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(54) Title: METHOD FOR TREATING VON WILLEBRAND'S DISEASE

(57) Abstract: Use of factor XIII for treating von Willebrand's disease. A patient having von Willebrand's disease is treated by administering factor XIII generally in conjunction with factor VIII concentrate, 1-desamino-8-D-arginine vasopressin (DDAVP) or desmopressin.



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5 METHOD FOR TREATING VON WILLEBRAND'S DISEASE

BACKGROUND OF THE INVENTION

10 Von Willebrand's disease (vWD) is the most common inherited bleeding disorder and may occur in as many as 1 in 800 individuals. The von Willebrand factor (vWF) is heterogeneous multimeric plasma glycoprotein with two major functions. It facilitates platelet adhesion under conditions of high shear stress by linking platelet membrane receptors to vascular subendothelium. It also serves as the plasma carrier for factor VIII. The normal plasma level of vWF is 10 mg/L. The vWF activity is
15 distributed among a series of plasma multimers with estimated molecular weights ranging from 400,000 to over 20 million. A single large vWF precursor subunit is synthesized in endothelial cells and megakaryocytes, where it is cleaved and assembled into the disulfide-linked multimers present in plasma, platelets, endothelial cells, and in the basement membrane of blood vessels. All of these pools of vWF contribute to the
20 protein's main function, which is to promote attachment of platelets to areas of vessel injury. To optimize the availability of vWF at the site of injury, a highly active form of the protein is stored in secretory granules of platelets and of endothelial cells. When these cells sense tissue injury (*e.g.* by contact with thrombin) they instantly mobilize the stored vWF. The released vWF binds to glycoprotein Ib (GPIb) on the platelet surface
25 and to components of the basement membrane, forming a bridge that can withstand high shear stress of blood flow. VWF is necessary for this initial attachment of platelets to the injured area. Together with other adhesive proteins, such as fibrinogen, fibronectin, and thrombospondin, vWF interacts with the GPIIb/IIIa on activated platelets and contributes to platelet spreading and aggregation.

30 A modest reduction in plasma vWF concentration, or a selective loss in the high-molecular weight multimers, decreases platelet adhesion and causes clinical bleeding. Although vWD is heterogeneous, there are certain clinical features that are common to all the syndromes. With one exception (type III disease), all forms are inherited as autosomal dominant traits and affected patients are heterozygous with one
35 normal and one abnormal vWF allele. In mild cases, bleeding occurs only after surgery or trauma. There are three major types of vWD. Patients with type I disease, the most common abnormality, have a mild to moderate decrease in plasma vWF. In the milder

cases, although hemostasis is clearly impaired, the vWF level is just below the lower limit of normal, less than 5 mg/L. In type I disease, there is a parallel decrease in vWF antigen, factor VIII activity, and ristocetin cofactor activity, with a normal spectrum of multimers detected by sodium dodecyl sulfate (SDS)-agarose gel electrophoresis.

- 5 Cultured endothelial cells derived from the umbilical cords of patients with vWD synthesize and secrete reduced quantities of vWF multimer and have a two- to fourfold reduction in vWF mRNA.

The variant forms of vWD (type II disease), which are much less common, are characterized by normal or near-normal levels of a dysfunctional vWF.

- 10 Patients with the type IIa variant of vWD have a deficiency in the high- and medium molecular-weight forms of vWF multimer detected by SDS-agarose electrophoresis. This is due either to an inability to secrete the high-molecular-weight vWF multimers or to proteolysis of the multimers soon after they leave the endothelial cell and enter the circulation. The quantity of vWF antigen and the amount of associated factor VIII are
15 usually normal. In the type IIb variant, there is also a loss in high-molecular-weight multimers. However, in type IIb disease, it is due to the inappropriate binding of vWF to platelets. This forms intravascular platelet aggregates that are rapidly cleared from the circulation, causing mild, cyclic thrombocytopenia.

- Approximately 1 in 1 million individuals have a very severe form of
20 vWD that is phenotypically recessive (type III disease). Type III patients are usually the offspring of two parents with mild type I disease. However, in many cases, the parents are very mildly affected or are asymptomatic. Type III patients may inherit a different abnormality from each parent (a doubly heterozygous or compound heterozygous state) or be homozygous for a single defect. Type III patients have severe mucosal bleeding,
25 no detectable vWF antigen or activity, and may have sufficiently low factor VIII that they have occasional hemarthroses like mild hemophiliacs.

- Prior art treatment of vWD depends on the symptoms and the underlying type of disease. One type of treatment involves the use of cryoprecipitate, a plasma fraction enriched in vWF, or factor VIII concentrates, which retain high-molecular-
30 weight vWF multimers (HUMATE-P®, KOATE HS®). A second therapeutic option, which avoid the use of plasma is use of 1-desamino-8-D-arginine vasopressin (DDAVP), or desmopressin.

- However, there are times when treating such patients with the above-described therapeutic agents produces less than satisfactory results, and hemorrhaging
35 continues. Thus, there is a need to develop additional therapies for treating vWD.

DESCRIPTION OF THE INVENTION

The present invention fills this need by administering factor XIII to patients with vWD, preferably in conjunction with either factor VIII concentrates,
5 plasma cryoprecipitate enriched in vWF, DDAVP or desmopressin acetate.

Diagnosis of von Willebrand's Disease

Once a bleeding disorder has been determined to be present, the physician must determine what is the cause of the disorder. Although a prolonged
10 bleeding time is the hallmark of vWD, this laboratory finding is not specific for vWD. Thus, the diagnosis of vWD is definitively established by means of additional laboratory tests. See Triplett, DA: Laboratory Diagnosis of von Willebrand's Disease, *Mayo Clin. Proc.* 66:832 (1991). These usually include measurements of the amount of vWF protein present in plasma, the functional activity of the vWF, and the procoagulant
15 activity of the associated factor VIII.

Treatment of von Willebrand's Disease with Factor VIII and Factor XIII

The method of the present invention improves upon the above-described treatment of von Willebrand's disease by administering factor XIII in conjunction with
20 cryoprecipitate enriched in vWF, factor VIII concentrate, DDAVP or desmopressin acetate. The factor XIII can be administered at any time alone or at the same time as the other therapies either to stop a hemorrhage or for prophylaxis.

Factor XIII, also known as fibrin-stabilizing factor, circulates in the plasma at a concentration of about 20 mg/ml. The protein exists in plasma as a tetramer
25 comprised of two A subunits and two B subunits. Each subunit has a molecular weight of 83,000 Da, and the complete protein has a molecular weight of approximately 330,000 Da. Factor XIII catalyzes the cross-linkage between the γ -glutamyl and ϵ -lysyl groups of different fibrin strands. The catalytic activity of factor XIII resides in the A subunits. The B subunits act as carriers for the A subunits in plasma factor XIII.
30 Recombinant factor XIII can be produced according to the process described in European Patent No. 0 268 772 B1. The level of factor XIII in the plasma can also be increased by administering a factor XIII concentrate derived from human placenta called FIBROGAMMIN® (Aventis Corp.) or by administration of recombinant factor XIII.

35 Administration of factor XIII to a subject is preferably intravenous. When administering therapeutic proteins by injection, the administration may be by

continuous infusion or by single or multiple boluses. A pharmaceutical composition comprising factor XIII can be formulated according to known methods to prepare pharmaceutically useful compositions, whereby the therapeutic proteins are combined in a mixture with a pharmaceutically acceptable carrier. A composition is said to be a
5 “pharmaceutically acceptable carrier” if its administration can be tolerated by a recipient patient. A suitable pharmaceutical composition of factor XIII will contain 1mM EDTA, 10mM Glycine, 2% sucrose in water. An alternative formulation will be a factor XIII composition containing 20 mM histidine, 3% wt/volume sucrose, 2 mM glycine and .01% wt/vol. polysorbate, pH 8. The concentration of factor XIII should
10 preferably be 1 – 10 mg/mL, more preferably about 5 mg/mL.

Other suitable carriers are well known to those in the art. See, for example, Gennaro (ed.), *Remington's Pharmaceutical Sciences*, 19th Edition (Mack Publishing Company 1995).

Factor XIII can be administered intravenously, intramuscularly or
15 subcutaneously to treat vWD. The levels of factor XIII in an individual can be determined by assays well known in the art such as the BERICHROM[®] F XIII assay (Dade Behring Marburg GmbH, Marburg, Germany). The normal adult has an average of about 45 ml of plasma per kg of body weight. Each liter of blood has 1000 units (U) of factor XIII. A dose of .45 U/kg would raise the level of factor XIII by about 1%
20 compared to normal. One unit of factor XIII is about 10 micrograms (mcg) of recombinant factor XIII, which contains only the dimerized, ‘A’ subunit. Thus, to raise the level of factor XIII by 1%, one would administer about 4.5 mcg of the A2 subunit per kilogram weight of the individual. So to raise the level 30% of normal, one would administer 13.5 U/kg. For a 75 kg individual this would be about 1,012.5 U. Some
25 patients may have consumptive coagulopathies that involve factor XIII losses. In such cases, a higher dosing (e.g., 1-2U/kg-%) or multiple dosing of factor XIII (e.g., 1-2U/kg-%-day) may be required.

Factor VIII concentrate is produced by a number of companies including HEMAFIL M (human, plasma-derived) produced by Baxter Healthcare Corp.;
30 HUMATE-P CONCENTRATE[®] (human, plasma-derived) produced by Centeon L.L.C.; KOATE-DVI[®] (human, plasma-derived) produced by Bayer Biological; KOATE HP (human, plasma-derived) produced by Bayer Biological; MONOCLATE-P[®] (human, plasma-derived) produced by Centeon L.L.C.

Desmopressin acetate and DDAVP are produced by Rhône-Poulenc Rorer, Collegeville, PA, by Ferring Pharmaceutical, Tarrytown, NY, and by Centeon, King of Prussia PA.

WHAT IS CLAIMED IS:

1. A method for treating von Willebrand's disease comprising administering to an individual having said disease factor XIII.
2. The method of claim 1 wherein the factor XIII is administered to said individual during a bleeding episode.
3. A method for treating von Willebrand's disease comprising administering to an individual having said disease factor XIII in conjunction with one or more additional therapeutic agents, wherein said therapeutic agent is selected from the group consisting of factor VIII concentrate, plasma cryoprecipitate, desmopressin and 1-desamino-8-D-arginine vasopressin (DDAVP).
4. The method of claim 3 wherein the factor XIII is administered prior to the administration of the additional therapeutic agent.
5. The method of claim 3 wherein the factor XIII is administered after the administration of the additional therapeutic agent.
6. The method of claim 3 wherein the factor XIII is administered simultaneously with the administration of the additional therapeutic agent.

INTERNATIONAL SEARCH REPORT

Int. Patent Application No

PCT/US 02/03742

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K38/36 A61K38/45 A61P7/04 A61K38/11 //(A61K38/36,
38:11)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE, PASCAL, SCISEARCH, CHEM ABS
Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 01 85198 A (PETERSEN LARS CHRISTIAN ;NOVO NORDISK AS (DK); ROEJKJAER RASMUS (D) 15 November 2001 (2001-11-15) page 16, line 9,10; claims 14,20 ---	1,2
X	NILSSON I M ET AL: "CHARACTERISTICS OF THE FACTOR-VIII PROTEIN AND FACTOR-XIII IN VARIOUS FACTOR-VIII CONCENTRATES" SCANDINAVIAN JOURNAL OF HAEMATOLOGY, vol. 24, no. 4, 1980, pages 340-349, XP001087526 ISSN: 0036-553X * abstract * page 346, column 2 -page 347, column 1; table 3 --- -/--	1-3,6



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

8 July 2002

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INTERNATIONAL SEARCH REPORT

Int. Patent Application No.

PCT/US 02/03742

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MORO G F ET AL: "Statistic considerations in the treatment of patients with coagulation disorders: 2 methods of approach!" RIVISTA ITALIANA DI STOMATOLOGIA. ITALY 1983 JUL-AUG, vol. 52, no. 7-8, July 1983 (1983-07), pages 589-592, XP001087506 ISSN: 0035-6905 page 590, column 1; table 2 ---	1,2
Y	BEERSMH ET AL: "The Merck Manual of Diagnosis and Therapy - 17th Edition", MERCK MANUAL OF DIAGNOSIS AND THERAPY, CENTENNIAL EDITION, WHITEHOUSE STATION, NJ: MERCK RES. LAB, US, PAGE(S) 888-889 XP002191646 ISBN: 0-911910-10-7 page 888, column 2 ---	1-6
Y	BERRY E W: "USE OF DDAVP AND CRYOPRECIPITATE IN MILD TO MODERATE HAEMOPHILLIA A AND VON WILLEBRANDS DISEASE" PROGRESS IN CLINICAL AND BIOLOGICAL RESEARCH, NEW YORK, NY, US, vol. 324, 1990, pages 269-278, XP001064004 ISSN: 0361-7742 page 273, paragraph 3 -page 274, paragraph 1; table 1 -----	1-6

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 02/03742

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-6 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
 information on patent family members

International Application No
 PCT/US 02/03742

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 0185198	A	15-11-2001	AU	5822801 A	20-11-2001
			AU	5823001 A	20-11-2001
			WO	0185198 A1	15-11-2001
			WO	0185199 A1	15-11-2001