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[54] INTRADERMAL ADMINISTRATION OF IMMUNOGLOBULIN G PREPARATION
免疫球蛋白 G 製品的皮內施用

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(54) **INTRADERMAL ADMINISTRATION OF IMMUNOGLOBULIN G PREPARATION**

INTRADERMALE VERABREICHUNG VON IMMUNOGLOBULIN-G-PRÄPARAT

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Description

BACKGROUND

Field

[0001] The present disclosure is related to a method for administration of IgG preparations by the intradermal (ID) route to a patient in need thereof and a composition for administration of IgG preparations by the ID route to a patient.

Description of the Related Art

[0002] Immunoglobulin G (IgG) is the most abundant immunoglobulin isotype in human serum, comprising approximately 80% of all immunoglobulins. IgG preparations are indicated for the treatment of various diseases such as primary immunodeficiency, in particular congenital agammaglobulinaemia and hypogammaglobulinaemia, idiopathic thrombocytopenic purpura, as an adjuvant in the treatment of Kawasaki's Disease and in transplant of bone marrow, hypogammaglobulinaemia associated with chronic lymphocyte leukaemia as part of HIV infection treatment in pediatric patients, among others.

[0003] The PCT patent application WO 2005/086773 A2 discloses formulations comprising one or more substances for intradermal delivery, wherein such substances are monoclonal antibodies of the IgG family for the treatment and the prevention of autoimmune and inflammatory diseases which include immunodeficiencies such as HIV-I and -II. Such formulations are delivered by intradermal methods of administration which comprise microneedle-based injection.

[0004] Scott B et al. (Scott A. Burton et al. "Rapid intradermal delivery of liquid formulations using a hollow microstructured array" Pharm. Res. Vol. 28, no. 1, p. 31-40) discloses an IgG formulation at 57 mg IgG/ml.

SUMMARY

[0005] The present invention refers to a composition comprising IgG for use in the treatment of an immunodeficiency in a subject in need thereof by intradermal administration (ID) route using a removable ID device comprising needles wherein the IgG composition has an IgG concentration of 15% to 30% (w/v) and a pH of the IgG composition is from 4.5 to 8.0.

[0006] In some embodiments of the composition, the pH is about 6.5.

[0007] In some embodiments, wherein the volume of the IgG composition is up to 10 mL per skin delivery site, more preferably the volume of the IgG composition is between 2 mL and 8 mL per skin delivery site. Even more preferably the volume of the IgG composition is between 4 mL and 6 mL per skin delivery site.

[0008] In some embodiments of the composition, the IgG preparation comprises one or more additional plas-

ma proteins.

[0009] In some embodiments, the subject is a pediatric patient.

[0010] In some embodiments, the subject is a non-pediatric patient.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] The present disclosure is described below in reference to the following figures.

FIG. 1 shows a line graph of plasma human IgG pharmacokinetics at 0-24 h in young farm pigs that were administered an IgG preparation (20 mg/kg) by the IV (n=4), SC (n=4) and ID (n=3) routes.

FIG. 2 shows a line graph of plasma human IgG pharmacokinetics at 0-240 h in young farm pigs that were administered an IgG preparation (20 mg/kg) by the IV (n=4), SC (n=4) and ID (n=3) routes

DETAILED DESCRIPTION

[0012] At present there is high demand for immunoglobulin G (IgG) which is polyvalent with a wide spectrum of human antibodies and has total functionality (neutralizing capacity, opsonization, half-life conserved), with intact molecules (integrity of the crystallizable Fc fragment) and a normal distribution of IgG subclasses identical or equivalent to natural plasma.

[0013] The usual routes for the therapeutic administration of IgG preparations include intravenous (IV), subcutaneous (SC) and intramuscular (IM). In addition, IgG may be administered by other routes such as the oral, nasal (inhaled) or topical routes. IV administration has become the standard approach for IgG supplementation in many countries, including the United States.

[0014] However, although IV administration offers the most useful therapeutic indications, for example, for the treatment of primary immunodeficiencies or for variable common immunodeficiency (deficit of IgG and IgA subclasses), secondary or acquired immunodeficiencies (for example infection by viruses such as cytomegalovirus, herpes zoster, human immunodeficiency) and diseases of an autoimmune origin (thrombocytopenic purpura, Kawasaki's Syndrome, for example), delivery of plasma-derived protein therapies such as IgG (Immune globulin G) to patients by IV administration route can be associated with infusion-related adverse effects such as flushing, fever, chills and diarrhea. IV infusions also require trained and qualified personnel to administer.

[0015] The current primary alternative to IV administration route for patients for IgG is the subcutaneous (SC) route. However, the SC route has been associated with slow progression to peak plasma concentration (T_{max}), low plasma area-under-curve (AUC), as well as pain and discomfort.

[0016] The intradermal (ID) route, also known as transdermal delivery or percutaneous permeation, is a

non-invasive delivery route which is advantageous for the administration of many drugs and/or biologics. ID delivery also overcomes many of the challenges associated with subcutaneous injection by greatly reducing patient discomfort, needle anxiety, risk of accidental needle stick injury to the personnel administering the injection and issues surrounding sharps disposal. In addition, ID systems allow for self-administration, provide sustained release of drugs and/or biologics for periods of time up to one week, and improve patient compliance. Furthermore, ID delivery systems are generally inexpensive.

[0017] Despite these many advantages, the ID delivery of drugs is confined to classes of molecules compatible with absorption through the skin. Delivery of therapeutic proteins is not typically viable with traditional ID delivery, as the skin provides an effective protective barrier to these molecules even in the presence of absorption-enhancing excipients. For example, it has been difficult to exploit the ID route to deliver macromolecules.

[0018] In addition, although much progress has been made in the development of systems for ID delivery, most commercially available devices that provide ID delivery of liquid formulations remain confined to relatively small volumes, typically less than 200 μ L. This makes the intradermal systems not to be considered as a viable alternative for IgG therapy in which grams of proteins have to be administered daily.

[0019] However, Burton et al. (Burton S.A. et al., *Pharmaceutical Research*, Vol. 28, Issue 1, pp. 31-40, (2011)) disclosed intradermal delivery into swine of up to 1.5 mL of a variety of formulations including a polyclonal antibody at a concentration of 57 mg/mL during 5-20 minutes using a microneedle delivery device. The amount of polyclonal antibody delivered with this system (approximately 85 mg) is still very low to be considered as an option for IgG therapy in which, for example, a patient with myositis is typically prescribed with 0.4 to 40 gm/kg over five days, which can be repeated every 4-6 weeks.

[0020] The present disclosure provides a method for ID administration of plasma proteins in general and IgG in particular. The method of the present disclosure overcomes the above-mentioned problems and limitations.

Composition

[0021] In some embodiments, the composition is a IgG for use in the treatment of an immunodeficiency in a subject in need thereof by intradermal (ID) route using a removable ID device comprising needles wherein the IgG composition has a concentration of IgG between 15% and 30% (w/v) and a pH of the IgG composition is from 4.5 to 8.0. In some embodiments, the composition for treating immunodeficiency has a pH of about 6.5. In some embodiments, the immunodeficiency is primary immunodeficiency. In some embodiments, the immunodeficiency is primary immunodeficiency in a pediatric patient.

[0022] In some embodiments, the pH is about 4.5, 4.75, 5.0, 5.25, 5.5, 5.75, 6.0, 6.25, 6.5, 6.75, 7.0, 7.25

7.5, 7.75 or 8.0. In some embodiments, the pH is about 6.5. The pH of the IgG preparation does not cause scabbing of the skin at administration site and is well tolerated.

[0023] In some embodiments, the composition is delivered at a skin delivery site that is proximal to where treatment is desired. In some embodiments, the composition is delivered at a skin delivery site that is distal to where treatment is desired. In some embodiments, the skin delivery site is where it is convenient to administer a drug. In some embodiments, the skin delivery site is where it is convenient to administer a drug and proximal to where treatment is desired. In some embodiments, the skin delivery site is where it is convenient to administer a drug and distal to where treatment is desired. In some embodiments, the skin delivery site is convenient for self-administration. In some embodiments, the skin delivery site is convenient for drug administration for the person administering a drug.

[0024] In some embodiments, the composition is administered at a volume of up to about 10 mL per site. In some embodiments, the volume is between about 2 mL and about 8 mL per site. In some embodiments, the volume is between about 4 mL and about 6 mL per site. In some embodiments, the volume is about 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 mL per site.

[0025] In some embodiments, the volume is dependent on the injection solution characteristics. In some embodiments, the volume is dependent on the viscosity of the IgG preparation. In some embodiments, the volume is dependent on the IgG concentration in the IgG preparation. In some embodiments, the volume is dependent on the limitation of the selected ID injection device.

[0026] In some embodiments, the duration and frequency of administration of the composition depend on, without limitation, the amount of IgG administered, how rapidly the IgG preparation is administered and the pharmacokinetics and pharmacodynamics of the IgG preparation. For example, in some embodiments, the duration of treatment can range from about 1 day to about 28 days. In some embodiments, the duration of treatment can be for about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28 days. In some embodiments, the duration of treatment can be for about 1 week to about 52 weeks. In some embodiments, the duration of treatment can be for about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 weeks. In some embodiments, the duration of treatment is indefinite, for example, the lifetime of a patient. In some embodiments, the frequency of administration is daily. In some embodiments, the frequency of administration is once, twice, thrice or four times daily. In some embodiments, the frequency of administration is daily and the duration of treatment is indefinite. In some embodiments, the frequency of administration is once, twice, thrice or four times daily and the duration of treatment is indefinite.

[0027] In some embodiments, the composition comprises an IgG preparation for the treatment of a disease.

In some embodiments, the disease comprises primary immunodeficiency. In some embodiments, the primary immunodeficiency comprises congenital agammaglobulinaemia and hypogammaglobulinaemia and idiopathic thrombocytopenic purpura. In some embodiments, the primary immunodeficiency is a pediatric primary immunodeficiency. In some embodiments, the pediatric primary immunodeficiency is hypogammaglobulinaemia associated with chronic lymphocyte leukaemia. In some embodiments, the pediatric primary immunodeficiency is hypogammaglobulinaemia associated with chronic lymphocyte leukaemia as part of HIV infection treatment in pediatric patients.

[0028] In some embodiments, the immunodeficiency is a variable common immunodeficiency. In some embodiments, the variable common immunodeficiency is deficiency of the IgG subclass. In some embodiments, the immunodeficiency is a secondary or acquired immunodeficiency. In some embodiments, the secondary or acquired immunodeficiency is due to infection, for example, by viruses such as cytomegalovirus, herpes zoster virus, human immunodeficiency virus. In some embodiments, the secondary or acquired immunodeficiency is due to a disease of autoimmune origin, for example, thrombocytopenic purpura, Kawasaki's Syndrome. In some embodiments, the IgG preparation can be used as an adjuvant in the treatment of Kawasaki's disease and in bone marrow transplant.

[0029] In some embodiments, the age of the subject is from about 18 years to about 70 years. The age of the subject may be 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65 or 70 years. In some embodiments, the age of the subject is lower than about 18 years. In some embodiments, the age of the subject is higher than about 70 years. In some embodiments, the composition enables treatment of pediatric patients. In some embodiments, the age of the pediatric patient can range from about 1 day to about 18 years. In some embodiments, the sex of the subject is a male. In some embodiments, the sex of the subject is a female.

[0030] In some embodiments, the composition can be administered in a hospital, a nursing home, an old age home or a pediatric care facility. In some embodiments, the composition can be administered at home. In some embodiments, the composition can be self-administered, administered by a health care worker or administered by a family member.

EXAMPLES

Example 1. Administration of an IgG preparation to pigs via IV, SC and ID

[0031] Young farm pigs (20-25 kg) were administered with IgG (20 mg/kg) by the IV (n=4), SC (n=4) and ID (n=3) routes. Venous blood samples were obtained at 2, 30 and 60 min; 3 and 6 hours and then daily for 10 days after IgG administration for measurement of human-spe-

cific IgG by immunoassay.

[0032] As shown in FIG. 1, the ID route had faster uptake of IgG into the plasma compartment as compared to the SC route. The plasma concentration of IgG approached C_{max} within 1 hour after administration by the ID route, whereas C_{max} for the SC route was not achieved for 24 hours. FIG. 1 and FIG. 2 show the time course of plasma IgG after administration by IV, ID and SC routes. The same plasma pharmacokinetic data are shown 0-24 hours (FIG. 1) as well as on a compressed X-axis over 10 days (FIG. 2). Clearly, 24 hours onwards in this experimental model, the plasma levels of IgG are similar irrespective of the route of administration. Thus, the elimination half-life ($T_{1/2}$) for all three routes is very similar.

Example 2. Influence of IgG preparation pH on the delivery site

[0033] To evaluate the influence of the IgG preparation pH on the delivery site, 2 mL of Gamunex® and IGSC 20% IgG formulations (Grifols Therapeutics Inc., USA) both at pH 4.0, and IGIM-S/D (Grifols Therapeutics Inc., USA) at pH 6.5, were administered to young farm pigs.

[0034] Three days following 2 mL administration of IgG, the low pH administration causes scabbing of the skin at administration site whereas neutral pH IgG appears to have good tolerability.

Example 3. Pediatric treatment

[0035] The method according to the present disclosure can be used for treating a pediatric patient with a primary immunodeficiency. The weight of the patient is about 25 kg. The typical dose range for such a patient is about 300 to about 800 mg/kg body weight over about 4 weeks. This does can be achieved using the present method with one ID administration of about 2 mL or about 4 mL of a concentrated IgG preparation. The concentrated IgG preparation has a concentration of IgG of about 16.5% or about 20% (w/v).

Claims

1. Composition comprising IgG for use in the treatment of an immunodeficiency in a subject in need thereof by an intradermal (ID) route using a removable ID device comprising needles wherein the IgG composition has an IgG concentration of 15% to 30% (w/v) and a pH of the IgG composition is from 4.5 to 8.0.
2. Composition for use according to claim 1, wherein the pH of the IgG composition is 6.5.
3. Composition for use according to claim 1, wherein the volume of the IgG composition is up to 10 mL per skin delivery site.

4. Composition for use according to claim 3, wherein the volume of the IgG composition is between 2 mL and 8 mL per skin delivery site.
5. Composition for use according to claim 3, wherein the volume of the IgG composition is between 4 mL and 6 mL per skin delivery site.
6. Composition for use according to claim 1, wherein the IgG composition comprises one or more additional plasma proteins.
7. Composition for use according to claim 1, wherein the subject is a pediatric patient.
8. Composition for use according to claim 1, wherein the subject is a non-pediatric patient.

Patentansprüche

1. IgG umfassende Zusammensetzung zur Verwendung bei der Behandlung eines Immundefekts bei einer Person, die dessen bedarf, durch einen intradermalen (ID) Weg unter Verwendung einer entfernbaren ID-Vorrichtung, die Nadeln umfasst, wobei die IgG-Zusammensetzung eine IgG-Konzentration von 15 % bis 30 % (w/v) aufweist und ein pH-Wert der IgG-Zusammensetzung von 4,5 bis 8,0 beträgt.
2. Zusammensetzung zur Verwendung nach Anspruch 1, wobei der pH-Wert der IgG-Zusammensetzung 6,5 beträgt.
3. Zusammensetzung zur Verwendung nach Anspruch 1, wobei das Volumen der IgG-Zusammensetzung bis zu 10 ml pro Hautabgabestelle beträgt.
4. Zusammensetzung zur Verwendung nach Anspruch 3, wobei das Volumen der IgG-Zusammensetzung zwischen 2 mL und 8 mL pro Hautabgabestelle liegt.
5. Zusammensetzung zur Verwendung nach Anspruch 3, wobei das Volumen der IgG-Zusammensetzung zwischen 4 mL und 6 mL pro Hautabgabestelle liegt.
6. Zusammensetzung zur Verwendung nach Anspruch 1, wobei die IgG-Zusammensetzung ein oder mehrere zusätzliche Plasmaproteine umfasst.
7. Zusammensetzung zur Verwendung nach Anspruch 1, wobei die Person ein pädiatrischer Patient ist.
8. Zusammensetzung zur Verwendung nach Anspruch 1, wobei die Person ein nicht pädiatrischer Patient ist.

Revendications

1. Composition comprenant de la IgG destinée à être utilisée dans le traitement d'une immunodéficience chez un sujet qui en a besoin, par une voie intradermique (ID) en utilisant un dispositif ID amovible comprenant des aiguilles, dans laquelle la composition de IgG a une concentration de IgG de 15% à 30% (p/v) et un pH de la composition de IgG est de 4,5 à 8,0.
2. Composition destinée à être utilisée conformément à la revendication 1, dans laquelle le pH de la composition de IgG est de 6,5.
3. Composition destinée à être utilisée conformément à la revendication 1, dans laquelle le volume de la composition de IgG va jusqu'à 10 ml par site d'administration cutanée.
4. Composition destinée à être utilisée conformément à la revendication 3, dans laquelle le volume de la composition de IgG est compris entre 2 ml et 8 ml par site d'administration cutanée.
5. Composition destinée à être utilisée conformément à la revendication 3, dans laquelle le volume de la composition de IgG est compris entre 4 ml et 6 ml par site d'administration cutanée.
6. Composition destinée à être utilisée conformément à la revendication 1, dans laquelle la composition de IgG comprend une ou plusieurs protéines plasmatiques supplémentaires.
7. Composition destinée à être utilisée conformément à la revendication 1, dans laquelle le sujet est un patient pédiatrique.
8. Composition destinée à être utilisée conformément à la revendication 1, dans laquelle le sujet est un patient non pédiatrique.

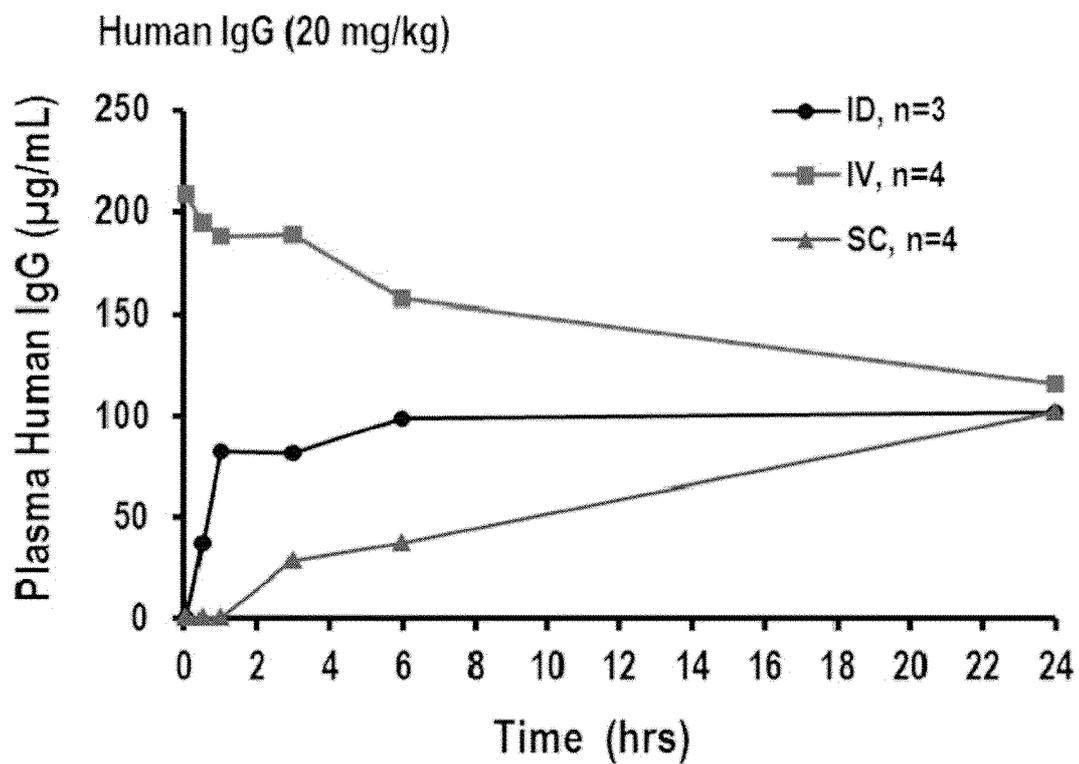


FIG. 1

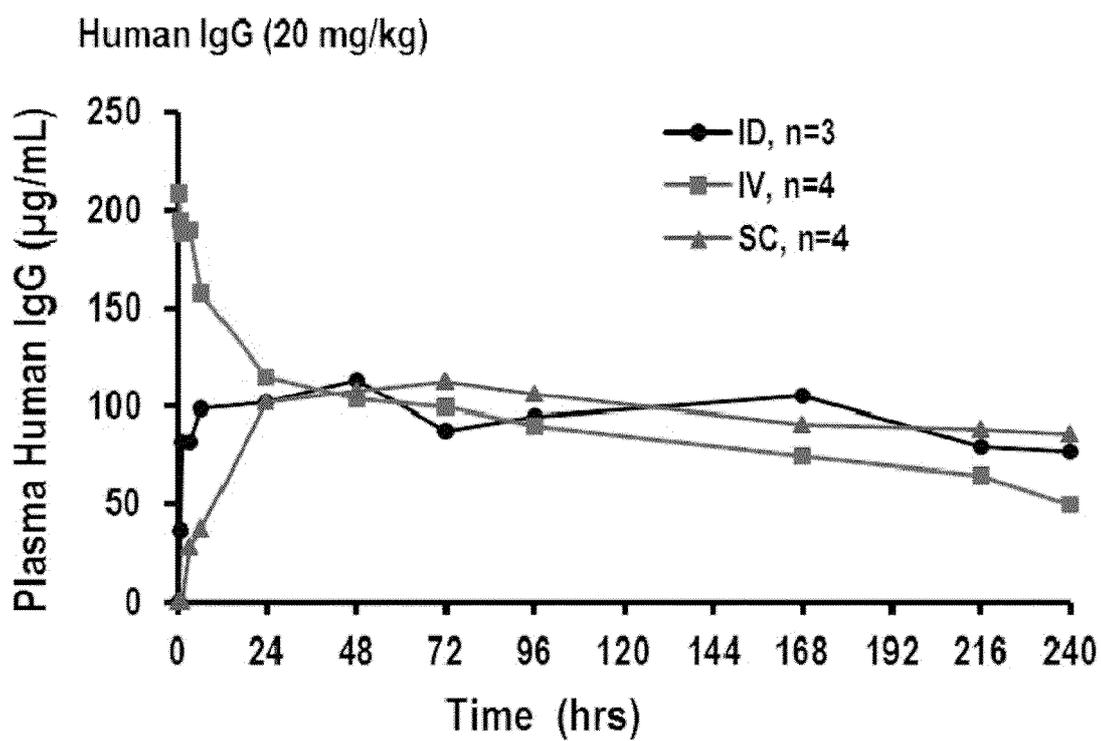


FIG. 2

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

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