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(54) **DIMETHYL FUMARATE FOR THE TREATMENT OF MULTIPLE SCLEROSIS**

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See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to the use of certain dialkyl fumarates for the preparation of pharmaceutical preparations for use in transplantation medicine or for the therapy of autoimmune diseases and said compositions in the form of micro-tablets or pellets. For this purpose, the dialkyl fumarates may also be used in combination with conventional preparations used in transplantation medicine and immunosuppressive agents, especially cyclosporines.

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DIMETHYL FUMARATE FOR THE TREATMENT OF MULTIPLE SCLEROSIS

REFERENCE TO RELATED APPLICATIONS

This is a Division of commonly-owned application Ser. No. 09/831,620, filed May 10, 2001, now U.S. Pat. No. 6,509,376, which is a 371 continuation of PCT Application PCT/EP99/08215, filed Oct. 29, 1999, the text of which is not in English, which PCT Application claims priority on German Application No. 198 53 487.6, filed Nov. 19, 1998, the text of which is not in English.

DESCRIPTION

The present invention relates to the use of dialkyl fumarates for preparing pharmaceutical preparations for use in transplantation medicine or the therapy of autoimmune diseases and pharmaceutical preparations in the form of micro-tablets or micro-pellets containing dialkyl fumarates.

On the one hand, therefore, it relates especially to the use of dialkyl fumarates for preparing pharmaceutical preparations for the treatment, reduction or suppression of rejection reactions of the transplant by the recipient, i.e. host-versus graft reactions, or rejection of the recipient by the transplant, i.e. graft-versus-host reactions. On the other hand, it relates to the use of dialkyl fumarates for preparing pharmaceutical preparations for treating autoimmune diseases such as polyarthritis, multiple sclerosis, juvenile-onset diabetes, Hashimoto's thyroiditis, Grave's disease, systemic Lupus erythematodes (SLE), Sjogren's syndrome, pernicious anaemia and chronic active (=lupoid) hepatitis.

Both graft rejection and autoimmune diseases are based on medically undesirable reactions or dysregulation of the immune system. Cytokins such as interleukins or tumour necrose factor a (TNF-α) are substantial mediators influencing the immune system. In general, both are treated by the administration of immunosuppressive agents such as cyclosporine.

In the overall result, autoimmune diseases may be defined as the failure of the tolerance of endogenic substances or antigens. As a rule, this tolerance can be maintained only if the antigens keep coming into contact with immunological cells. When this tolerance is lost, autoantibodies are formed, i.e. a humoral immunoresponse against endogenic tissue. The exact nature of the involvement of TNF-α is not known.

Transplantations are tissue or organ transplantations, i.e. the transfer of tissues such as cornea, skin, bones (bone chips), vessels or fasciae, of organs such as kidney, heart, liver, lung, pancreas or intestines, or of individual cells such as islet cells, α-cells and liver cells, the kidney having the greatest significance as a transplanted organ.

According to the degree of relationship between the donor and the recipient we differentiate between autotransplantation (transfer to another part of the body of the same individual), iso-transplantation (transfer to another, genetically identical individual) and allogenic transplantation (transfer to another individual of the same species). Depending on the site of origin and transplantation, we further differentiate between homotopic transplantation (transfer to the same site) and heterotopic transplantation (transfer to a different site). The above-mentioned transplantations play an important role in modern medicine.

A major problem in transplantation medicine is graft rejection after transplantation of the tissue, organ or cell by

immunological defense reaction of the organism against the heteroprotein often results in rejection or dissolution of the grafts. In host-verses-graft reactions, different stages may be distinguished. Depending on the degree of difference between the recipient and the donor, this reaction takes place at different speeds so that we speak of an acute, sub-acute or chronic reaction. The acute rejection process is accompanied by the irreversible loss of the transplant (necrotisation) as a result of arteriitis or arteriolitis within 48 hours and cannot be influenced by the administration of drugs. The sub-acute rejection reaction becomes manifest as a rejection crisis from day 12 to month 4 with reversible functional disorders as a result of a transplant vasculopathy. Finally, the loss of function of the transplant as a result of vascular changes such as obliterating arteriopathy, which proceeds over weeks or years and can practically not be influenced by drugs, is termed a chronic rejection reaction.

Vice-versa, rejection reactions of the transplant against the recipient, the so-called graft-versus-host reactions, may occur when immunocompetent tissues are transplanted, i.e. primarily in bone marrow transplantation. Again, the severity of the reaction is graded, and substantially similar complications result as in host-versus-graft-reactions, namely arteriopathies and necroses.

To avoid such rejection reactions, i.e. the host-versus-graft reaction and the graft-versus-host reaction, transplantation medicine essentially makes use of immunosuppression, i.e. a weakening of the normal immunoresponse. For this purpose, anti-lymphocyte sera are often used in combination with corticosteroids and so-called anti-metabolites, e.g. purine analogues such as 6-mercaptopurine and thioguanine which affect the nucleic acid and protein synthesis and thus prevent cell division and proliferation. This leads to suppression of the production of antibodies and the cellular immune response. The immunosuppressive agents used for therapy are substances which suppress or weaken the immunoreaction in the body either specifically or non-specifically. Non-specific immunosuppressive agents are cytostatic agents such as, for example, alkylating agents or antimetabolites.

In addition, active ingredients are known which cause at least partial specific immunosuppression, such as corticosteroids, antisera, antibodies FK-506, tacrolimus, mycophenolatemofetil and primarily cyclosporines such as cyclosporine A. As a result of using modern immunosuppressive agents, the most important representatives of which are the cyclosporines, especially cyclosporine A, it was possible to improve the results of transplantation considerably over the last few years. At present, the survival rate after one year is about 60% for liver transplantations, about 80% for heart transplantations and over 90% for kidney transplantations.

Autoimmune diseases where the endogenic immune system attacks endogenic organs, tissues and cells are comparable to graft-versus-host reactions. These are also medically undesirable reactions of the immune system which may be treated with immunosuppressive agents, too.

The danger in using immunosuppressive agents lies in weakening the body's defense against infectious diseases and the increased risk of malignant diseases. Therefore, it is the object of the invention to provide a pharmaceutical preparation to be employed in transplantation medicine which may be used to treat, especially to suppress weaken and/or alleviate host-versus-graft reactions and graft-versus-host reactions, but does not have the above disadvantage.

It is another object of the invention to provide a pharma-

sclerosis, juvenile-onset diabetes, Hashimoto's thyroiditis, Grave's disease, systemic Lupus erythematodes (SLE), Sjogren's syndrome, pernicious anaemia and chronic active (=lupoid) hepatitis, without the disadvantages of immunosuppression.

The object of the invention is achieved by using certain dialkyl fumarates for preparing pharmaceutical preparations for use in transplantation medicine and for the therapy of autoimmune diseases and pharmaceutical preparations in the form of micro-tablets and micro-pellets containing these dialkyl fumarates. The individual subject matters of the invention are characterized in detail in the claims. The preparations according to the invention do not contain any free fumaric acids per se.

It is known that pharmaceutical preparations which, upon biological degradation after administration, enter into the citric acid cycle or are part thereof gain increasing therapeutic significance—especially when given in high dosages—since they can alleviate or heal diseases caused cryptogenetically.

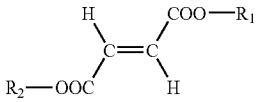
Fumaric acid, for example, inhibits the growth of the Ehrlich ascites tumour in mice, reduces the toxic effects of mitomycin C and aflatoxin and displays antipsoriatic and anti-microbial activity. When administered parenterally, transdermally and especially perorally, high dosages of fumaric acid or its derivatives known so far such as dihydroxyl fumaric acid, fumaramide and fumaronitrile have such unacceptably severe side effects and high toxicity that, in most cases, such a therapy had to be abandoned in the past.

Surprisingly, investigations carried out by the applicant have shown that methyl hydrogen fumarate, a metabolite of the dimethyl fumarate, initially increases the endotoxin-stimulated TNF-α secretion in human mononuclear cells of periphere blood (periphere blood mononuclear cells=PBMC cells) and in isolated monocytes. In addition, the applicant was able to show that fumaric acid has an effect on in vitro and in vivo haemagglutination which is comparable to that of cyclosporine.

Surprisingly, it has now been found that dialkyl fumarates are advantageous for preparing pharmaceutical compositions for use in transplantation medicine and for the therapy of autoimmune diseases. This is because compositions containing such dialkyl fumarates surprisingly permit a positive modulation of the immune system in host-versus-graft reactions, graft-versus-host reactions and other autoimmune diseases.

European Patent Application 0188 749 already describes fumaric acid derivatives and pharmaceutical compositions containing the same for the treatment of psoriasis. Pharmaceutical compositions for the treatment of psoriasis containing a mixture of fumaric acid and other fumaric acid derivatives are known from DE-A-25 30 372. The content of free fumaric acid is obligatory for these medicaments.

DE-A-26 21 214 describes medicaments containing the fumaric acid monoethyl ester and its mineral salts as active ingredient for the treatment of psoriasis. The publication "Hautarzt (*Dermatologist*) (1987) 279-285" discusses the use of fumaric acid monoethyl ester salts. Pharmaceutical preparations containing a mixture of fumaric acid monoalkyl ester salts and a fumaric acid diester for the treatment of psoriasis, psoriatic arthritis, neurodermatitis and enteritis regionalis Crohn are known from EP 0 312 697 B1.



wherein R_1 and R_2, which may be the same or different, independently represent a linear, branched or cyclic, saturated or unsaturated C_{1-20} alkyl radical which may be optionally substituted with halogen (Cl, F, I, Br), hydroxy, C_{1-4} alkoxy, nitro or cyano for preparing a pharmaceutical preparation for use in transplantation medicine or for the therapy of autoimmune diseases.

The C_{1-20} alkyl radicals, preferably C_{1-8} alkyl radicals, most preferably C_{1-5} alkyl radicals are, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, t-butyl, pentyl, cyclopentyl, 2-ethyl hexyl, hexyl, cyclohexyl, heptyl, cycloheptyl, octyl, vinyl, allyl, 2-hydroxyethyl, 2 or 3-hydroxy propyl, 2-methoxy ethyl, methoxy methyl or 2- or 3-methoxy propyl. Preferably at least one of the radicals R_1 or R_2 is C_{1-5} alkyl, especially methyl or ethyl. More preferably, R_1 and R_2 are the same or different C_{1-5} alkyl radicals such as methyl, ethyl, n-propyl or t-butyl, methyl and ethyl being especially preferred. Most preferably, R_1 and R_2 are identical and are methyl or ethyl. Especially preferred are the dimethyl fumarate, methyl ethyl fumarate and diethyl fumarate.

The dialkyl fumarates to be used according to the invention are prepared by processes known in the art (see, for example, EP 0 312 697).

Preferably, the active ingredients are used for preparing oral preparations in the form of tablets, micro-tablets, pellets or granulates, optionally in capsules or sachets. Preparations in the form of micro-tablets or pellets, optionally filled in capsules or sachets are preferred and are also a subject matter of the invention. The oral preparations may be provided with an enteric coating. Capsules may be soft or hard gelatine capsules.

The dialkyl fumarates used according to the invention may be used alone or as a mixture of several compounds, optionally in combination with the customary carriers and excipients. The amounts to be used are selected in such a manner that the preparations obtained contain the active ingredient in an amount corresponding to 10 to 300 mg of fumaric acid.

Preferred preparations according to the invention contain a total amount of 10 to 300 mg of dimethyl fumarate and/or diethyl fumarate.

According to a preferred embodiment, the size or the mean diameter, respectively, of the pellets or micro-tablets is in the range from 300 to 2,000 μm, especially in the range of 500 or 1,000 μm.

In addition to graft-versus-host reactions (see above), the following autoimmune diseases to be treated may be named: polyarthritis, multiple sclerosis, graft-versus-host reactions, juvenile-onset diabetes, Hashimoto's thyroiditis, Grave's disease, systemic Lupus erythematodes (SLE), Sjogren's syndrome, pernicious anaemia and chronic active (lupoid) hepatitis. Autoimmune diseases in a wider meaning also comprise psoriasis, psoriatic arthritis, neurodermatitis and enteritis regionalis Crohn.

In addition to the preparations for peroral administration in the form of micro-pellets, micro-tablets, capsules (such as soft and hard gelatine capsules), granulates and tablets cited above, suitable pharmaceutical preparations are preparations for cutaneous and transdermal administration in the form of

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