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—【Original】—原　著—

Increased use of immunoglobulin preparations and its factors in Japan

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In recent years, the shortage of immunoglobulin has become a serious issue worldwide. Japan is facing a similar situation, especially since 2019, due to the rapid increase in immunoglobulin usage, and the need for urgent imports is unavoidable. We analyzed two factors that immediately preceded the surge in immunoglobulin consumption: approved indications for the prevention of chronic inflammatory demyelinating polyneuropathy (CIDP) progression and launches of concentrated preparations. Although the use of the immunoglobulin for CIDP demonstrated a continuing upward trend, there was no significant increase before or after approval. However, the launch of a concentrated preparation, 10% Venoglobulin® (Japan Blood Products Organization (JB)), has led to shorter treatment times and changes in the form of treatment from inpatient to outpatient or home-based care, especially in patients with hypogammaglobulinemia and agammaglobulinemia (PID/SID) requiring continuous administration, which has resulted in a sharp increase in the use of the immunoglobulin. This may be because treatment needs hidden by hospitalization were unearthed with the increased availability of outpatient treatment. In the future, as companies strive to shorten treatment time, additional needs will be created for diseases that require continuous medication.

In the midst of the heated international plasma products market, careful debate is needed on how far to promote the appropriate use of immunoglobulin, how to extend approved indications, and how to adjust the quantity of demand.

Keywords: chronic inflammatory demyelinating polyneuropathy, hypogammaglobulinemia/agammaglobulinemia, appropriate immunoglobulin usage, administration rate, concentrated plasma preparation

Introduction

The shortage of immunoglobulin has become increasingly serious in recent years. The consumption of plasma in the world increased approximately 1.8 times over 8 years from 2010. In the United States, the average price of plasma has risen by about 20%[1], and its use has also increased 1.7-fold in just 6 years since 2012[2)3)].

European countries were forced to import plasma from the United States in the 1990s due to the outbreak of variant Creutzfeldt-Jakob disease, and have continued to rely on import ever since. Concerned about the current situation in which 70% of the world's plasma is supplied by selling blood in the United States, European countries have begun to pursue policies for domestic self-sufficiency for immunoglobulin. Countries such as Australia and Canada have also expressed concern about rising prices due to the global shortage of plasma and have called for the proper use of immunoglobulin products and are hastening to establish their own domestic self-sufficiency systems.

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Meanwhile, Japan had almost achieved domestic self-sufficiency for intravenous immunoglobulin (IVIG), but that situation changed in 2019 when production could not keep up with the rapid increase in the amount used, forcing urgent imports. In addition, the law was amended to allow the establishment of a second blood collection center outside of the Japanese Red Cross Society (JRC) to secure plasma, making it possible for foreign companies to enter the Japanese market. For many years, Japan has attracted the attention of European and American companies as an ideal market for both the collection of source plasma and purchase of plasma derivatives due to its economic strength, medical care level, and infrastructure[4].

In order for Japan to maintain its domestic self-sufficiency and stable supply of safe immunoglobulin without becoming involved in the heated international blood business in the future, the causes of the surge in immunoglobulin use need to be determined, and sensible policies should be put in place to address them.

Methods

Using information on medical receipts from social health insurance societies at the Japan Medical Data Center (JMDC), we analyzed how all types of immunoglobulin were used in approximately 5.25 million patients under the age of 75 years. Focusing on four diseases with a particularly high use, IgG2 deficiency (IgG2), Kawasaki disease (KD), chronic inflammatory demyelinating polyneuropathy (CIDP), and hypogammaglobulinemia and agammaglobulinemia (PID/SID), we examined the status of switching to concentrated derivatives and changes in both the form of treatment and amount used, and explored their relevance in the rapid increase in demand for immunoglobulin. The data used in this study covered an eight-year period from July 2011 to June 2019, with July of the previous year to June of the next year considered a single year, and was adjusted based on the age-specific population. However, no adjustment was made for data correction for those aged 75 years and older because of diseases for which age composition data were not available. The number of patients with each disease was obtained from the data on a grant-in-aid program for chronic diseases at the Japan Intractable Diseases Information Center (2010-2018). For global trends, data from Market Research Brew, Inc.[3] were used. Statistical analysis was conducted using SPSS Statistics 26, IBM statistical analysis software, and a one-sample t-test was employed to evaluate the rate of increase ($p < 0.01$).

The present study was conducted with the approval of the Tokyo Medical and Dental University Ethics Committee and Conflict of Interest Committee.

Results

1) Changes in the amount of total immunoglobulin used following additional indications

Fig. 1 shows the development of additional indications and changes in the total amount of immunoglobulin used in Japan. Since 2010, when changes in doses of PID/SID were introduced, the use of immunoglobulin has been steadily increasing as result of the successive addition of their indications. In 2016, when the immunoglobulin was approved to prevent CIDP progression, there was no significant increase in its use, but in 2018, when a 10% preparation was launched, the amount used was significantly higher.

2) Changes in the amount of immunoglobulin used for each disease

Fig. 2 shows changes in the amount of immunoglobulin used for each disease. The amount of immunoglobulin used for IgG2, CIDP, PID/SID, and KD was higher than that for other diseases. Focusing on these four diseases, in 2018, when domestic demand levels increased sharply, their use significantly increased for PID/SID, but not for IgG2, KD, and CIDP. Although the amount used for CIDP showed a continuous upward trend, there was no significant increase in either 2016 or 2018 when new drugs, Glovenin® (Takeda Pharmaceutical Co. Ltd (Takeda)) and Venoglobulin®, were approved to prevent the progression of hypokinesia in CIDP.

3) Changes in the amount of immunoglobulin used to treat IgG2

In 2018, approximately 40% of preparations were switched from 5% to 10%.

The use of 20% Hizentra® (CSL Behring (CSL)) for subcutaneous injection has also increased gradually since 2013, when it was approved. In terms of treatment, there was an increase in outpatient services and a decrease in the diagnosis-procedure combination (DPC) and hospitalizations based on fee-for-service. However, their total use did not increase, but in fact decreased (Fig. 3-1, 3-2).

4) Changes in the amount of immunoglobulin used for KD

In 2018, 32% of the immunoglobulin used was

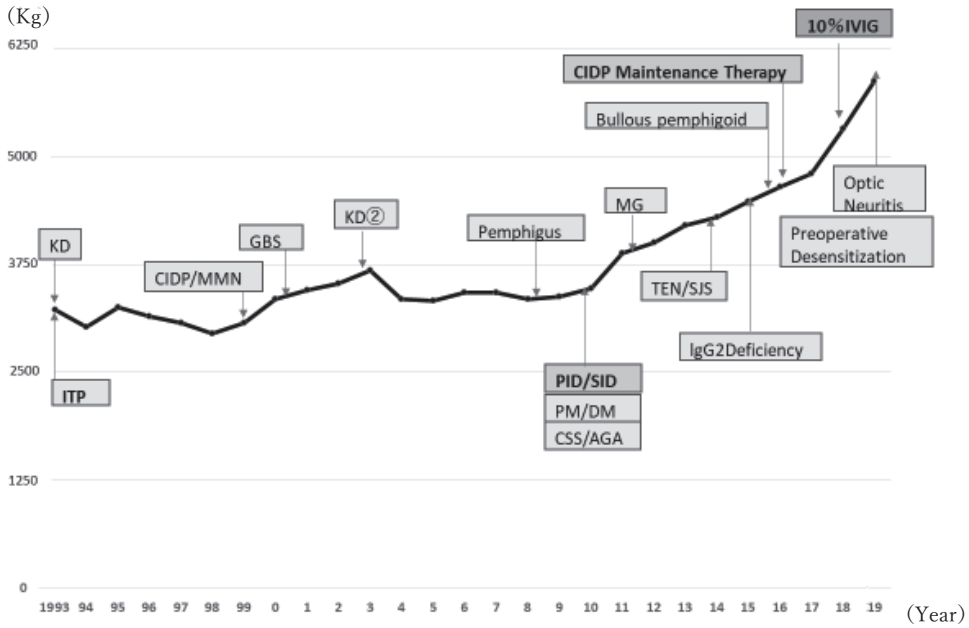

Fig. 1　Supply of IVIG/SGIG

Since 2010, the use of immunoglobulin preparations has increased as additional indications have been approved.

There was no significant increase in the year of treatment for the prevention of CIDP progression was approved, but there was a significant increase in the year when 10% concentration preparations were approved.

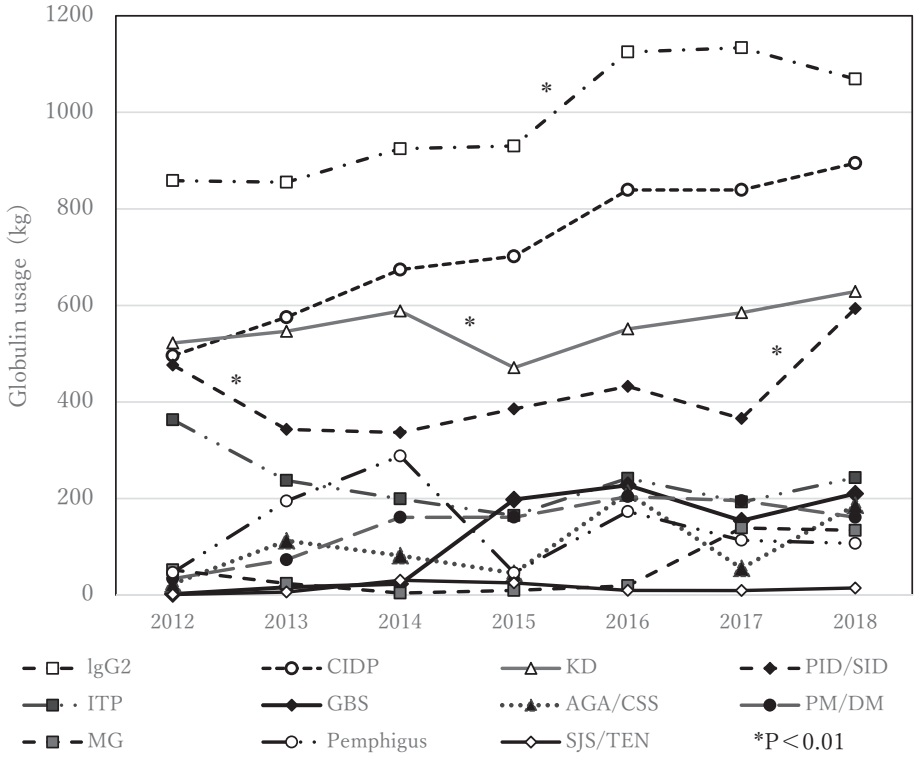

Fig. 2　Changes in usage by disease

High usage for IgG2, CIDP, KD, and PID/SID. Focusing on these four diseases, especially the used for PID/SID treatment increased significantly (*P＜0.01) in the year when the 10% preparation became available on the market.

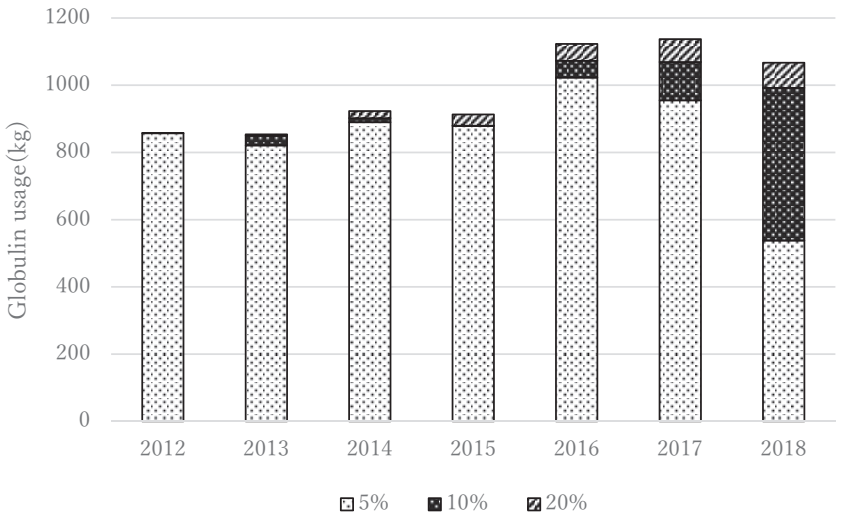

Fig. 3-1 IgG2: Changes in usage by concentration

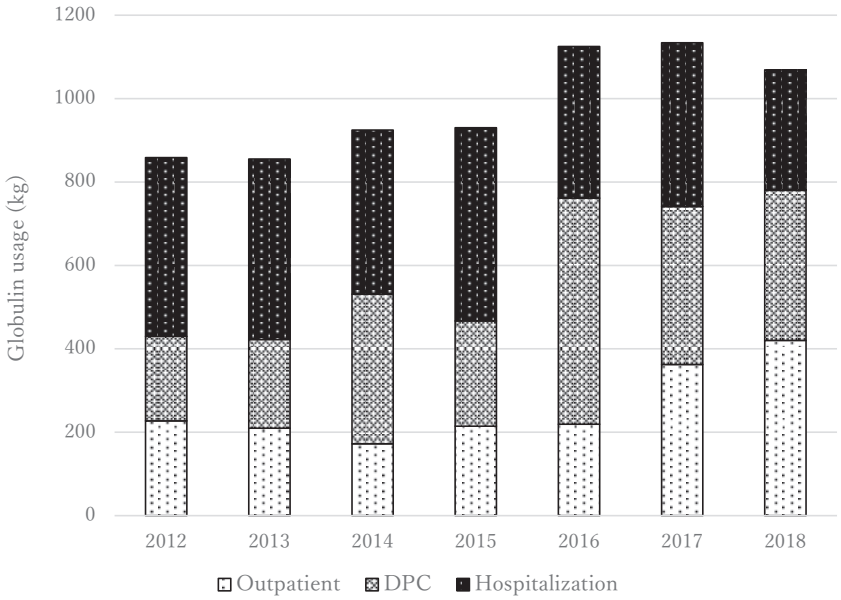

Fig. 3-2 IgG2: Changes in usage by medical treatment type
There are changes in the concentration and medical treatment type, but no increase in the total amount used.

switched from 5% to 10%. In terms of the form of treatment, KD was not treatable as an outpatient disease to begin with, and the number of outpatients remained very low (0.6% of the total) and DPC accounted for 95% of cases. There was a 7.5% increase in the total amount of immunoglobulin used (Fig. 3-3, 3-4).

5) Changes in the amount of immunoglobulin used for CIDP

Glovenin® and Venoglobulin® have been approved for the "improvement of muscle weakness" and "prevention of progression of hypokinesia." Each of these two preparations were analyzed for their each use for CIDP, total use, and use by form of treatment.

1. Changes in the amount used of each preparation and total amount used

Glovenin® had a significant increase in its use in 2016 when it was approved. Venoglobulin® also had a very large increase in 2018, which coincided with its approval to prevent CDIP progression and the launch of the 10% preparation. However, the increases and decreases in the two preparations cancelled each other out, and overall, there was no significant increase in either year, nor even when imported Hizentra® and Privigen® (CSL) were also included (total, 15.5Kg) (Fig.

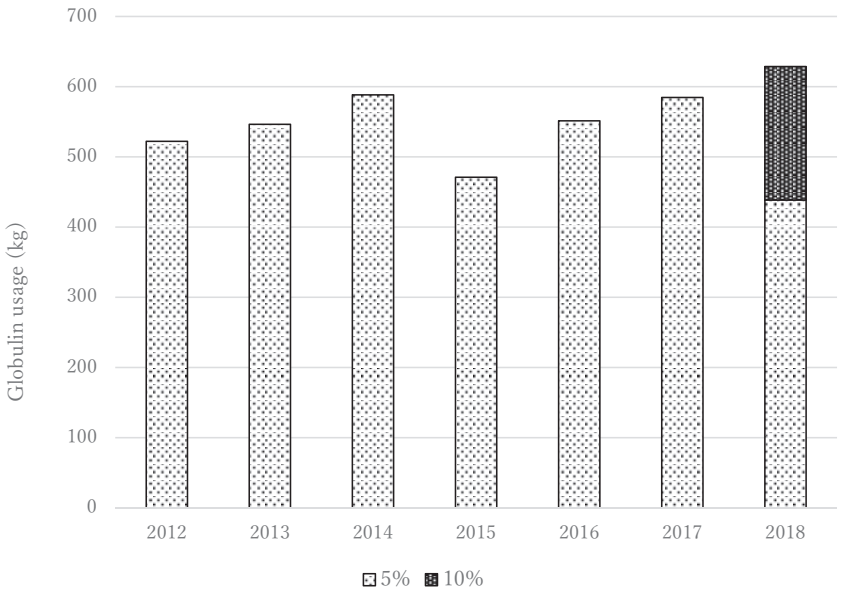

Fig. 3-3　KD: Changes in usage by concentration

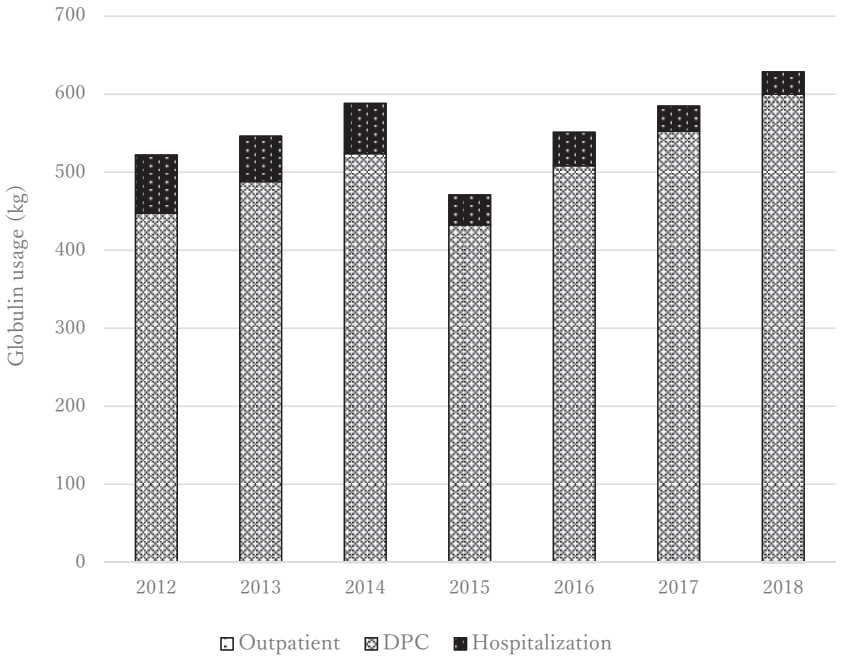

Fig. 3-4　KD: Changes in usage by medical treatment type
The concentration has changed, but the medical treatment type has not changed significantly and the total amount used has not increased.

3-5, Fig. 4).

2. Changes in the amount used of each preparation by form of treatment

The change of use in 2016 (the year that Glovenin® first received approval for the prevention of CIDP progression) and 2018 (the year that Venoglobulin® received the same approval and the 10% concentration was launched) was drawn to attention (Fig. 5).

Outpatient: Although Glovenin® use had not so much increase in 2016 but Venoglobulin® use had significant increases in 2018 ($P < 0.01$).

DPC: In 2016, there was no significant increase in the use of the two preparations; in 2018, there was a large increase in Venoglobulin® use and a large decrease in Glovenin® use ($P < 0.01$).

Hospitalizations based on fee-for-service: In 2016,

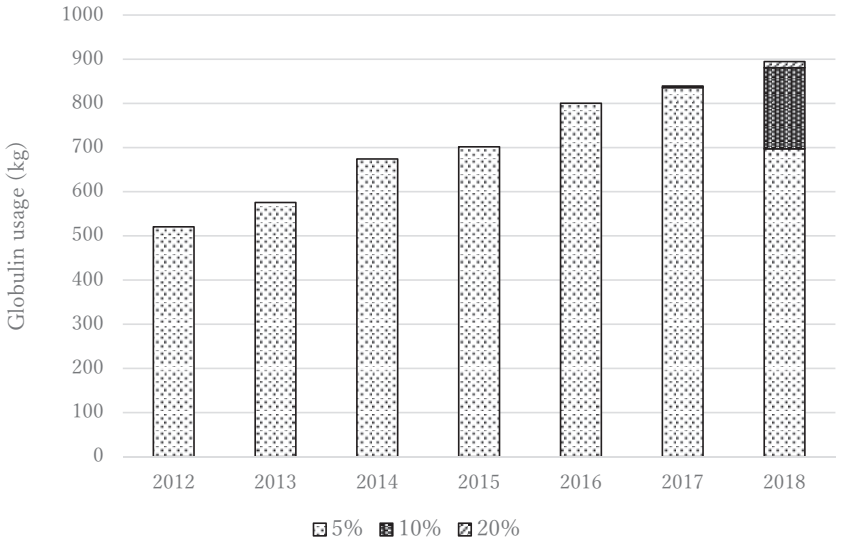

Fig. 3-5 CIDP: Changes in usage by concentration
Usage has continuously increased. Although there was switching from the 5% preparation to the 10% preparation in 2018, the size of the switch was smaller than that for the other diseases.

Table 1 Comparison of domestic and foreign preparations
Foreign preparations approved for the prevention of CIDP progression are more convenient than domestic preparations in terms of the time required for their administration.

Preparation	Obtained authorization	Sales	Donation blood or not	Dosage used	Annual usage*	Administration rate	The minimum administration time	
							Take two days	Take a day
5%Glovenin®	2016. 12	Takeda	Donation blood	1,000mg/kg/ every 3-4 weeks	869g	First 30 minutes is 0.01ml/kg/min, then up to 0.06ml/kg/ min. Next time from that speed	day 1: 3.2h day 2: 2.8h	6h
10%Venoglobulin®	2018. 2	JB	Donation blood	1,000mg/kg/ every 3-4 weeks	869g	First 60 minutes is 0.01ml/kg/min, then up to 0.06ml/kg/ min. Next time from that speed	day 1: 2.2h day 2: 1.4h	3.6h
10%Privigen®	2019. 3	CSL	Include non-donated blood	1,000mg/kg/ every 3-4 weeks	869g	First 30 minutes 0.005ml/kg/min, then up to 0.08ml/ kg/min, next time from that speed	day 1: 1.6h day 2: 1h	2.6h
20%Hizentra®	2019. 4	CSL	Include non-donated blood	20 ～ 400mg/kg/ every 1 week	1,040g	Up to 50ml per hour	day 1: 2h day 2: 2h	4h

* Maximum annual usage of 50kg patients

there was a significant increase in the use of Glovenin® ($P < 0.01$), but a decrease in that of Venoglobulin®. In 2018, the use of both preparations increased despite the introduction of the 10% preparation to the market and the availability of outpatient treatment.

3. Comparison of administration rates (time) for prevention of CIDP progression

Table 1 shows the minimum administration times for patients weighing 50 kg for the four drugs approved for the prevention of CIDP progression.

Table 2 PID/SID: Change in usage by concentration and usage per person

Year	5% (kg)	10% (kg)	20% (kg)	Total (kg)	Usage per person (g)
2012	43.7	0.0	0.0	43.7	45.7
2013	31.4	15.5	2.8	33.3	33.0
2014	30.3	12.2	10.1*	32.6	34.2
2015	34.2	22.8	20.9	38.5	34.4
2016	33.0	53.2	48.9	43.2	42.4
2017	22.7	82.4	50.3	36.0	31.5
2018	21.7	302.9*	70.3	59.0*	53.0*

*P<0.01

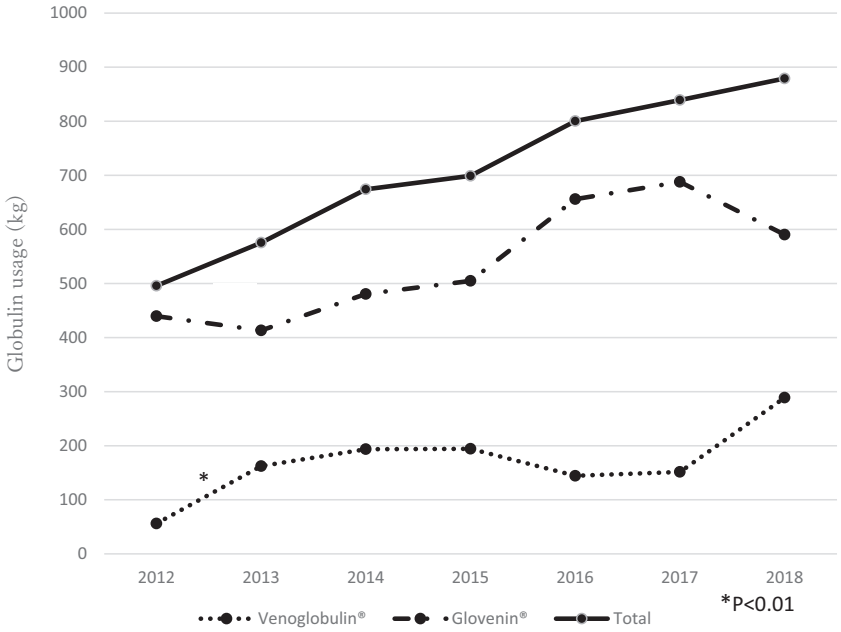

Fig. 4　Venoglobulin® and Glovenin® usage and Total for CIDP
Venoglobulin® and Glovenin®, which are approved for the prevention of CIDP progression, showed significant growth in the year they were approved (*P＜0.01), but the total value of the two did not change significantly because of the decline in the use of the other preparation.

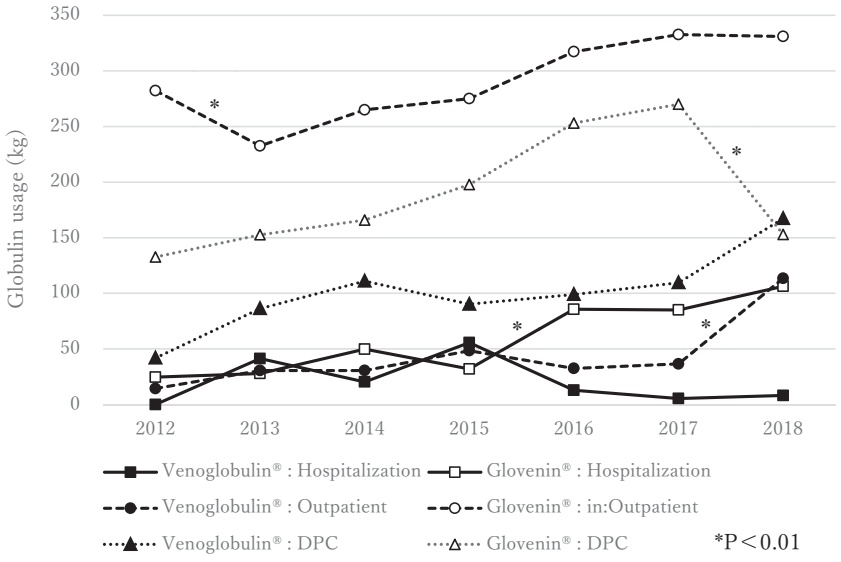

Fig. 5　Amount used in CIDP by preparation and treatment type
The previously approved Glovenin® continued to dominate the CIDP market, and there was no switch from 5% Glovenin® to 10% Venoglobulin® in outpatient settings. Glovenin® in the DPC was switched to Venoglobulin® in the DPC and in outpatient departments.

Glovenin® 5% (JB) administered on two separate days requires 3.2 h on the first day and 2.8 h on the second day, or 6 h if administered on one day. Venoglobulin® 10% (Takeda) requires 2.2 h on the first day and 1.4 h on the second day, or 3.6 h if administered on one day. Privigen® 10% (CSL) requires 1.5 h on the first day and 1 h on the second day, or 2 h if administered on a single day. Hizentra® 20% (CSL) has an administration limit of

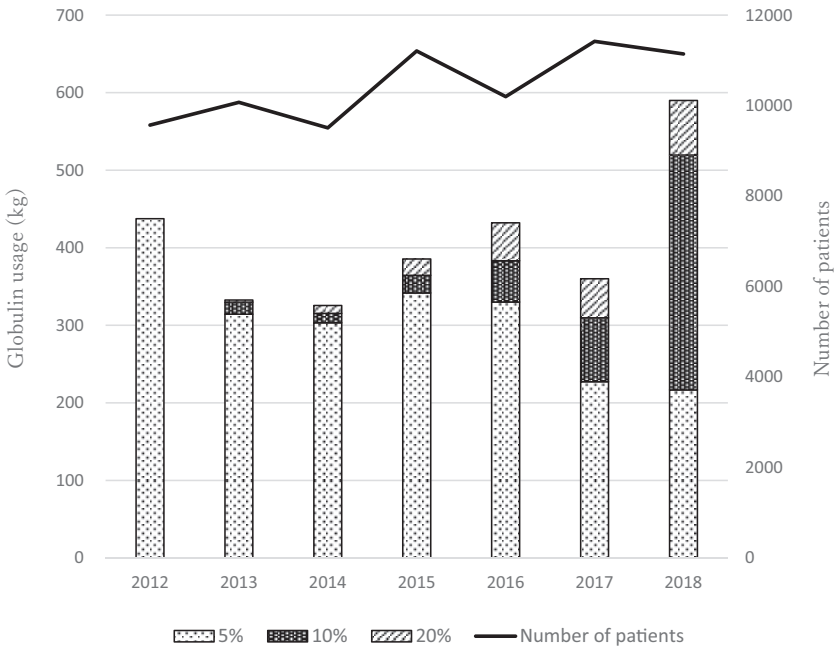

Fig. 6 PID/SID: Number of patients and change in usage by concentration
In 2018, there was a large switch to 10% immunoglobulin preparations, and the per capita use of these preparations increased significantly.

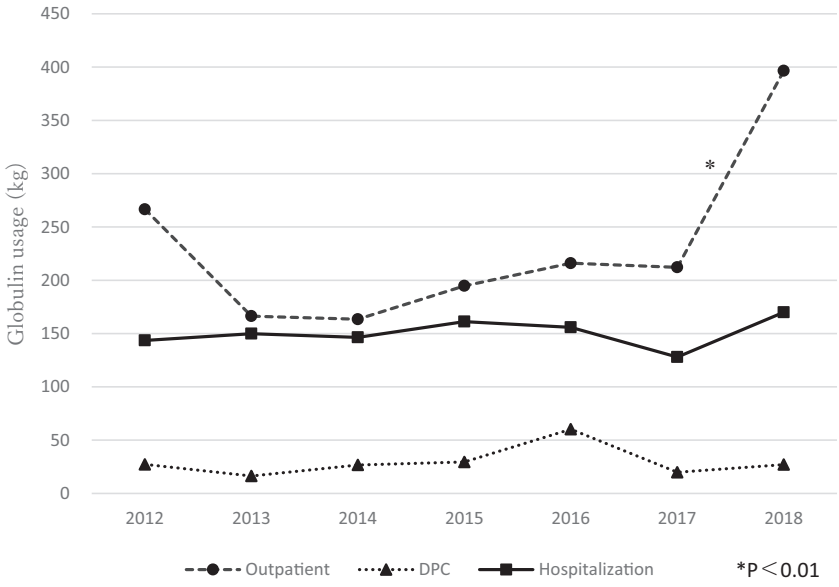

Fig. 7 Amount used for PID/SID by treatment type
Especially, the outpatient used of immunoglobulin preparations for PID/SID treatment increased significantly (*P＜0.01) in the year when the 10% preparation became available on the market.

50 m*l*/h and requires administration for 2 h on the first day and 2 h on the second day.

Compared with domestic globulin preparations, overseas globulin preparations require much shorter administration times. Therefore, outpatient treatment can be easily performed without hospitalization.

6) Changes in the number of PID/SID patients and the amount of immunoglobulin used for each concentration and form of treatment for PID/SID

Table 2 and Fig. 6 show the amount used of each concentration of immunoglobulin for PID/SID. Since all preparations have been approved for PID/SID, they

were categorized by concentration and their total amount was calculated. With the launch of 10% Venoglobulin® in 2018, the market share of the 10% preparation increased significantly, and the total amount used also increased significantly. The use of 20% Hizentra® for subcutaneous injection has also increased significantly since 2013, when it was approved. Hizentra® is the only immunoglobulin that can be administered at home and is also used to prevent CIDP progression, with the total use increasing approximately 27-fold in the four years since 2014[5].

In terms of the form of treatment, outpatient use increased sharply with the launch of the 10% concentration preparation (Fig. 7). Although there was no significant change in the total number of patients, the total number of outpatients surged, and the average per capita use increased significantly.

Discussion

1) Changes in the amount of IgG2 and KD

Treatment for IgG2 was switched to the higher concentration preparation, with patients being transferred to the outpatient setting, but there was no increase in overall use. In patients with KD, there was no transfer to outpatient settings, and the switch to the higher concentration preparation was performed either at the DPC or in hospitalizations based on fee-for-service. Since many patients with KD are infants[6], it is likely that the switch was made with the aim of reducing treatment time. The increase in overall use was also not significant ($P=0.52$). These results suggest that these two diseases were not direct factors leading to the immunoglobulin shortage.

2) Changes in the amount used for prevention of CIDP progression

It has been said that the current surge in domestic demand for immunoglobulin has largely been influenced by the amount of CIDP use, which was approved as an indication for prevention of CIDP progression immediately before the surge in consumption of the immunoglobulin[7]. Indeed, immediately after approval, there was an increase in the use of its preparation, but the use of the other preparation decreased by a similar amount, resulting in a non-significant increase in the total amount used. In terms of the form of treatment, as reported in a previous study, "High-cost medical care in intractable neuro immunological diseases: Is the DPC/PDPS payment system efficient for this population?"[8], DPC is unprofitable unless the hospitalization is extended to the break-even point of profitability, and the switch to outpatient treatment is thought to have been proactively made to avoid this problem. However, no change in the preparation or treatment was observed for hospitalizations based on fee-for-service or outpatient, and the launch of 10% Venoglobulin® had little effect on overall usage. These results suggest that the use of CIDP was not a direct cause of the sudden immunoglobulin shortage.

3) Changes in the form of treatment and creation of new treatment needs through the development of concentrated preparations

Due to the development of concentrated preparations and accelerated drip rates, the forms of treatment for CIDP and PID/SID have changed from inpatient to outpatient to home-based. Notably, in the case of PID/SID, the amount of immunoglobulin used to treat PID/SID per patient in the outpatient setting increased rapidly after the 10% preparation was launched. This indicates that new treatment needs have been created by increasing the frequency of outpatient and home-based treatment in conjunction with the decline in inpatient treatment, which is a major hindrance in daily life for patients requiring continuous care.

Shorter treatment times are an important factor in market competition, which is heavily influenced by the development of concentrated preparations and faster rates of administration. The newly approved 10% Privigen® takes approximately one-third the time to administer compared with that required for the domestically produced 5% Glovenin®. In other words, the use of 10% Privigen® requires one 2-h outpatient visit, whereas 5% Glovenin® requires two 3-h outpatient visits. Privigen® has also been approved for the treatment of PID/SID. To administer a 20 g per dose in continuous treatment, Glovenin® 5% requires a minimum of 183 minutes（approximately 3 hours), whereas Privigen® requires 61 minutes（approximately 1 hour).

The reason for the lack of a new need for CIDP treatment at this time is likely because 5% Glovenin®, which was approved in 1999, has captured 90% of the market and has subsequently continued to maintain its share. In the future, if 10% Glovenin® is developed, or if the market share of 10% Venoglobulin® and 10% Privigen® expands in the outpatient setting, new treatment needs will be created to prevent the progression of CIDP, as well as PID/SID.

It is also important to note that many immunoglobulins are consumed in continuous treatment. The dosage to improve symptoms in other diseases is usually 400 mg/kg for 5 days, which is approximately 124 g in a standard man, assuming an average body weight of 61.9 kg.

However, to prevent the progression of CIDP or to continue treatment for PID/SID, 1,000 mg/kg or 200-600 mg/kg is administered at 3-4 weeks intervals, resulting in a maximum annual dose of 1,076 g with CIDP for standard men and 885 g for standard women. Assuming that all CIDP patients receive preventive treatment for progression every three weeks (4,315 patients in fiscal year 2018[9], male to female ratio of 1.6:1[10]), this would amount to an annual consumption of approximately 4.3 tons, which is more than two-thirds of the current total domestic consumption. Considering that the population of SID/PID patients is also large and the number of patients has been increasing every year, further increases in demand are expected in the future.

The rapid increase in the use of immunoglobulin among patients with CIDP or PID/SID has attracted attention overseas as well. In the United States, the amount of immunoglobulin used to treat PID/SID alone has increased by 1.25 tons in the six years since 2012[3]. Foreign companies have embarked on large capital investments, and the United States blood industry business will reach a size of approximately 4.81 trillion yen by 2024[3].

Conclusions

This study revealed that the main factor behind the rapid increase in the use of immunoglobulin is the reduction in treatment time due to the introduction of concentrated preparations.

The demand level for immunoglobulin in Japan is expected to continue to increase in the future, and one of the most important issues is how to deal with this situation. The following three measures may be considered to address the shortage of plasma.

A. The JRC will continue to operate the blood collection service exclusively and collect necessary amounts through business improvements.

B. A second blood collection center will be established and efforts will be made to collect plasma at facilities operated by centers other than the JRC to ensure the necessary amount is available.

C. The shortfall in immunoglobulin products will be covered by imports from overseas.

First, regarding the proposal that the JRC works to improve its business and focuses on improving the efficiency of plasma collection, a fundamental reform will be necessary because the JRC's collection capacity is limited and the amount of plasma used will continue to increase in the future. At the same time, it is also necessary to take measures to promote appropriate use of immunoglobulin and adjust the amount used.

Next, the proposal to establish a second blood collection center also presents many challenges that are difficult to overcome in view of the economic burden of establishing and operating the center and its future prospects. Creating incentives for Japanese citizens to go to blood collection centers other than the JRC is one major issue. Therefore, it is important to consider the possibility that foreign companies may request the introduction of a blood collection system, which is permitted in the United States. Furthermore, if paid blood collection is introduced, there is a risk that the number of donors for free blood collection will decrease, which may affect the blood transfusion product business[11].

Furthermore, when considering the method of covering the shortage with imports, foreign countries have already succeeded in developing a 20% subcutaneous preparation and accelerating the infusion speed and are far ahead of domestic preparations in terms of competitiveness. As a result, foreign preparations that have received approval are rapidly penetrating the Japanese market. If the importation of immunoglobulin is promoted in the future, demand will be concentrated on foreign products, which may lead to a contraction in the continued production of less convenient domestic products made using domestic plasma. Considering superior manufacturing technology, quality, and manufacturing costs, there may be a move to outsource production to overseas plants in the future.

However, unless the production capacity and extraction rates of the immunoglobulin in foreign companies are clarified, it is not guaranteed that 100% of the products made with Japanese plasma will return to Japan. We are also concerned about the fact that the newly revised 2019 edition of the "Basic Policy for Improving the Safety and Ensuring the Stable Supply of Blood Products" rather disturbingly omits the important phrase "based on fair and transparent" deliberation regarding the determination of the distribution of domestic plasma[12].

If Japan becomes dependent on other countries in the production of the immunoglobulin, domestic companies will become vulnerable and will not be able to provide a stable supply in the event of a disaster[13]. Furthermore, if there is a global shortage of immunoglobulin, it may be difficult to be obtained from overseas[14)15)]. In order to avoid such a situation, many foreign countries do not regard the amount used as the amount of demand, but instead ensure proper use and make supply and demand plans based on a figure calculated from the amount of possible production. Many countries are concerned about the blood industry's current reliance on plasma collected from overheated American blood selling and have adopted policies to switch to domestic self-sufficiency[11)16)].

Japan is now at a critical juncture in the blood business. The question of what policy Japan should choose for the future is a very difficult one, but as plasma is in short supply worldwide, the optimization of plasma use is an urgent issue. Guidelines for the use of immunoglobulins to prevention of CIDP progression with few overseas approvals and for continuous use in PID/SID should be established with particular urgency, and measures should be taken to prevent their overuse. There should be extensive debate when deciding on indications for their approval, and careful consideration should be given to the limits of their medical costs, so that these demands are not fuelled by overseas blood industry forces. To ensure a steady supply of safe blood for the future, wise choices need to be made now.

Conflict of interest: None

Katsunori Ohyama is employee of Glaxo SmithKline Co., Ltd.

The authors have no conflicts of interest directly relevant to the content of this article.

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我が国における免疫グロブリン製剤の使用量増加とその要因

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要旨：

近年，世界においてグロブリン製剤の不足が深刻化している．我が国においても使用量は 2010 年からの 10 年間で約 1.5 倍に増加しており，特に 2019 年は需要予測を大幅に上回り，緊急輸入を余儀なくされた．

2019 年の使用量急増の直前に加えられた 2 つの要因「CIDP 進行抑制への適応認可」と「濃厚製剤の上市」について分析したところ，CIDP に対するグロブリン製剤の使用量は継続的に増加傾向にはあったものの認可の前後で有意な増加は認められなかった．しかし，濃厚製剤 10% ヴェノグロブリンの上市によって，治療時間が短縮され，入院から外来，在宅へと治療形態が変化しており，特に継続的投与を必要とする低及び無ガンマグロブリン血症において使用量が急増していたことが確認された．入院によって妨げられていた隠れた治療ニーズが外来治療が可能になることによって掘り起こされたものと考えられる．今後，企業による治療時間の短縮化が進むと継続的投与を必要とする疾患において更なるニーズが創生されるものと考えられる．

白熱した国際的血液事業ビジネスが繰り広げられる中，グロブリン製剤適正使用の推進と適応症の認可をどこまで広げ，需要量をどのように調節するのかについての慎重な論議が必要である．

キーワード：

慢性炎症性脱髄性多発神経炎，低及び無ガンマグロブリン血症，免疫グロブリン適正使用，投与速度，
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