Patents

Treatment of HLA-DR-associated immunodeficiency with interferon-gamma

Abstract

The invention pertains to the use of interferon- gamma in treating diseases involving a reduction in HLA-DR expression on monocytes, especially certain forms of septic diseases.

Classifications

- A61K38/217 IFN-gamma

DE4437868A1

Germany

Find Prior Art Similar

Other languages: German

Inventor: Ruediger Prof Dr Baehr, Hans-Dieter Prof Dr Volk, Gerhard G Prof Dr Steinmann, Susanne C Dr Querner

Current Assignee : Boehringer Ingelheim International GmbH

Worldwide applications

1994 ~~DE~~ 1995 WO ~~AU~~ ~~CA~~ ZA

Application DE4437868A events

1994-10-22	Application filed by Boehringer Ingelheim International GmbH
1994-10-22	Priority to DE4437868A
1995-10-19	Priority to CA002203255A
1995-10-19	Priority to AU50959/96A
1995-10-19	Priority to PCT/EP1995/004099
1995-10-23	Priority to ZA958950A
1996-04-25	Publication of DE4437868A1
Status	Withdrawn

Info: Patent citations (2), Non-patent citations (2), Cited by (2), Legal events, Similar documents, Priority and Related Applications

External links: Espacenet, Global Dossier, DPMA, Discuss

Claims (8)

Hide Dependent
translated from German

1. Use of interferon-γ for the manufacture of a medicament for treatment diseases caused by a decrease in the monocytic HLA-DR antigen Expression are marked. 2. Use according to claim 1, characterized in that the disease septic disorder and / or a severe infection. 3. Use according to claim 1 or 2, wherein the medicament for parenteral Administration of interferon-γ in a dosage of 25-200 µg once or several times a day, or in daily intervals. 4. Use according to claim 1 to 3, wherein the monocytic HLA-DR express sion is <30%. 5. Use according to claim 1 to 4, wherein the duration of the lowered HLA-DR- Antigen expression is more than two days. 6. Use according to claim 1 to 5, wherein the interferon-γ together with a or more antibiotics is given. 7. Use according to claim 6, wherein one of the antibiotics is an antibacterial Agent is. 8. Use according to claim 1 to 7, wherein the interferon-γ together with a or more antifungals is given.

Description

translated from German

The invention relates to the treatment of immunodeficiency with serious and long ongoing decrease in HLA-DR monocytic expression is associated with In terferon-γ (IFN-γ).

The major histocompatibility complex (MHC) plays a central role in the immune system's ability to distinguish between "self" and "not-self". The MHC refers to a cluster of genes that are responsible for the production of cell membrane surface molecules. The cell membrane molecules that are produced in response to the MHC genes are called human leukocyte antigens (HLA). Three HLA classes were identified (see **Fig.** 1). HLA class I antigen (referred to as HLA-A, -B, -C and HLA-E), HLA class H antigen referred to as HLA-D (DR, DQ, DP, DZ, DX and DV), and HLA Class III (Trowsdale J. et al., Immunology Today 9: 34-35, 1988). While HLA class I antigens are expressed on the surface of most cells in the human body, HLA class H antigens are only expressed on the cell membranes of a limited number of cell types including monocytes / macrophages and B lymphocytes.

Antigen-presenting cells (APC) such as macrophages process the micro and present it in association with HLA class-H. T helper cells with a receptor binding site that is specific for this antigen bind to the exposed th complex of macrophages (Allen P.M., et al., Nature 327: 713-716, 1987). This ak activates the T helper cells. These activated T helper cells regulate all aspects of Immune response including antibody production by B lymphocytes and Activity of the cytotoxic T cells. So this activation is a critical step in the Triggering the specific immune response. The density of HLA class II molecules on the Macrophage cell surface is one of the most important determinants in recognition and response of T helper cells to processed antigen.

Interferon-γ plays a central role in the regulation and coordination of the Im response. Interferon-γ is synthesized by activated T cells and NK cells (Vilcek J. et al., Lymphokines 11: 1-32, 1985). Alone or in combination with other cytokines interferon-γ regulates many aspects of the immune response. Interferon-γ is a potent asset Tor of macrophages, which play a central role in phagocytosis and antigen presentation play. Interferon-γ increases HLA class I and HLA class II expression, intensifies so the detection by T-lymphocytes and triggering of the specific immune response. Interferon-γ modulates antibody production by B lymphocytes, stimulates IgG Production and inhibits IgE production. Interferon-γ activates a wide range of target cells that can destroy antigen, including macrophages, granulocytes, Natural killer cells (NK cells) and cytotoxic T cells. In particular, interferon-γ a strong influence on HLA class II expression. This is remarkable because of that HLA class II expression by antigen-presenting cells is essential for triggering solution of the specific immune response and antibody formation (Janeway CA et al., Im Munology Today 5: 99-105, 1984). The density of HLA class II expression on anti gene-presenting cells such as macrophages / monocytes directly affect the extent of T cell activation. Interferon-γ increases HLA class II expression antigen presentation of cells and can induce expression on cells that are normally HLA class II-negative, like endothelial, epithelial and endocrine cells.

Septic diseases induce an initial excessive inflammatory response with a dominant production of inflammatory cytokines including tumor necro sefaktor (TNF), Interleukin (IL) -1 and IL-6. This leads to the induction of immunosuppressi ver mediators (e.g. IL-10, transforming growth factor β (TGF-β)) to a renew Most immune depression with monocyte inactivation (Docks W. et al., In: Reinhart, K., Eyrich, K., Sprung, C. (eds.) Sepsis. Springer-Verlag, Berlin Heidelberg New York 1994). A serious and long-lasting decrease in HLA-DR expression by monocytes is observed in a subset of patients with septic shock and organ failure respect. Although this subset overcomes the initial phase of septic shock has, these are immunodeficient patients with standard intensive care through a then serious and long-lasting decrease in their number of HLA-DR positive Characterized monocytes. Despite advances through improved antibiotic treatment and modern intensive care, the mortality of this subgroup is extremely high. This HLA DR-associated immunodeficiency is due to a decrease in HLA-DR expression of Monocytes characterized to less than 20% (by Baehr R. et al., Z. Klin. Med. 45: 1130-1137, 1990; Volk H. D. et al., Behring Inst. Mitt. 88: 208-215, 1991). It is important to note that healthy individuals or sepsis patients who have the kriti overcome the initial phase, HLA-DR is more than 65-90% continuous on their monocytes Nuclear or following a brief reduction in HLA-DR-Ex monocytic express pression. However, if sepsis patients are at the decreased monocytic HLA-DR expression usually persists for more than three days, the mortality of this is Patients extremely high (Docks W. et al., In: Reinhart, K., Eyrich, K., Sprung, C. (eds.) Sepsis. Springer-Verlag, Berlin Heidelberg New York 1994). In these patients the Ex pression of HLA-DQ antigen also suppressed. In contrast, the HLA Class II antigen expression of the B lymphocytes and the HLA class I antigen expresses sion normal. The selective loss of HLA-DR expression on the surface of mono cytocytes decrease the ability of monocytes / macrophages to present antigen (Volk H. D. et al., The Microbiologist 3: 20-26, 1992).

The decreased HLA-DR expression in this patient subset is a valid one and reliable prognostic indicator of fatal outcome or survival (Volk H. D. et al., In: Masihi, K. N. and Lange, W. (eds.) Immunotherapeutic prospects of infectious diseases. Springer Verlag, Berlin Heidelberg, 1990; Barthlen W. et al., In: Trede Seifert Hartel (eds.) Surgical Forum 1994 for experimental and clinical research. Springer-Verlag, Berlin Heidelberg 1994).

U.S. Patent No. 5198212 of March 30, 1993 describes the prophylactic Treatment of mice followed by an experimental traumatic event Exposed to the in vitro treatment of human cells from trauma patients and prophylactic treatment of patients with serious injury immediately after the inpatient admission with interferon-γ.

Interferon-γ was known to be an extremely efficient enhancer of monozyti HLA-DR expression. The critical condition of sepsis patients with HLA-DR However, degradation is characterized by a sharp increase in TNF secretion. It was also known that interferon-γ is able to induce TNF. That was why in the public scientific discussion suggested that the treatment of Sepsis patients with interferon-γ could be harmful. Because interferon-γ is the TNF product tion in monocytes, it has always been considered a dangerous drug for these patients and considered contraindicated.

The object of the present invention was to provide agents for the treatment of diseases to provide genes associated with a decrease in HLA-DR expression which are characterized by immunodeficiency. Such diseases are in particular be certain forms of septic diseases and serious infections.

The task could be solved by providing interferon-γ as a means the. Surprisingly, the use of interferon-γ resulted in a therapeutic one Benefits for the indicated indication. The invention thus relates to the use of inter feron-γ for the treatment of diseases caused by a decrease in monocytic HLA-DR antigen expression is marked, especially if it is long lasting and serious, as well as pharmaceutical compositions for this indication, the Inter feron-γ included. In particular, the present invention relates to the use of Interferon-γ to treat a subset of patients who have septic shock have experienced with or without organ failure and that through a serious and long-lasting Lowering of HLA-DR monocytic expression are characterized. Especially Therapy is advantageous if the monocytic HLA-DR expression is <30% and / or the duration of decreased HLA-DR antigen expression more than two days is.

A person skilled in the art is now responsible for realizing the present invention Plenty of options available to IFN-γ using both conventional methods as well also by recombinant DNA. If he chooses the first path, he can choose for example the Yip method. Y.K., immune. 34, 131-139, 1981. For the more recently, more attractive methods, human IFN-γ via recombinant DNA either To manufacture in prokaryotic or in eukaryotic systems, z. B. Gray P.W. et al., Nature 295: 503-508, 1982; Derynck, R. et al., Nucl. Acid. Res. 11: 1819- 1837, 1983, Simons, G. et al. Gene 28: 55-64, 1984, Scatill, J. et al., Proc. Natl. Acad. Sci. USA 80: 4654-4658, 1983, or according to EP-A 77 670, EP-A 254 345, EP-A 273 373 be moved. The invention also includes IFN-γ derivatives which are known per se th methods can be produced (e.g. EP-A 170 917, EP-A 219 781). Also included are IFN-γ polypeptides that are based on known synthetic methods on the protein and DNA level can be produced (e.g. EP-A 161 504; Tanaka S. et al. (1982)).

Those skilled in the art will find the use of interferon according to the invention known and customary pharmaceutical or pharmaceutical formulations for respective application into consideration, but preferably that for parenteral application, especially for intravenous, intramuscular, subcutaneous, intracutaneous, intra-articular, intrathecal, intraperitoneal infusion or injection, with continuous infusions or intermit infusions with the pumps available for the specialist or the Administration via microencapsulated preparations z. B. based on liposomes z. B. according EP-A 213 523 are included.

To prepare a ready-to-use solution for the inventive use of interferon, for example as a bolus injection or as an injection or infusion hen the expert the aqueous infusion and injection known to him for this purpose tion solutions available, possibly together with the auxiliary, Trä known to him ger- and / or stabilizing substances. A ready-to-use solution for the invention For example, use is to be made in the manner of highly purified interface ron in "water for injections" or in physiological buffered with phosphate Saline solution (pH 7 to 7.5), optionally with tween and / or gelatin or an Al bumin supplemented, dissolved before application and placed in suitable containers (e.g. syringes, Ampoules, bags) is filled sterile.

The amount of interferon to be administered for use in the invention is based on the dosages known to the person skilled in the art, on the severity of the er disease, the response rate and the further course of the disease as well as the Side effects. In general, it can be assumed that the dosage is close to individual duel criteria. A possible dosage is 25-200 µg, which is more times a day, or at daily intervals, taking the duration and dose the interferon-γ administration depends on the level of HLA-DR expression reached. It can As a rule, it can be assumed that values of approx. 50% and more will end Show interferon-γ therapy.

Interferon-γ therapy can advantageously be combined with other forms of therapy are, particularly preferably with antibiotic or antifungal therapy. Examples for antibiotics that can be used in such combinations are ampicillin, Fosfomycin, cephazohn, chloramphenicol, netilmicin, colistin, cefotaxim, cefamandol, Cefoperazone, polymyxin B, cefotiam, cefine oxime, ceftizoxime, ceftriaxone, ceftazidime, Aztreonam, imipenem, cilastatin, gentamicin, ofloxacin, cefotetan, cytarabine, ciproflox acin, teicoplanin, gentamicin and amoxicillin. Examples of antifungals used in such Combinations that can be used are Amphotericin B, Natamycin, Clotrimazole, Bifonazole, 4-

hexylresorcinol, griseofulvin, tolnaftate, miconazole nitrate and nystatin. At combined therapy, the different classes of active substances can be carried out simultaneously or sequentially be applied via the appropriate route.

Illustrations

Fig. 1 Arrangement of the human MHC loci on chromosome 6. DP, HLA-DP; DN, HLA-DN; DO, HLA-DO; DQ, HLA-DQ; DR, HLA-DR, the designations A1, A2, B1, B2 etc. each denote the different (α1, α2, β1 or β2 chains; BF, proper factor B (des Complements); C2, Complement- Component 2; C4, genes A and B; CYP21 and CP21P, cytochrome P450, steroid hydroxylase genes and pseudogenes; RD, repeated dipeptide locus; TNF-α and -β, tumor necrosis factors alpha and beta.Arrows indicate the direction of transcription. The number and order of class I loci is unknown.

Fig. 2 HLA-DR expression of monocytes from a sepsis patient who was treated with IFN-γ (see example). Cytofluorometric analysis of peripheral mononuclear cells. ICU = intensive care unit.

example

A pilot study of surgical patients suffering from sepsis with immunodeficiency, as Associated with serious and long-term degradation of the monocytic HLA-DR-Ex pression, suffering, is still going on. Sepsis was defined by tachypnea (breathing <20 Breaths / min. [if the patient is mechanically ventilated, <10 l / min., FiO_2 <0.4 in Anwe Sensitivity of PEEP 5 cm H_2O]), tachycardia (heart rate <110 beats / min.), hyper thermal or hypothermic (core or rectal temperature <38.5 ° C or <35.6 ° C.

Peripheral blood mononuclear cells from sepsis patients were separated by cytotoxic fluorometric analysis examined for HLA-DR expression. Here was the method according to Docks et al. (Docks, W. D., P. Reinke, R. v. Baehr, H.-D. Volk. Monitoring der monocytic HLA-DR antigen expression in transplantation and sepsis. In: Schmitz, G., G. Rothe (ed.). Flow cytometry in clinical cell diagnostics. Pp. 163-177. Stuttgart gart, New York. Schattauer, 1994) used, to which reference is made in full becomes.

The therapy of sepsis patients consisted of an optimal antibiotic / antimy kotika scheme and interferon-γ. Vancomycin (750 mg, IV, active ingredient) were used as antibiotics Vancomycin HCl), Fortum (6 g, IV, active ingredient ceftazidime × 5 H_2O), Certomycin (400 mg, IV, active ingredient netilmicin sulfate), Targocid (800 mg, IV, active ingredient Teicoplanin) and Tobramycin (120 mg, i.v.) given. As antifungals, diflucan (200 mg, IV, active ingredient fluconazole) and amphomoronal (8 ml, per os, active ingredient amphotericin B) given. Interferon-γ administration (100 µg / 0.5 ml, subcutaneously) started on day 2 of one decreased HLA-DR expression <30%. Interferon γ therapy was discontinued, though HLA-DR expression had exceeded 50%.

The first sepsis patient (**Fig.** 2) showed an immunodeficiency with significantly reduced HLA-DR expression (22%). Interferon-γ therapy led to a temporary recovery of HLA-DR antigen expression, a further decrease (day 12-15) and finally to an ongoing recovery with normal HLA-DR expression. The duration of the stay in the intensive care unit during the study was only 9 days. The patient survived.

Patent Citations (2)

Publication number	Priority date	Publication date	Assignee	Title
US5198212A *	1988-10-31	1993-03-30	University Of Lousville Research Foundation Incorporated	Method and compositions for treatment of trauma-associated sepsis with gamma interferon
Family To Family Citations				
DE3829180A1 *	1988-08-29	1990-03-08	Boehringer Ingelheim Int	NEW MEDICINE FOR PREVENTING AND TREATING DISEASES CAUSED BY PRIMARY IMMUNE-DEFECTIVE

* Cited by examiner, † Cited by third party

Non-Patent Citations (2)

Title
VOLK, H.-D., et. al.: Behring Inst., Mitt. 88, (1991) 208-215 *
VOLK, H.-D., et. al.: The Microbiologist 3, (1992) 20-26 *

* Cited by examiner, † Cited by third party

Cited By (2)

Publication number	Priority date	Publication date	Assignee	Title
WO2007000234A1 *	2005-06-24	2007-01-04	Bayer Healthcare Ag	Moxifloxacin therapeutic use for treating immune system functional disturbances
Family To Family Citations				
DE10218328A1 *	2002-03-05	2003-09-25	Humboldt Uni Zu Berlin Medizin	Preventive therapy for acute stroke

* Cited by examiner, † Cited by third party, ‡ Family to family citation

Similar Documents

Publication	Publication Date	Title

EP1984006B1	2009-10-21	Conditioned blood composition and method for its production
EP0203580B1	1993-01-07	Gamma-ifn as an agent for the inhibition (hindering) of the decay process of bones
DE202009017772U1	2011-04-21	Combination preparations with cytokine antagonist and corticosteroid
DE69934305T2	2007-07-12	USE OF DEXMEDETOMIDINE FOR SEDATION ON THE INTENSIVE STATION
Wildfeuer et al.	1997	Fluconazole: comparison of pharmacokinetics, therapy and in vitro susceptibility
DE69533873T2	2005-12-29	CANCER THERAPY WITH LYMPHOTOXIN
NZ243953A	1997-06-24	Gm-csf composition for treating leukocyte dysfunction
DE69533311T2	2005-07-21	METHOD FOR TREATING AUTOIMMUNE DISEASES BY TYPE-1 INTERFERONS
DE69627367T2	2004-02-12	THERAPEUTIC APPLICATION OF A HEMOGLOBIN TO PROMOTE Wound Healing
DE69433789T2	2005-06-23	METHODS OF INHIBITION OF HIV-ASSAYED DISEASE BY MONOCLONAL ANTIBODY AGAINST SELF-TESTED CYTOTOXIC T CELLS
DE4437868A1	1996-04-25	Treatment of HLA-DR-associated immunodeficiency with interferon-gamma
DE69833225T2	2006-08-10	USE OF HISTAMINE TO INCREASE THE BLOOD CONCENTRATION OF THE HISTAMINE
DE3436638C2	1992-10-08	Use of preparations containing interferon-gamma (IFN-gamma) for the treatment of rheumatic diseases
EP0885013B1	2001-08-01	Use of multipotent parapox immunity inducers from attenuated, non-immunogenic pox viruses or parapox viruses for the preparation of medicaments
DE69737088T2	2007-04-12	THERAPEUTIC AGENT FOR THE TREATMENT OF FIV INFECTIONS
DE69531086T2	2004-04-01	Therapeutic use of hemoglobin in the treatment of blood vessel blockage
EP2195014B1	2012-02-08	Use of g-csf for the treatment of stroke
EP0391224B1	1993-10-20	Drugs and their uses for treating parasitosis
EP0411395A2	1991-02-06	Use of ACE inhibitors for atherosclerosis-prophylaxis
DE4435352C2	1998-05-20	Use of a drug to treat AIDS
EP0356900B1	1992-11-25	Use of drugs containing interferon-gamma for treatment and prevention of primary immunodeficiency
EP0592476B1	1996-10-30	Use of interleukine 10 to produce drugs with a tumour-inhibiting action
EP1425303A2	2004-06-09	Use of proteins for the production of a medicament for stimulating the innate non specific immune system
Daderian et al.	2000	An unusual case of multiple cranial nerve palsies in Wegener's granulomatosis.
EP0711170A1	1996-05-15	T-lymphocyte-containing pharmaceutical composition for treating infections

Priority And Related Applications

Priority Applications (5)

Application	Priority date	Filing date	Title
DE4437868A	1994-10-22	1994-10-22	Treatment of HLA-DR-associated immunodeficiency with interferon-gamma
CA002203255A	1994-10-22	1995-10-19	Treatment of hla-dr-associated immunodeficiency with .gamma.-interferon
AU50959/96A	1994-10-22	1995-10-19	Interferon-gamma treatment of HLA-DR-associated immunodeficiency
PCT/EP1995/004099	1994-10-22	1995-10-19	INTERFERON-η TREATMENT OF HLA-DR-ASSOCIATED IMMUNODEFICIENCY
ZA958950A	1994-10-22	1995-10-23	Treatment of hla-dr associated immunodeficiency with gamma-interferon

Applications Claiming Priority (1)

Application	Filing date	Title
DE4437868A	1994-10-22	Treatment of HLA-DR-associated immunodeficiency with interferon-gamma

Legal Events

Date	Code	Title	Description
1996-04-25	OP8	Request for examination as to paragraph 44 patent law	
1998-07-09	8130	Withdrawal	

Concepts

machine-extracted

Download Filter table

Name	Image	Sections	Count	Query match
Interferon-gamma		title,claims,abstract,description	32	0.000
Interferon-gamma		title,claims,abstract,description	32	0.000
interferon gamma		title,claims,abstract,description	31	0.000
HLA-DR Antigens		title,claims,abstract,description	29	0.000
HLA-DR Antigens		title,claims,abstract,description	29	0.000
Immunodeficiency		title,description	6	0.000
disease		claims,abstract,description	12	0.000
antigen		claims,description	16	0.000
antigens		claims,description	16	0.000
antigens		claims,description	16	0.000
biocidal		claims,description	7	0.000
manufacturing process		claims,description	6	0.000
anti bacterial agent		claims,description	5	0.000
Antibiotic throat preparations		claims,description	4	0.000
Antibiotics FOR TREATMENT OF HEMORRHOIDS AND ANAL FISSURES FOR TOPICAL USE		claims,description	4	0.000
Antibiotics for systemic use		claims,description	4	0.000
Antitubercular Antibiotics		claims,description	4	0.000
Gynecological Antibiotics		claims,description	4	0.000
Topical Antifungal Antibiotics		claims,description	4	0.000
anti-fungal		claims,description	4	0.000
intestinal antibiotics		claims,description	4	0.000
ophthalmologic Antibiotics		claims,description	4	0.000
antifungals		claims,description	3	0.000
diseases by infectious agent		claims,description	3	0.000
drug		claims,description	3	0.000
parenteral administration		claims	1	0.000
Monocytes		abstract,description	11	0.000

Show all concepts from the description section