USE OF CYCLOSPORINS IN THE TREATMENT OF INFLAMMATORY AUTOIMMUNE DISEASES

The present invention relates to novel uses of cyclosporins, and in particular to new pharmaceutical uses of non-immunosuppressive, cyclophilin binding cyclosporins.

Non-immunosuppressive, cyclophilin binding cyclosporins and their use in the treatment and prevention of AIDS and AIDS-related disorders are described in European Patent no. 484281, which includes a general description of the cyclosporin class of compounds, their nomenclature and mode of action. The disclosure of EP 0,484,281 B, in particular the general description referred to above and other parts of the description referred to hereinafter, is included by reference in the teaching of the present application.

Surprisingly, it has now been found that cyclosporins which bind to cyclophilin, but are not immunosuppressive, exhibit an inhibitory effect upon inflammatory autoimmune diseases and conditions.

A cyclosporin is considered as binding to cyclophilin if it binds to human recombinant cyclophilin at least one fifth as well as does Ciclosporin (also referred to as cyclosporin A) in the competitive ELISA test described by Quesniaux in Eur. J. Immunol. 1987, 17, 1359-1365. In this test, the cyclosporin to be tested is added during the incubation of cyclophilin with coated BSA-Ciclosporin and the concentration required to give a 50% inhibition of the control reaction without competitor is calculated (IC_{50}). The results are expressed as the Binding Ratio (BR), which is the log to the base 10 of the ratio of the IC_{50} of the test compound and the IC_{50} in a like test using Ciclosporin in place of the test cyclosporin. Thus a BR of 1.0 indicates that the test compound binds cyclophilin one factor of ten less well than does Ciclosporin, and a negative value indicates binding stronger than that of Ciclosporin.

The cyclosporins active as inhibitors of inflammatory autoimmune diseases have a BR lower than 0.7, (since $\log_{10} 5 = 0.7$ approx), preferably equal to or lower than zero.

A cyclosporin is considered to be non-immunosuppressive when it has an activity in the Mixed Lymphocyte Reaction (MLR) of no more than 5%, preferably no more than 2%, that of Ciclosporin. The Mixed Lymphocyte Reaction is described by T. Meo in "Immunological Methods", L. Lefkovits and B. Peris, Eds., Academic Press, N.Y. pp. 227-239 (1979). Spleen cells (0.5×10^6) from Balb/c mice (female, 8-10 weeks) are co-incubated for 5 days with 0.5×10^6 irradiated (2000 rads) or mitomycin C treated spleen cells from CBA mice (female, 8-10 weeks). The irradiated allogeneic cells induce a proliferative response in the Balb c spleen cells which can be measured by labelled precursor incorporation into the DNA. Since the stimulator cells are irradiated (or mitomycin C treated) they do not respond to the Balb/c cells with proliferation but do retain their antigenicity. The IC_{50} found for the test compound in the MLR is compared with that found for Ciclosporin in a parallel experiment.

It has been found that compounds which are judged as non-immunosuppresive in the MLR above are often inactive in an IL-2 Reporter Gene Assay, and thus an IL-2 Reporter Gene Assay may be used, e.g. as a primary screen, for selection of non-immunosuppressive, cyclophilin-binding cyclosporin compounds for use in the invention.

The non-immunosuppressive, cyclophilin-binding cyclosporin compounds which are active as inhibitors inflammatory autoimmune conditions are hereinafter referred to as Active Compounds.

The Active Compounds are particularly useful for the treatment, prevention, or amelioration of autoimmune disease and of inflammatory conditions, in particular inflammatory conditions with an aetiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases. Specific auto-immune diseases for which the Active Compounds may be employed include autoimmune haematological disorders (including e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic

sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis and Crohn's disease), pancreatitis, endocrine ophthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary biliary cirrhosis, diabetes, e.g. juvenile diabetes (diabetes mellitus type I), uveoretinitis (Behcets disease), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy), asthma and other inflammatory airways diseases including an autoimmune component, thyroiditis (Hashimoto Ghoto disease), encephalomyelitis, inflammatory conditions of the central nervous system, and similar autoimmune disorders.

The activity of cyclosporins as inhibitors of inflammatory autoimmune conditions may be demonstrated in the following test systems:

Experimental autoimmune uveitis (EAU)

Female Lewis rats, 12 weeks of age (BRL, Basel) are injected in the right foot-pad with 50 µg of purified bovine retinal S-antigen. The antigen is diluted with phosphate-buffered saline and emulsified 50:50 (v/v) with Freund's complete adjuvant and Bacto M Tuberculosis H37 RA (Difco). The volume injected is 0.1 ml, containing 50 µl complete adjuvant and 1.14 mg Mycobacterium tuberculosis. Starting at day 10 after injection, the eyes are inspected daily using a slit lamp. The extent of ocular inflammation is scored in a semi-quantitative way using a scale from 0 - 4:

0 no visible change

1 minimal change in the vasculature, some dilatation of the iris and conjunctival blood vessels

2 moderate change, loss of vascular clearness, dilated iris and blood vessels, cloudy media

3 marked change, ocular protrusion, obscured pupil, pronounced loss of vascular architecture, some haemorrhage

4 severe change, marked ocular protrusion, complete loss of architecture, diffuse haemorrhage

Reference: Wacker W. B., Donoso L. A., Kalsow C. M., Yakeelov J. A. Jr., Organisciak D. T.: Experimental Allergic Uveitis. Isolation, Characterisation and Localization of a soluble Uveitopathogenic antigen from bovine retina. J. Immunol. 119 (1977) 1949-1958

Experimental autoimmune encephalomyelitis (EAE) in the Rat

Male Wistar rats are injected in the hind paws with a mixture of bovine spinal cord and complete Freund's adjuvant. Symptoms of the disease (paralysis of the tail and both hind legs) usually develop within 16 days. The number of diseased animals as well as the time of onset of the disease are recorded. Inhibition of disease onset in the above test model is indicative of pharmaceutical utility.

Reference: Levine et al., Am. J. Path. 47 (1965) 61; McFarlin et al, J. Immunol. 113 (1974) 712; Borel, Transplant. & Clin. Immunol. 13 (1981) 3].

Freund's Adjuvant-induced Arthritis

OFA and Wistar rats (male or female, 150g body weight) are injected i.c. at the base of the tail or in the hind paw with 0.1 ml of mineral oil containing 0.6 mg of lyophilised heat-killed Mycobacterium smegmatis. In the developing arthritis model, treatment is started immediately after the injection of the adjuvant (days 1 - 18); in the established arthritis model treatment is started on day 14, when the secondary inflammation is well developed (days 14-20). At the end of the experiment, the swelling of the joints is measured by means of a micro-caliper. Prevention or inhibition of disease progression in the developing or established test models is indicative of pharmaceutical utility.

Reference: Winter & Nuss, Arthritis and Rheumatism 9 (1966) 394; Billingham & Davies, Handbook of Experimental Pharmacology (Vane & Ferreira Eds, Springer Verlag, Berlin,) 50/II, (1979) 108-144]

Collagen Induced Arthritis

Rats are immunized with collagen type II administered intra-dermally around the base of the tail. 10-12 days later, onset of arthritis occurs, typified by erythema and swelling in the joints. Treatment of the animals bid p.o. with test compound, normally at two different doses is started shortly after the onset of swelling and continued for up to 10 days. Control arthritic animals and rats treated with a proprietary COX-inhibitor are included in the study. Swelling of the hind paws is assessed regularly. At the end of the study, animals are sacrificed and joints are prepared for the assessment of histological parameters. Test compounds which show good inhibition of swelling, e.g. about 50% or more of the effect of the proprietary COX-inhibitor are chosen for further study.

Chemotaxis in vitro (e.g. using the Boyden Chamber) and cyclophilin induced infiltration of neutrophils and similar assays may also be used.

It is found that many of the Active Compounds have structures differing from that of Ciclosporin specifically at the 4 and/or 5 positions. Other positions at which the structures of the Active Compounds may differ from that of Ciclosporin are positions 6 and 7.

One group of Active Compounds are cyclosporins in which the MeLeu group at position 4 is replaced by a different N-methylated amino acid for example γ-hydroxy-MeLeu, MeIle, MeVal, MeThr, MeAla, Me Tyr or MeTyr(O-PO(OH)$_2$), or Pro. In addition to MeIle and MeThr, the allo-forms MeaIle and MeaThr may also be used. In the allo-form, the stereochemistry at the β-position has the opposite configuration to that of the natural amino acid, so that the normal form and the allo-form constitute a pair of diastereoisomers.

A further group of Active Compounds is that in which Val at the 5-position is replaced by an N-alkyl-, preferably N-methyl-, amino acid. Preferably the amino acid which is N-alkylated is Val or Leu. Preferably the hydrogen of the imino group of [Val]^5 is replaced by a non-branched C_{1-6}alkyl group, preferably methyl, ethyl or n-propyl, particularly methyl. The latter preferred group of Active Compounds are all novel.

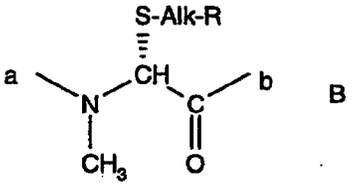
Additionally or alternatively, certain Active Compounds may differ from Ciclosporin at the 1, 2, 3, and/or 6 positions.

A particular class of Active Compounds for use in the present invention are Ciclosporin derivatives of formula A

MeBmt-αAbu-B-C-Val-MeLeu-Ala-(D)Ala-MeLeu-MeLeu-MeVal

1 2 3 4 5 6 7 8 9 10 11 A

wherein B is an amino acid residue of formula B



B

wherein a denotes the bond to the αAbu residue in position 2;

b denotes the bond to the the residue C in the 4 position;

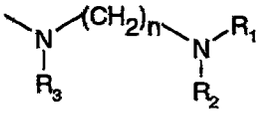
Alk represents straight or branched chain alkylene containing from 2 to 6 carbon atoms or cycloalkylene containing from 3 to 6 carbon atoms, and

R represents

a carboxy or alkyloxycarbonyl radical;

a radical $-NR_1R_2$ in which R_1 and R_2 are the same or different and represent hydrogen, alkyl, C_{2-4} alkenyl, C_{3-6}cycloalkyl, phenyl (optionally substituted by halogen, alkoxy, alkoxycarbonyl, amino, alkylamino or dialkylamino) or a benzyl or saturated or unsaturated heterocyclyl radical containing 5 or 6 ring atoms and 1 to 3 heteroatoms, or in which $R_1$and R_2 form together with the nitrogen atom to which they are attached a saturated or unsaturated heterocycle containing 4 to 6 ring atoms and optionally containing a further heteroatom selected from nitrogen, oxygen or sulphur and optionally substituted by alkyl, phenyl or benzyl;

a radical of formula

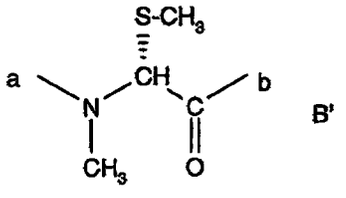


wherein R_1 and R_2 are as defined above, R_3 represents hydrogen or an alkyl radical and n is a whole number from 2 to 4,

and wherein alkyl denotes straight or branched chain alkyl containing from 1 to 4 carbon atoms;

C is MeLeu or or 4-hydroxy-MeLeu; and the pharmaceutically acceptable salts thereof.

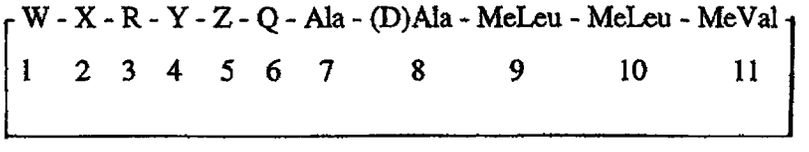
This class of Ciclosporin derivatives is further described in published International patent applications Nos. WO 98/28328, WO 98/28329 and WO 9828330. A particularly preferred compound of this class is the compound of formula A in which B is the amino acid residue B'



B'

and C is the amino acid residue 4-hydroxy-MeLeu.

A particularaly preferred group of Active Compounds is constituted by the compounds of Formula I:



I

in which W is MeBmt, dihydro-MeBmt or 8'-hydroxy-MeBmt;

X is αAbu, Val, Thr, Nva or O-methyl threonine (MeOThr);

R is Sar or (D)-MeAla;

Y is MeLeu, γ-hydroxy-MeLeu, MeIle, MeVal, MeThr, MeAla, Me Tyr, MeTyr(O-$PO(OH)_2$), MeaIle or MeaThr, or Pro;

Z is Val, Leu, N-Alk-Val or N-Alk-Leu

wherein Alk represents Me or Me substituted by

vinyl optionally substituted by

phenyl, or an N S or O heteroaryl containing 6 ring members, or

phenyl optionally substituted by

halogen; and

Q is MeLeu, γ-hydroxy-MeLeu or MeAla and the pharmaceutically acceptable salts thereof.

The groups W,X,Y,Z and Q have, independently, the following preferred significances:

W is preferably W' where W' is MeBmt or dihydro-MeBmt;

X is preferably X' where X' is αAbu or Nva, more preferably X" where X" is αAbu;

Y is preferably Y' where Y' is γ-hydroxy-MeLeu, MeVal, MeThr, MeAla or MeTyr(O-$PO(OH)_2$);

Z is preferably Z' where Z' is Val or MeVal; and

Q is preferably Q' where Q' is MeLeu;

One especially preferred group of Active Compounds are the compounds of Formula I in which W is W', X is X', Y is Y', Z is Z' and Q is Q'.

Particularly preferred Active Compounds of Formula I are:

a) [dihydro-MeBmt]^1-[γ-hydroxy-MeLeu]^4-Ciclosporin,

b) [MeVal]^4 -Ciclosporin,

c) [MeIle]^4 -Ciclosporin,

d) [MeThr]^4 -Ciclosporin,

e) [γ-hydroxy-MeLeu]^4 -Ciclosporin,

f) [Nva]^2-[γ-hydroxy-MeLeu]^4-Ciclosporin,

g) [γ-hydroxy-MeLeu]^4-[γ-hydroxy-MeLeu]^6 -Ciclosporin,

h) [MeVal]^5-Ciclosporin,

i) [MeOThr]^2-[(D)MeAla]^3-[MeVal]^5-Ciclosporin,

j) [8'-hydroxy-MeBmt]^1 -Ciclosporin,

k) [MeAla]^6-Ciclosporin,

l) [DMeAla]^3-[MeTyr(OPO(OH)$_2$)]^4-Ciclosporin,

m) [N-Benzyl-Val]^5-Ciclosporin,

n) [N-5-Fluoro-Benzyl-Val]^5-Ciclosporin,

o) [N-Allyl-Val]^5-Ciclosporin,

p) [N-3-Phenyl-Allyl-Val]^5-Ciclosporin,

q) [Pro]^4-Ciclosporin

Especially preferred Active Compounds are [MeIle]^4-Ciclosporin and [γ-hydroxy-MeLeu]^4-Ciclosporin, most especially [MeIle]^4 -Ciclosporin.

In addition to the compounds of Formula I, preferred Active Compounds include, for example

r) [γ-hydroxy-MeLeu]^9-Ciclosporin.

The Active Compounds may be obtained by methods including:

1) Fermentation

2) Biotransformation

3) Derivatisation

4) Partial Synthesis

5) Total Synthesis.

These methods are described generally and more specifically in Examples 1 to 10 of EP 0484281 B. This general description and the teaching of these Examples are incorporated by reference in the present application. Example 11 of EP 0484281 B describes

measurement of the immunosuppressive and cyclophilin-binding activities of representative Active Compounds relative to Ciclosporin, and the teaching of this examples is also included within the disclosure of the present application.

The Active Compounds are indicated for use both for the prevention and the treatment of inflammatory autoimmune conditions and diseases in patients.

Thus the invention provides use of a nonimmunosuppresive, cyclophilin-binding cyclosporin in the manufacture of a medicament for treating or preventing an inflammatory autoimmune disease or condition.

The invention further provides a method for the treatment or the prevention of inflammatory autoimmune conditions and diseases in a patient suffering or at risk of such a disease or condition, comprising administering to said patient an effective amount of an Active Compound of the invention.

The Active Compound may be administered by any conventional route, in particular enterally, e.g. orally, for example in the form of solutions for drinking, tablets or capsules or parenterally, for example in the form of injectible solutions or suspensions. By the intravenous route an indicated daily dosage may be from 1 to 20 mg/kg, preferably from 3 to 10 mg/kg, and by the oral route from 1 to 50 mg/kg, preferably from 10 to 30 mg/kg.

The toxicity of the Active Compounds is believed to be less to that of Ciclosporin. As the Active Compounds are not immunosuppressive, certain side effects of Ciclosporin related to immunosuppression are avoided. Other side effects associated with Ciclosporin, particularly nephrotoxicity and central nervous system toxicity in long term use, are conveniently less than with Ciclosporin.

The Active Compounds may be used for treatment and prevention of inflammatory autoimmune diseases either alone or in combination with other therapeutic compounds, e.g. antinflammatory compounds and/or immunosuppressive compounds. In particularly

preferred embodiments the Active Compounds are used in combination with Sanglifehrins, a recently identified class of immunosuppressive, cyclophilin-binding compounds which do not inhibit calcineurin activity. The Sanglifehrins and methods for their preparation are described in WO 9702285 and WO 9807743 . Particularly preferred Sanglifehrins for use in combination with the the Active Compounds are the Sanglifehrins A through L, especially Sanglifehrins A, B, C and D.

Thus in preferred embodiments the invention provides a process for the treatment or the prevention of inflammatory autoimmune conditions and diseases in a patient suffering or at risk of such a disease or condition, comprising administering to said patient an effective amount of a combination comprising an Active Compound of the invention and a Sanglifehrin.

The invention also provides a pharmaceutical composition, e.g. for the treatment or prevention of an inflammatory autoimmune disease or condition, comprising an Active Compound of the invention and a Sanglifehrin.

The pharmaceutical compositions of the invention are coveniently in the form of a combined preparation for simultaneous, separate or sequential use in therapy. Thus the Active Compound and the Sanglifehrin may be administered together in the form of a fixed composition, or may be administered separately and at different times. Typically the compositions may be in unit dosage form comprising an effect amount of the combined preparation.

Preferred galenic formulations for the Active Compounds include those based on microemulsions as described in British Patent Application 2 222 770A, which include topical as well as oral forms; also oral and injectable forms obtained from solid solutions comprising a fatty acid saccharide monoester, e.g. saccharose monolaurate, as described in British Patent Application 2 209 671A. Suitable unit dosage forms for oral administration comprise e.g. from 25 to 200mg Active Compound per dosage.

Formulation Examples A, B, C and D of EP 0484281 B are incorporated herein by reference:

The individual components of these formulations, as well as the methods for their preparation, are fully described in British Patent Application 2 222 770, the contents of which are incorporated herein by reference.

When the Active Compounds are administered together with other compounds, e.g. Sanglifehrins, similar formulations may be used, with appropriate ratios of Active Compound and other compound. Thus, for example, Active Compound and Sanglifehrin are preferably used in the weight ratio range from about 5:1 to about 50:1 (Active Compound po : Sanglifehrin sc) with an Acitve Compound po dose of about 10 to about 100 mg/kg.

The activities of representative Active Compounds are tested in animal model Biological Activity Assays A, B and C, which refer to the accompanying diagrams in which:

Figure 1 is a graph of disease scores (y-axis) in the EAE assay for control animals (A. black bars) and [MeIle]^4-Cs treated animals (B. grey bars) from 9 to 18 days after immunisation (x-axis);

Figure 2 is a graph showing percentage inhibition of swelling (y-axis) in the developing adjuvant arthritis assay for groups of animals treated with A. - 30 mg/kg [MeIle]^4-Cs p.o.; B. - 1 mg/kg Sanglifehrin A s.c.; and C - 30 mg/kg [MeIle]^4-Cs p.o. + 1 mg/kg Sanglifehrin A s.c., and

Figure 3 is a graph showing swelling of hind paws (in mm - y-axis) in the collagen induced arthritis assay for rats treated with vehicle (-□-; EtOH 10%/Corn oil /5 ml/kg p.o., 6 animals), [MeIle]^4-Cs (-○-; 2 x 12.5 mg/kg/day p.o., 7 animals), [MeIle]^4-Cs (-△-; 2 x 25 mg/kg/day p.o., 7 animals) and a proprietary COX-inhibitor (-▼-; 2 x 2.5 mg/kg/day p.o., 4 animals) with immunisation on day 12 anf treatment on days 0 to 9 (x-axis)

Biological Activity Assays

A. Experimental autoimmune encephalomyelitis (EAE) in the Rat

A representative Active Compound of the invention, [MeIle]^4-Ciclosporin is tested in the acute EAE assay as described above at a dose of 30 mg/kg and is found to significantly inhibit onset of the disease. The results obtained are given in Figure 1 which is a graph showing severeness of disease for control animals and Active compound treated animals on days 9 to 18 following immunisation. The control group animals have scores of over 0.5 on day 11 and scores approaching 2.0 on days 15 and 16; whereas the [MeIle]^4-Cs treated animals have no measurable score until day 12 and have maximum scores of about 0.5 on days 15 to 17, decreasing thereafter.

B. Experimental autoimmune uveoretinitis (EAU) in the Rat

i) [MeIle]^4-Ciclosporin and Sanglifehrin A are also tested in the EAU assay described above on their own, and in combination with Sanglifehrin A. the results obtained are given in Table I below.

Table I

Effect of [MeIle]^4-Ciclosporin and Sanglifehrin A in Experimental Autoimmune Uveoretinitis

Group	Dose	Maximum Score (4 = Max.)	on Day
Control	-	3.3	17.2
[MeIle]^4-Ciclosporin	25 p.o.	1.9	29.5
Sanglifehrin A	1 s.c.	2.5	17.7
Sanglifehrin A	3 s.c.	2.5	23.9
[MeIle]^4-Ciclosporin + Sanglifehrin A	25 p.o. + 1 s.c.	1.0	33.8
[MeIle]^4-Ciclosporin + Sangglifehrin A	25 p.o. + 3 s.c.	0	37

ii) [MeIle]^4-Ciclosporin, [γ-hydroxy-MeLeu]^4-Ciclosporin and [N-benzyl-Val]^5-Ciclosporin and an ethanol in corn oil placebo are also tested in in the EAU assay essentially as described above. The results obtained are given in Table II below.

Table II

Compounds given in ethanol/corn oil p.o.

Compound	Dose mg/kg p.o.	Presence of uveitis on day 12 # of eyes affected / total # eyes	Maximum score (0-4) 0 = no uveitis 4 = very severe	On day
Placebo ethanol/corn oil	5 ml / kg	4 / 10	4	14
NIM811	25	0 / 10	2	18.4
211-810	25	2 / 10	3.66	16.7
224-602	25	5 / 10	4	13.5

[MeIle]^4-Ciclosporin and Sanglifehrin A are also tested on their own and in combination in the developing adjuvant arthritis assay as described above. The results obtained are given in Figure 2, which is a graph for the average inhibition of swelling obtained for groups of 5 animals treated with 30 mg/kg po of [MeIle]^4-Ciclosporin, 1 mg/kg sc of Sanglifehrin A, or the combination of 30 mg/kg po of [MeIle]^4-Ciclosporin plus 1 mg/kg sc of Sanglifehrin A.

C. Collagen Induced Arthritis

The non-immunosuppressive cyclosporin, [Me-Ile^4]-Ciclosporin (also referred to as NIM 811) is investigated in a therapeutic protocol in the rat collagen-induced arthritis model. Rats are immunized with collagen type II administered intra-dermally around the base of the tail. 10-12 days later, onset of arthritis occurs, typified by erythema and swelling in the joints. Treatment of the animals bid p.o. with [Me-Ile^4]-Ciclosporin (in ethanol 10% /

corn oil vehicle, two different doses) is started shortly after the onset of swelling and continued for up to 10 days. Control arthritic animals and rats treated with a proprietary COX-inhibitor are included in the study. Swelling of the hind paws is assessed regularly. At the end of the study, animals are sacrificed and joints are prepared for the assessment of histological parameters.

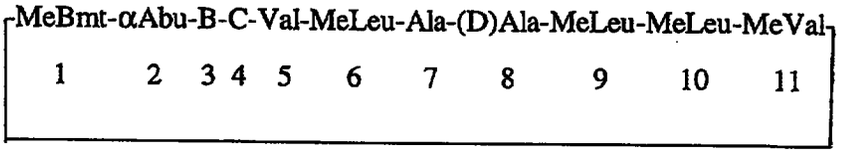
[Me-Ile^4]-Ciclosporin exerts good inhibition of swelling at both doses used (12.5 and 25 mg/kg bid p.o.) up to approx. 60% of the effect of the proprietary COX-inhibitor at day 9 (dosed at 2.5 mg/kg bid p.o.) (Figure 3). Comparison with data for Ciclosporin (CyA, effective ED_{50} around 10-15 mg/kg p.o. - see Smith R. J. and Sly L. M., J. Pharmacol. Exp. Ther., June 1996; 277(3): 1801-1813) shows a similar potency to that of [Me-Ile^4]-Ciclosporin in this model of rheumatoid arthritis.

CLAIMS

1. Use of a nonimmunosuppresive, cyclophilin-binding cyclosporin in the manufacture of a medicament for treating or preventing an inflammatory autoimmune disease or condition.

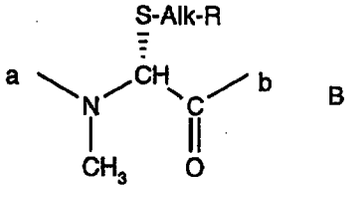
2. A method for the treatment or the prevention of an inflammatory autoimmune condition or disease in a patient suffering from or at risk of suffering from such a disease or condition, comprising administering to said patient an effective amount of a nonimmunosuppresive, cyclophilin-binding cyclosporin.

3. A use according to claim 1 or a method according to claim 2 in which the nonimmunosuppresive, cyclophilin-binding cyclosporin is a compound of Formula A



A

wherein B is an amino acid residue of formula B



B

wherein a denotes the bond to the αAbu residue in position 2;

b denotes the bond to the the residue C in the 4 position;

Alk represents straight or branched chain alkylene containing from 2 to 6 carbon atoms or cycloalkylene containing from 3 to 6 carbon atoms, and

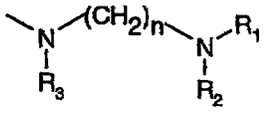
R represents

a carboxy or alkyloxycarbonyl radical;

a radical $-NR_1R_2$ in which R_1 and R_2 are the same or different and represent hydrogen, alkyl, C_{2-4} alkenyl, C_{3-6}cycloalkyl, phenyl (optionally substituted by halogen, alkoxy, alkoxycarbonyl, amino, alkylamino or

dialkylamino) or a benzyl or saturated or unsaturated heterocyclyl radical containing 5 or 6 ring atoms and 1 to 3 heteroatoms, or in which R_1 and R_2 form together with the nitrogen atom to which they are attached a saturated or unsaturated heterocycle containing 4 to 6 ring atoms and optionally containing a further heteroatom selected from nitrogen, oxygen or sulphur and optionally substituted by alkyl, phenyl or benzyl;

a radical of formula



wherein R_1 and R_2 are as defined above, R_3 represents hydrogen or an alkyl radical and n is a whole number from 2 to 4,

and wherein alkyl denotes straight or branched chain alkyl containing from 1 to 4 carbon atoms;

C is MeLeu or or 4-hydroxy-MeLeu; and the pharmaceutically acceptable salts thereof.

4. A use according to claim 1 or a method according to claim 2 in which the nonimmunosuppresive, cyclophilin-binding cyclosporin is a compound of Formula I:

W - X - R - Y - Z - Q - Ala - (D)Ala - MeLeu - MeLeu - MeVal
1 2 3 4 5 6 7 8 9 10 11

in which W is MeBmt, dihydro-MeBmt or 8'-hydroxy-MeBmt;

X is αAbu, Val, Thr, Nva or O-methyl threonine (MeOThr);

R is Sar or (D)-MeAla;

Y is MeLeu, γ-hydroxy-MeLeu, MeIle, MeVal, MeThr, MeAla, Me Tyr, MeTyr(O-$PO(OH)_2$), MeaIle or MeaThr, or Pro;

Z is Val, Leu, N-Alk-Val or N-Alk-Leu,

wherein Alk represents Me or Me substituted by

vinyl optionally substituted by

* C L M S *

phenyl, or an N S or O heteroaryl containing 6 ring members, or phenyl optionally substituted by halogen; and

Q is MeLeu, γ-hydroxy-MeLeu or MeAla.

5. A use according to claim 1 or a method according to claim 2 in which the nonimmunosuppresive, cyclophilin-binding cyclosporin is a compound selected from the group comprising:

a) [dihydro-MeBmt]^{1}-[γ-hydroxy-MeLeu]^{4}-Ciclosporin;

b) [MeVal]^{4} -Ciclosporin;

c) [MeIle]^{4} -Ciclosporin;

d) [MeThr]^{4} -Ciclosporin;

e) [γ-hydroxy-MeLeu]^{4} -Ciclosporin;

f) [Nva]^{2}-[γ-hydroxy-MeLeu]^{4}-Ciclosporin;

g) [γ-hydroxy-MeLeu]^{4}-[γ-hydroxy-MeLeu]^{6} -Ciclosporin;

h) [MeVal]^{5}-Ciclosporin;

i) [MeOThr]^{2}-[(D)MeAla]^{3}-[MeVal]^{5}-Ciclosporin, or

j) [8'-hydroxy-MeBmt]^{1} -Ciclosporin.

m) [N-Benzyl-Val]^{5}-Ciclosporin,

n) [N-5-Fluoro-Benzyl-Val]^{5}-Ciclosporin,

o) [N-Allyl-Val]^{5}-Ciclosporin,

p) [N-3-Phenyl-Allyl-Val]^{5}-Ciclosporin,

q) [Pro]^{4}-Ciclosporin, or

r) [γ-hydroxy-MeLeu]^{9}-Ciclosporin.

6. A use according to claim 1 or a method according to claim 2 in which the nonimmunosuppresive, cyclophilin-binding cyclosporin is [MeIle]^{4} -Ciclosporin or [γ-hydroxy-MeLeu]^{4} -Ciclosporin.

* C L M S *

7. A process for the treatment or the prevention of inflammatory autoimmune conditions and diseases in a patient suffering or at risk of such a disease or condition, comprising administering to said patient an effective amount of a combination comprising a nonimmunosuppresive, cyclophilin-binding cyclosporin and a Sanglifehrin.

8. A pharmaceutical composition, e.g. for the treatment or prevention of an inflammatory autoimmune disease or condition, comprising a nonimmunosuppresive, cyclophilin-binding cyclosporin and a Sanglifehrin.

