considered to indicate statistical significance. The study protocol was approved by the Institutional Review Board of Pusan National University Hospital, Busan, Korea (D-1512–013–047). The need for informed consent was waived by the IRB.

3. Results

The baseline characteristics of patients are shown in Table 1. Among 88 patients, 24 (27.3%) were male, and 64 (72.7%) were female. The median ages were 45 years in the group that decreased in the WBC count and ANC from the baseline and 41 years in the group that did not decreased in the WBC count and ANC compared the baseline. The groups were comparable in age, sex distribution, initial white blood cell (WBC) count, and absolute neutrophil count (ANC). The WBC and ANC counts before and after IVIG administration were compared. In the group with decreased the WBC count and ANC compared the baseline, the WBC count before the IVIG therapy ranged from 2510 to 12,740/μL, with the median of 6,280/μL. And the ANC before the IVIG therapy ranged from 1520 to 8810/μL, with the median of 3,840/μL. After the treatment with IVIG, 43 out of 88 patients (48.9%) showed a decrease in the WBC count and ANC from the baseline, and neutropenia developed in 8 patients (18.7%). Nadir WBC count ranged 1460 to 7910/μL, with the median of 4530/μL, and nadir ANC ranged 690 to 6830/μL, with the median of 2840/μL in the groups with decreased in the WBC count and ANC from the baseline. There was a statistically significance difference between 2 groups in nadir WBC and ANC count after IVIG treatment. Both WBC and ANC count returned to their previous values within 2 to 47 days with no treatment; the mean recovery time was 8.72 days after the end of the IVIG treatment (Table 1). In one patient, for whom the infectious etiology was not documented, neutropenic fever developed and subsided soon without any antibiotic treatment.

4. Discussion

Traditionally, IVIG is used as an immunomodulatory agent in treating various autoimmune diseases. In ITP, IVIG has been studied in patients who were unresponsive to corticosteroids and other therapies. Approximately 80% of patients have a response; however, sustained remission is infrequent, and the cost of using IVIG is considerable.[9] IVIG is generally considered a safe therapy, and the adverse effects of IVIG are generally mild. Approximately one half of patients experience headaches, while a smaller number of patients also experience rigidity, drowsiness or lethargy, fever, and/or photophobia.[10,11] Renal failure and pulmonary insufficiency may occur, and anaphylaxis may occur in recipients who have a congenital deficiency of IgA.[12–14] In some studies, the use of IVIG in children with ITP has been reported to induce neutropenia.[5–7] For example, in a study performed by Park et al, 32 out of 42 children with ITP had a WBC count lower than the baseline after IVIG treatment.[6] The reassuring facts are that IVIG-induced neutropenia is transient and that no severe infectious complications have been reported to occur during the neutropenic episode. However, there is no previous report of neutropenia developing as a complication of IVIG therapy in adult patients with ITP. Clinically, we have observed that some adults with ITP have exhibited a significant decline in their ANC following therapy with IVIG. In this regard,

Table 1

Patients' baseline characteristics.

	Group with decreased in the WBC count and ANC from the baseline	Group with not decreased in the WBC count and ANC from the baseline	*P* value
Number of patients (%)	43 (48.9)	45 (51.1)	
Median Age, years (range)	45 (19–75)	41 (24–79)	.729
Sex			.075
Male (%)	8 (18.6)	16 (35.6)	
Female (%)	35 (81.4)	29 (64.4)	
Baseline WBC, /μL (range)	6,280 (2,510–12,740)	5,860 (2,610–18,420)	.715
Nadir WBC, /μL (range)	4,530 (1,460–7,910)	8,210 (3,240–18,840)	.001
Baseline ANC, /μL (range)	3,840 (1,520–8,810)	3,710 (1,830–15,100)	.373
Nadir ANC, /μL (range)	2,840 (690–6,830)	4,210 (2,100–16,040)	.002
ANC 1000–1500/μL, *n* (%)	6 (14)	0	
ANC 500–1000 /μL, *n* (%)	2 (4.7)	0	
ANC <500 /μL, *n* (%)	0	0	
Mean recovery time, day (range)	8.72 (2–47)	N/A	
Neutropenic fever, *n*	1	0	

ANC = absolute neutrophil count; N/A = not applicable; WBC = white blood cell.

Table 2

Summary of the reported cases of intravenous immunoglobulin induced neutropenia.

Authors (year of publication)	Patients	Age, yrs	Nation	Etiology	Baseline ANC	Nadir ANC	Neutropenia	Recovery day
Ansari et al (2014)[5]	89	3.9 (0.1–18)	Iran	Immune thrombocytopenic purpura	4,752±2,641	4,725±3,631	21%	N/A
Park et al (2008)[6]	42	3.97±3.4	Korea	Immune thrombocytopenic purpura	4,445±2,317	1,709±904	38.1%	5–7
Niebanck et al (2005)[7]	64	4.0±4.9	USA	Immune thrombocytopenic purpura	4,063±2,597	2,659±2,053	28%	N/A
Berkovitch et al (1999)[22]	14	5.5 (0.5–11.5)	Israel	Immune thrombocytopenic purpura	4,600±1,900	N/A	29%	N/A
Matsuda et al (2003)[23]	14	50.5 (26–78)	Japan	Neuroimmunologic disorder	3,153±1,626	1,879±1,201	31.3%	7-14
Lemos et al (2009)[24]	42	13.9 (3.5–23.9)	Brazil	Primary antibody immunodeficiency	N/A	71–1,488	23.8%	N/A
Chae et al (2013)[25]	43	2.73±3.3	Korea	Immune thrombocytopenic purpura	2,839±2,516	2,196±1,809	20%	N/A
Present case	88	45 (19–75)	Korea	Immune thrombocytopenic purpura	3,840 (1,520–8,810)	2,840 (690–6,830)	18.7%	8.72 (2–47)

N/A = not available.

our data were meaningful in that they suggested the prevalence and courses of neutropenia after IVIG treatment in adults with ITP.

The precise mechanism of the development of neutropenia after IVIG remains unclear; however, a few mechanisms have been proposed. For one, neutropenia may occur due to the migration of neutrophils to the vascular wall upon activation by complement or immunoglobulins from the IVIG product.[15] Another explanation involves immune clearance induced by anti-neutrophil cytoplasmic antibodies or antibodies to sialic acid-binding Ig-like lectin 9 (Siglec-9) in the IVIG.[16–18] Others have suggested that increases in leucocyte aggregation by IVIG lead to neutropenia.[19] In some cases, the neutropenia may be a feature of IVIG-induced neutrophil apoptosis.[20] It is most likely to be transient, and in most cases, intervention is not required. However, if a patient develops neutropenia in the setting of a life-threatening condition like transfusion-related acute lung injury or infection, measures such as premedication with glucocorticoids, slowing the infusion rate, and reduction of the IVIG dose into smaller doses to be given over several days should be considered for IVIG infusions.

Our study assessed the duration of neutropenia following IVIG therapy: the mean recovery time of WBC count was 8.72 days after the end of the IVIG administration. Prior studies suggested that the duration of neutropenia is short.[21] Berkovitch et al showed a resolution of IVIG-related neutropenia after 48 hours in their small sample of 14 pediatric ITP patients.[22] Another previous study, which investigated neutropenia after IVIG treatment in 16 patients with neuroimmunologic disorders, reported that both WBC and neutrophil returned to their previous values within 7 to 14 days with no treatment, except for in 2 patients.[23]

Including the present case, we identified previous reports of neutropenia developing as a complication of IVIG therapy in the English literature (Table 2). The majority of reports of neutropenia following IVIG therapy are pediatric patients with ITP.[5–7,22,25] There were 2 reports on the incidence of neutropenia induced IVIG in adults except for pediatric patients with ITP. Matsuda et al reported neutropenia induced by high-dose IVIG in adult patients with neuro-immunologic disorders.[23] And Lemos et al reported acute neutropenia in patients with primary antibody-deficiencies, after receiving IVIG.[24] However, as mentioned earlier, there has been no reports of neutropenia following IVIG therapy in adult patients with ITP. Therefore, this study is the first report of neutropenia after IVIG therapy in adult patients with ITP. Although further studies are required in order to clarify the precise mechanism of neutropenia following IVIG treatment, this would be the important report of neutropenia following IVIG therapy in adult patients with ITP. However, our study has a limitation by high number of variables tested in a very limited patient number in a retrospective setting, and thus we should be cautious regarding the interpretation of our results. Therefore, independent validation of large-scale patients is needed in the future.

Data from this study emphasize the common occurrence of neutropenia following IVIG treatment. Only 2 patients in this study developed a post-treatment ANC of less than 1000/μL, and only one patient developed neutropenic fever. Except for one patient, most of patients suffering from neutropenia had no infectious complications during the neutropenic episodes, and we conclude that neutropenia after IVIG is of little clinical concern. Therefore, an awareness of this common association of neutropenia following IVIG treatment in adult patients with ITP is likely to aid physicians in caring for these patients.

Author contributions

Conceptualization: Sang Bo Oh, Ho-Jin Shin.
Data curation: Sang Bo Oh.
Formal analysis: Sang Bo Oh.
Investigation: Sang Bo Oh, Ho-Jin Shin.
Methodology: Ho-Jin Shin.
Resources: Sang Bo Oh.
Supervision: Ho-Jin Shin.
Validation: Sang Bo Oh, Ho-Jin Shin.
Visualization: Sang Bo Oh, Ho-Jin Shin.
Writing – original draft: Sang Bo Oh.
Writing – review & editing: Sang Bo Oh.

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