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The invention relates to a pharmaceutical composition containing interferon gamma (IFN γ) for preventing and treating diseases caused by primary immune deficiencies. The drug is particularly directed against diseases which may occur regularly or sporadically as the result of a "severe combined immune deficiency (SCID)".

Primary immune deficiencies lead to a sharply increased risk of infection. In the most severe forms, the infections may result in the death of the patient within the first year of his life.

The term "primary immune deficiencies" is used here to denote those immune deficiencies which are genetically determined and may be inherited and are to be distinguished from secondary immune deficiencies which become apparent as a consequence of other events (e.g. virus infections, drug treatments).

The primary immune deficiencies discussed here include both humoral and cellular immune deficiencies as well as the combined immune deficiencies which are characterised by loss of function in the humoral and cellular immune response. These include those congenital diseases which result in reduced maturation of the functional immuno-competent cells or reduced expression of the antigens on the cell surface which are required for interaction (for example LFA 1 Deficiency Syndrome).

Typical immunological findings in humoral immune deficiencies include the complete absence of both circulating B-lymphocytes and also B-lymphocytes and plasma cells in the lymph nodes, the spleen and other lymphatic systems. The classic primary cellular immune deficiency, on the other hand, exhibits partial or complete absence of T-lymphocytes in the peripheral blood accompanied by severe lymphopenia, a reduced number of lymphocytes in the corresponding lymph organs

(e.g. the spleen and lymph nodes) and reduced capacity to carry out cellular immune response.

In addition to these more or less isolated immune deficiencies which on their own will result in a considerably increased risk of infection and include both extracellular and also intracellular pathogens such as viruses, fungi and bacteria (mycobacteria), the primary combined immune deficiencies lead to a loss of capacity to carry out humoral and cellular immune responses - with almost always lethal consequences for the patients involved.

What is fatal to these patients is the fact that immunisation with various antigens which induce the formation of antibodies when the immune status is normal will not produce any immunological response of any kind. The primary combined immune deficiencies manifest themselves in a clinical picture which is dominated by recurrent and very severe infections caused by viruses, fungi and bacteria. The fungal infections are caused for example by types of *Candida* and *Pneumocystis* which may cause pneumonia. The sensitivity to opportunist infections is high. Furthermore, dystrophies and symptoms in the gastrointestinal tract accompanied by severe diarrhoea occur frequently. The very early start of these infections is characteristic, and in the course of the neonatal phase the patients do not exhibit normal development or weight gain. In addition, there is a disruption of the phagocytosis capacity of granulocytes or monocytes. The prognosis for the patients ranges from very poor to unfavourable, since hitherto these infections have been only very inadequately controlled, if at all. Many patients therefore die prematurely as a result of these multifactorial polytopic infections.

Histologically, the pathognomonic findings with these patients are more or less hypoplastic lymphoid tissue and a more or less embryonic thymus. Both the B- and T-cell areas of the peripheral lymphatic tissue show

a sharp decline in the number of lymphocytes.

One of the main reasons why there have hitherto been no effective therapies for these infectious diseases, particularly in the case of SCID, is the virtually complete absence of any immunological function.

The therapeutic measures known hitherto are directed particularly to compensation of the immune deficiency. For example, it is known to carry out bone marrow transplants with the aim that the stem cells should develop, in the recipient of the transplant, into mature T- and B-cells. However, this is a very high-risk procedure since severe graft-versus-host reactions can be expected if the donor and recipient are not precisely compatible. Consequently, there is the major problem of finding a suitable donor before a lethal infection sets in. Therapeutic measures for combatting the recurrent and persistent infections have not been available hitherto since even treatment with antibiotics does not have the desired effect.

It should be emphasised once more that the complex of diseases under discussion here is clearly distinguished from those diseases which are caused for example by secondary infections produced by retroviruses or by common infections when the immune status is otherwise normal and which can be successfully treated by known, conventional methods.

The problem which the present invention set out to solve was to find an agent which will provide an effective treatment of the infections caused by primary immune deficiencies, particularly by primary combined immune deficiencies, which will prevent such infections from starting or which, by compensating for these genetically caused immune deficiencies, will establish the prerequisites for successful treatment by additional means, e.g. by the use of antibiotics.

It has been found, to our complete surprise, that

the severe complications described above can be prevented, controlled and cured by the use of interferon gamma (IFN γ) according to the invention. It has been found that with IFN γ progressive infection can be halted and the lesions produced by infection can be healed.

The invention therefore includes the prevention and treatment of complications caused by congenital disorders which lead to impaired maturation of the functional immuno-competent cells or reduced expression of the antigens on the cell surface which are necessary for interaction, as is the case, for example, in LFA 1 Deficiency Syndrome (leucocyte function antigen).

This dramatic effect could not have been expected on the basis of the properties of the immune modulator IFN γ known from the prior art. In fact, IFN γ itself has no direct effect on pathogens such as viruses. Rather, IFN γ acts as a biological messenger the function of which appears to be rather to activate or stimulate functional components of the existing immune system. Even in immunosuppressed patients, the reactivity is regarded as inadequate (Borecky, L. Fuchsberger, N., *Acta Virol.* 27, 359-370, 1983).

The publication by Paganelli, R. et al., *Clin. exp. Immunol.* 72, 124-129, 1988, indicates a correlation, based on tests carried out in vitro, between primary immune deficiencies and the defective production of interleukin and interferon controlled by T-lymphocytes. It is also pointed out that primary immune deficiencies are due to a suppressed function of T-lymphocytes, which in turn regulate the production of lymphokines (such as γ -interferon) in other cell types.

Strassmann G. et al. *Cell. Immunol.* 97 (1), 110-120, 1986, report that IFN- γ is capable of modulating or inducing the expression of cell surface proteins (HLA class II and LFA-1 antigens) and postulate that IFN- γ is capable of triggering molecular events of

an unexplained nature in macrophages.

The publication by DePréval, C. et al., The New England Journal of Medicine 318, 1295-1300, 1988, reports on the ineffectiveness of IFN- γ in in vitro tests on the activation of HLA class II antigens and stresses that IFN- γ will be useless in patients with SCID.

In patients with the severe clinical picture of an SCID described above, in whom there is virtually no functioning immune system, for the reasons given above one would have expected IFN γ to have no effect and treatment with IFN γ would most likely be regarded as hopeless.

The scope of use of IFN γ which have been known up till now includes a group of patients with tumour diseases and infections, with normal immune status or with immune diseases which are completely different from the disease complex on which the present invention is based.

In EP-A 254 593 it is proposed to use IFN γ in so-called "HUIFN-gamma susceptible diseases", i.e. in diseases in which it is known from the outset that they can be prevented or treated by the administration of IFN γ . In addition to conventional viral diseases and tumour diseases, immunopathies are also mentioned, which the person skilled in the art will take to mean autoaggressive diseases or immunocomplex diseases. Accordingly, EP-A 254 593 lists atopic allergy, myoasthenia, collagenosis, pernicious anaemia, articular rheumatism and systemic lupus erythematosus. However, the specification neither teaches nor makes obvious to the person skilled in the art that IFN γ should be used in diseases in which IFN γ therapy must appear to be without prospects of success, as previously appeared to be the case, with good reason, for the diseases which accompany primary immune deficiencies, particularly SCID.

In order to put the present invention into practice, the person skilled in the art nowadays has a number of possible ways of producing IFN γ both by conventional methods and by DNA recombination. If he chooses the former method, he may use the method described by Yip Y.K. Infect. Immun. 34, 131-39, 1981, for example. For the more recent and attractive method of producing authentic human IFN γ , DNA recombination either in prokaryotic or in eukaryotic systems, reference may be made for example to Gray P.W. et al. Nature 295, 503-508, 1982; Derynck, R. et al. Nucl. Acid Res. 11, 1819-37, 1983; Simons G. et al. Gene 28, 55-64, 1984; Scatill, J. et al. Proc. Nat. Acad. Sci. USA 80, 4654-58, 1983; or EP-A 77 670, EP-A 254 345 or EP-A 273 373. The invention therefore also includes any IFN γ derivatives which may be prepared by methods known per se (for example EP-A 170 917 and EP-A 219 781). Also included are IFN γ polypeptides which can be prepared by known methods of synthesis at the protein and DNA level (e.g. EP-A 161 504; Tanaka S. et al. Nucl. Acids Res. 11, 29-32, 1982).

IFN γ preparations obtained by DNA recombination methods are preferred, since these procedures generally result in qualitatively and quantitatively better yields.

Both natural, synthetic, semisynthetic and recombinant IFN γ or pharmaceutical compositions produced therefrom may be administered either systemically (e.g. i.v., i.a., i.m.) and/or, if the focus of infection is very local, topically in or on the site of infection.

The dosage will depend on the severity of the disease and the state of health of the patient.

However, since the group of patients in question generally consists of new born babies or small children with abnormal development and to a lesser extent adults requiring the treatment according to the invention, the

dosage will preferably be guided either according to the surface area of the body (if this is $>0.5 \text{ m}^2$) or by the body weight (if the surface area of the body is $<0.5 \text{ m}^2$). Generally, in the former case, it can be assumed that injections or infusions of IFN γ of a specific activity from 1 to $2 \times 10^7 \text{ I.U./mg}$ in a dosage range from 0.01 mg/m^2 to 2 mg/m^2 , corresponding to about $2 \times 10^5 \text{ I.U.}$ to about $4 \times 10^7 \text{ I.U./m}^2$, preferably from 0.05 to 0.5 mg/m^2 , more particularly from 0.1 to 0.2 mg/m^2 , will be effective. For the latter case, the single dose should range from $0.15 \text{ } \mu\text{g/kg}$ to 0.015 mg/kg , preferably from $0.5 \text{ } \mu\text{g/kg}$ to $5.0 \text{ } \mu\text{g/kg}$, more particularly $1.5 \text{ } \mu\text{g/kg}$. The parenteral administration may take place three times a week, for example. Depending on the clinical and immunological course of the disease in question, the period of treatment may last up to 12 months or more.

In order to help the controlling or curing of the infections, it may be expedient to accompany the IFN γ therapy with antibiotics or chemotherapeutic antibacterial, antiviral or antimycotic procedures known to those skilled in the art. According to the invention, both consecutive, alternating and simultaneous parenteral or enteral administration of at least one bacteriostatic or bacteriocidal antibiotic and/or a virostatic and/or an antimycotic (e.g. sulfanilamide, tetracyclines, macrolides, penicillins and cephalosporins, aminoglycosides, rifamycines, bacitracin and polymyxines or acyclovir, purine derivatives or griseofulvin, amphotericin, clotrimazole, to name but a few), optionally combined with one another, are included. Preventive treatment on this basis may also be advisable in order to prevent the outbreak of a first infection or an additional, subsequent infection.

The forms for administration, particularly solutions for injection or infusion of IFN γ , may be

prepared using the adjuvants known to those skilled in the art.

The following Example is intended to illustrate the use and effectiveness of IFN γ in a particularly severe case but is not intended to restrict the subject matter of the invention in any way.

Patient:

8 month old girl (birth weight 1120 grams) with reduced T-cells, no mitogenic or allogenic immune response, a high number of B-cells, with aberration at chromosome 1 in the heterochromatic region, and with significant mental retardation.

Diagnosis:

SCID, discovered on the day of birth.

Complication:

Development of severe ulceration of the base of the tongue during the seventh month of life caused by viral infection, chronic secretor of echoviruses in the faeces.

Previous

treatment: substitution with immunoglobulin, prophylactic administration of bactrim® (trimethoprim plus sulfamethoxazole), but the lesion continues to progress.

IFN γ treatment: 0.2 mg/m² (corresponding to 0.06 mg, approx. 10⁶ I.U.) i.m. for six days. After this there is a reduction to half the dose for a further 4 days because of side effects (fever, tachycardia).

Results:

Rapid and complete healing of the tongue lesion within 20 to 24 days after the start of treatment; accompanied by significant improvement in the clinical condition of the child. In parallel, there was an improvement in the immune status by a regression in the lymphocyte subpopulation CD-19 from 32% to 7% (or 16%), which was quantified by means of the corresponding and known monoclonal antibodies using the so-called CD (Cluster Defined) antigens. The increase in OKT-9 (transferrin receptor) positive cell populations from 1% to 6% can similarly be interpreted as an improvement in the immune condition.

Claims

1. Use of interferon-gamma (IFN γ) in the preparation of a pharmaceutical composition for preventing and treating diseases caused by primary immunodeficiencies.
2. Use of IFN γ according to claim 1 in the prevention and treatment of diseases caused by humoral primary immunodeficiencies.
3. Use of IFN γ according to claim 1 in the prevention and treatment of diseases caused by cellular primary immunodeficiencies.
4. Use of IFN γ according to claim 1 in the prevention and treatment of diseases caused by combined primary immunodeficiencies (SCID).
5. Use of IFN γ according to claim 1 in the prevention and treatment of diseases caused by Leucocyte Function Antigen (LFA1) deficiency syndrome.
6. Use of IFN γ according to one of claims 1 to 5, characterised in that the IFN γ is natural, synthetic or semi synthetic IFN γ or IFN γ produced by DNA recombination.
7. Use of IFN γ according to one of claims 1 to 6, characterised in that the IFN γ is a derivative with IFN γ activity which has been modified from genuine IFN γ
8. Use of IFN γ according to one of claims 1 to 7, characterised in that the IFN γ is present in conjunction with at least one antibacterial and/or antiviral and/or antimycotic active substance.