PSEHB/PED Notification No. 0630-5
June 30, 2023

To: Directors of Prefectural Health Departments (Bureaus)

Director, Pharmaceutical Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare

(Official seal omitted)

Principles for Obtaining Indications based on Comparative Evaluation, etc. of the Quality Attributes of Intravenous Human Immunoglobulin Products

The principles for obtaining indications based on comparative evaluation, etc. of the quality attributes of intravenous human immunoglobulin products have been formulated as presented in the attachment. Please inform related parties under your jurisdiction of this notification.

ATTACHMENT

Principles for Obtaining Indications based on Comparative Evaluation, etc. of the Quality Attributes of Intravenous Human Immunoglobulin Products

1. Introduction

An intravenous human immunoglobulin product (hereinafter referred to as “IVIg”) is a pharmaceutical that contains the active ingredient of human immunoglobulin G (IgG), which is highly purified from human plasma.

At the time of conducting the associated research[i)], there are 6 approved IVIg products in Japan, which include 5 intact products purified from human plasma retaining full-length IgG with no processes such as modification and 1 product processed through sulfonation of the interchain disulfide bonds of IgG. IgG highly purified from human plasma is a common active ingredient in all of these IVIg products. However, approval has been granted for each indication of these individual products based on clinical study results in many cases because the possibility cannot be ruled out that differences in the characteristics of source plasma obtained from different countries as well as differences in manufacturers, manufacturing methods, etc. may cause differences in the quality attributes of each product, which may affect its efficacy and safety.

In Europe, on the other hand, a core SmPC has been prepared commonly for IgG products, and a guideline on the clinical development and obtaining indications of IVIg products[1)] has been prepared. As a result, for an IVIg product shown to be effective for both primary immunodeficiency (PID) and idiopathic thrombocytopenic purpura (ITP), it is permitted to extrapolate the indications of Guillain-Barré syndrome (GBS), Kawasaki disease, multifocal motor neuropathy (MMN), and chronic inflammatory demyelinating polyneuropathy (CIDP) without conducting clinical studies to confirm its efficacy and safety. Also taking account this possible extrapolation of indications in Europe, it remains to be further discussed whether a separate clinical study of an IVIg product should still be mandatory even if it is possible to explain its expected efficacy in an indication to be obtained with no major safety concerns based on sufficient clinical use results in Japan and other grounds.

Considering these circumstances, the research group has decided to formulate principles for obtaining an indication(s) approved for a different IVIg product based on comparative evaluation of quality attributes, etc. without conducting clinical studies, taking into account the regulatory status in Japan and overseas and published literature information on the clinical use and mechanisms of action of IVIg products.

The research group, which is supported by a Health, Labour and Welfare Policy Research Grant, hopes that the formulated principles will be utilized appropriately to solve policy issues. In Japan, for blood products including IVIg products, necessary measures are required in accordance with the “Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as “PMD Act”)” and the “Act on Securing a Stable Supply of Safe Blood Products (hereinafter referred to as “Blood Act”).” Therefore, the research group expects that the principles presented in this document will contribute to obtaining indications under the PMD Act as well as ensuring safe supply of IVIg products based on the basic philosophy of the Blood Act.

[i)] A study on the quality evaluation of intravenous human immunoglobulin supported by the Ministry of Health, Labour and Welfare of Japan.
https://mhlw-grants.niph.go.jp/project/165764 (Japanese only)

2. Scope

This document applies to IVIg products containing the active ingredient of highly purified intact IgG derived from human plasma, which have a certain amount of usage after initial approval based on clinical study results in Japan and re-examination of an approved indication(s). On the other hand, this document does not apply to IVIg products containing the active ingredient of processed IgG, which affects the molecular structure, because of a limitation in the comparison of quality attributes due to the structural difference of the active ingredient between intact IgG and processed IgG. Of the IVIg products covered by this document, IVIg for which a new indication(s) is to be obtained by utilizing the principles presented in this document is called a "generic IVIg product" and IVIg which has an indication(s) to be extrapolated is called an "original IVIg product."

3. Indications for which IVIg is used

The indications for which IVIg is used are roughly divided into the following two categories: Passive immunization and immunomodulation. For passive immunization, IVIg is administered to secure a certain level of serum IgG level mainly for the purpose of preventing the onset of infections. For immunomodulation, IVIg is administered in anticipation of various IgG functions such as regulation of Fab, Fc, and cellular immunity, although the mechanism of action remains largely unknown. With regard to the indications approved in Japan, the information shown in Table 1 has been obtained. Recommended or non-recommended cases that focus on the relationship between the quality attributes and mechanisms of action of individual IVIg products have not been presented in guidelines in Japan and overseas.[2)-11)]

To date, clinical studies have been required in many cases for obtaining approval for a new indication(s) of IVIg in Japan. On the other hand, since individual intact IVIg products already approved in Japan are expected to have a high similarity in active ingredients, their quality attributes can be compared and evaluated. Guidelines in Japan and overseas do not basically recommend the use of different products based on the quality attributes of IVIg. In addition, for the indications commonly approved in Japan, their use results have been accumulated because they are similarly positioned clinically and are interchangeable. Given these facts, individual intact IVIg products are all assumed to have multiple biological activities of IgG related to passive immunization and immunomodulation described above, although differences among products in quality attributes related to different manufacturing methods cannot be ruled out. Therefore, if a comparison of quality attributes show a high degree of similarity between an original IVIg product and a generic IVIg product, it may be possible to require no clinical studies to obtain an indication(s).

Based on the above, the principles for comparative studies, etc. of quality attributes when obtaining an indication(s) without conducting clinical studies are discussed in the next section.

4. Evaluation of Quality Attributes including Comparative Studies

Evaluating the quality attributes of a generic IVIg product in comparison with its original IVIg product as a comparator is an important step in determining the need for clinical studies. For the quality attributes of the generic IVIg product, it is necessary to perform

thorough analysis using state-of-the-art analytical techniques as well as evaluation including comparative studies with the original IVIg product to a scientifically valid and reasonable extent. The release specification test conducted for each IVIg product, which is used to confirm the consistency of the product manufactured based on the established manufacturing method, is not likely to be sufficient as a study to evaluate such a high degree of similarity of quality.

Evaluation items for quality attributes are required to be selected with reference to the evaluation items, etc. exemplified in Japanese and overseas guidelines, etc. related to the characterization and comparability assessment of IVIg products and biopharmaceuticals. However, given that IVIg is a polyclonal IgG product purified from human plasma, there is generally a limitation in the comparison of structure/physicochemical properties, which should be considered to select evaluation items prior to evaluation of quality attributes. In addition, depending on the indication to be obtained, it is necessary from the viewpoint of ensuring its efficacy to establish related evaluation items (e.g. antibody titer against microorganisms such as measles virus, biological activity, and content by IgG subclass). Furthermore, considering the differences in the country for blood collection, manufacturer, and manufacturing method among IVIg products, it is necessary to perform evaluation of the active ingredient itself as well as evaluation in view of the differences in its quality attributes such as related substances and impurities profiles. For planning an evaluation of the similarity of quality attributes, it is recommended to refer to ICH Q5E,[11)] the Guideline for Ensuring Quality, Safety, and Efficacy of Biosimilars,[12)] and the guideline on the clinical development and obtaining indications of IVIg products,[1)] although there is a limitation in using these guidelines because they are not intended for blood products.

For all evaluation items, studies need to be conducted using analytical methods that can sufficiently evaluate the quality attributes of IVIg. It is also important to be able to explain the validity of the selected evaluation items including their sensitivity.

If conducting a study to compare the selected evaluation items, it is necessary to consider setting acceptance criteria for similarity. It is desirable to set acceptance criteria appropriately in consideration of the effect of any difference in the quality attributes on the efficacy and safety of the IVIg product based on the characteristics of the study comparing the evaluation items, the results of trend evaluation in the past manufacturing of IVIg, published literature, etc.

In the evaluation, it is necessary to clarify the degree of similarity of quality attributes by the comparison of quality attributes using multiple lots of products. If the comparison of quality attributes reveals any difference between the original IVIg product and the generic IVIg product, depending on its details, it is necessary to examine the difference from the viewpoint of the effect on the efficacy and safety of the generic IVIg product based on the information in published literature, etc. If the formulation of the original IVIg product affects the comparative study, it may be necessary to prepare the sample so that its composition will not affect the study. If the sample is prepared, it is required to explain the validity of the preparation method.

In the comparative study, a product approved in Japan and manufactured by the manufacturing method for commercial products should be used in principle.

5. Obtaining Indications based on Quality Attributes Evaluation Results

For drugs containing a biologically derived ingredients as an active ingredient, it is generally required to examine the necessity of conducting nonclinical studies and clinical studies when a generic drug obtains an indication(s) of an original drug, even if a comparative study of the quality attributes has shown a high similarity in the quality attributes between the original drug and the generic drug, or even if it has been sufficiently explained that the differences observed in the comparative study will have no effect on the clinical efficacy and safety of the generic drug. For IVIg products, on the other hand, they are expected to have a high similarity in active ingredients, their use results in Japan have been accumulated, and they are similarly positioned for the common indications as described above. Given these facts, assuming that highly similar quality attributes can be shown based on study results, it may be possible to obtain a new indication without conducting clinical studies, provided that it can be fully explained at the time of application that the generic IVIg product is expected to have similar pharmacological actions related to passive immunization or immunomodulation to the original IVIg product for the indication to be obtained, and that there are no major concerns about the safety of the generic IVIg product in the indication.

Even if highly similar quality attributes are shown, however, the conduct of clinical studies is basically required to obtain an indication, when the mechanism of action is largely different between the indication to be obtained newly and the approved indication such as when a generic IVIg product only having an indication related to passive immunization obtains an indication related to immunomodulation (or vice versa), when the dose of the IVIg product for the indication to be obtained newly significantly exceeds the dose for the approved indication in a certain period, and when safety concerns may occur in patients with specific backgrounds when the generic IVIg product is used for the approved indication.

Only an indication(s) of the original IVIg product used as the comparator can be obtained without the conduct of clinical studies. When it is intended to additionally obtain an indication that only another original IVIg product has, individual discussion is required separately.

6. References

1) EUROPEAN MEDICINES AGENCY, Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg) (EMA/CHMP/BPWP/94033/2007 rev. 4)(https://www.ema.europa.eu/en/clinical-investigation-human-normal-immunoglobulin-intravenous-administration-ivig-scientific#current-effective-version-section)

2) U.S. Food and Drug Administration, Guidance for Industry Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-efficacy-and-pharmacokinetic-studies-support-marketing-immune-globulin-intravenous-human)

3) Japanese Society of Intensive Care Medicine, Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2020 (https://www.jsicm.org/news/news210225.html)

4) British Committee for Standards in Haematology General Haematology Task Force. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. Br J Haematol. 2003 Feb;120(4):574-96. doi: 10.1046/j.1365-2141.2003.04131.x. PMID: 12588344.

5) Japanese Society of Pediatric Cardiology and Cardiac Surgery, Guidelines for Medical Treatment of Acute Kawasaki Disease (2020 Revised Version) (http://jpccs.jp/10.9794/jspccs.36.S1.1/index.html)

6) Development Committee for the Practical Guideline for Chronic Inflammatory Demyelinating Polyradiculoneuropathy and Multifocal Motor Neuropathy, Practical Guideline for Chronic Inflammatory Demyelinating Polyradiculoneuropathy and Multifocal Motor Neuropathy 2013 (https://www.neurology-jp.org/guidelinem/cidp.html)

7) Development Committee for the Practical Guideline for Myasthenia Gravis, Practical Guideline for Myasthenia Gravis 2014 (https://www.neurology-jp.org/guidelinem/mg.html)

8) Development Committee for the Guidelines for the Management of Pemphigoid (including Epidermolysis Bullosa Acquisita), Japanese Guidelines for the Management of Pemphigoid (including Epidermolysis Bullosa Acquisita) (https://www.dermatol.or.jp/uploads/uploads/files/guideline/bullous%20pemphigoid.pdf)

9) British Transplantation Society, Guidelines for Antibody Incompatible Transplantation (https://bts.org.uk/wp-content/uploads/2016/09/02_BTS_Antibody_Guidelines-1.pdf)

10) Development Committee for the Clinical Practice Guidelines for Sever Erythema Exsudativum Multiforme, Clinical Practice Guidelines for Sever Erythema Exsudativum Multiforme, Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (https://www.nichigan.or.jp/member/journal/guideline/detail.html?itemid=307&dispmid=909)

11) PFSB/ELD Notification No. 0426001 dated April 26, 2005 issued by the Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare “Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process” (https://www.pmda.go.jp/int-activities/int-harmony/ich/0045.html)

12) PSEHD/PED Notification No. 0204-1 dated February 4, 2020 issued by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare) “Guideline for Ensuring Quality, Safety, and Efficacy of Biosimilars” (https://www.mhlw.go.jp/hourei/doc/tsuchi/T20200206I0010.pdf)

End of Document

Table 1　Mechanisms of Action of IVIg Products related to Individual Indications Approved in Japan

Indication	Presumed mechanism of action
Agammaglobulinemia or hypogammaglobulinemia[2)]	● IVIg contains antibodies against many pathogens. ● As the IgG trough level becomes higher, the protective effect against infection increases.
Concomitant use with antibiotics for severe infections[3)]	● IVIg contains antibodies specific to various pathogenic microorganisms and toxins. When binding to antigens, they exert opsonic effects, activate complements, neutralize toxins/viruses, and suppress inflammatory cytokine production.
ITP[4)]	● Inhibition of Fc receptors on macrophages etc. ● Inhibition of binding of autoantibodies to platelets by anti-idiotype antibodies.
Acute Kawasaki disease[5)]	● Increase in phagocytosis of neutrophils and macrophages. ● Neutralization of bacterial toxins. ● Alleviation of complement-mediated damaging effects and immune complex-mediated inflammation. ● Induction of anti-inflammatory cytokines. ● Regulation of matrix metalloproteinase activity. ● Modulation of T-cell cytokine and chemokine production and neutralization of T-cell superantigens. ● Inhibition of differentiation and maturation of dendritic cells and regulation of inflammatory cytokine and chemokine production. ● Inhibition of the activation of vascular endothelial cells and inhibition of the production of autoantibodies against vascular endothelial cells. ● Inhibition of mRNA of inflammation-related genes (S100) expressed in monocytes.
Improvement of muscle weakness in CIDP/MMN (acute and maintenance treatments)[6)]	● Saturation of Fc receptors on macrophages. ● Inhibition of activated complement deposition. ● Neutralization of autoantibodies by anti-idiotype antibody activity. ● Suppression of T-cell activity and enhancement of suppressor T-cell activity. ● Inhibition of antibody production by B cells. ● Modulation of cytokine production and release.
Generalized myasthenia gravis[7)]	● Competitive action with autoantibodies and inhibition of the complement cascade reaction. ● Fc receptor-mediated effects. ● Neutralization of antibody activity by anti-idiotype antibodies. ● Modulation of cytokine production and release. ● Changes in T-cell function.
Bullous pemphigoid[8)]	● Inhibition of autoantibody production from various sites of action in immunocompetent cells. ● Effect of binding to Fcγ receptors to inhibit recycling of pathogenic antibodies in serum and to promote degradation.
Pre-operative desensitization in anti-donor antibody-positive kidney transplantation[9)]	● Neutralization of donor-specific antibodies, inhibition of complement activity, and inhibition of immune activity through the inhibition of Fcγ receptors.
SJS and toxic epidermal necrolysis[10)]	● Inhibition of apoptosis by anti-Fas antibody.