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(54) USE OF MICROSOMAL TRIGLYCERIDE TRANSFER PROTEIN (MTP) INHIBITORS FOR REDUCING THE NUMBER OF POSTPRANDIATRIGLYCERIDE-RICH LIPOPROTEIN PARTICLES (PPTRL)

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(57) **ABSTRACT**

The invention relates to the use of inhibitors of the microsomal triglyceride transfer protein (MTP) for reducing the number of postprandial triglyceride-rich lipoprotein particles (ppTRL) or for reducing their decomposition products i.e. the cholestcrol-rich "small remnant particle" (remnants). Said particles are associated with apolipoprotein B-48 (ApoB-48) and are designated as "ppTRL" in the further course of events.

USE OF MICROSOMAL TRIGLYCERIDE TRANSFER PROTEIN (MTP) INHIBITORS FOR REDUCING THE NUMBER OF POSTPRANDIATRIGLYCERIDE-RICH LIPOPROTEIN PARTICLES (PPTRL)

[0001] The invention relates to the use of inhibitors of microsomal triglyceride transfer protein (MTP) for reducing the postprandial triglyceride-rich lipoprotein particles (ppTRL) and for reducing their degradation products, the cholesterol-richer small remnant particle (remnants). Said particles are associated with apolipoprotein B-48 (ApoB-48) and are referred to hereinafter as "ppTRL".

[0002] Substances which inhibit the release of ApoB-100-associated lipoproteins are well known to the skilled worker. Such compounds are described for example in the publications EP 705 831, EP 779 279, EP 779 276, EP 802 198 and EP 799 828. These compounds, which reduce the plasma/serum levels of ApoB-100-associated lipoproteins, are MTP inhibitors. These applications mentioned also describe a rat test used to determine the effect of some substances on intestinal triglyceride absorption. In this rat test, the substances diminished the postprandial serum triglyceride increase.

[0003] Zaiss et al., Circulation 100 (18, Suppl. I):258 Abstr. 1343 (1999) describe the results of a mouse test. In this test, the MTP inhibitor implitapide prevents the formation of atherosclerotic plaques.

[0004] The prophylaxis and treatment of metabolic disorders, especially those affecting lipoprotein and lipid metabolism and associated with cardiovascular disorders and manifestations of neuronal degeneration, remains an essential aim of modern pharmaceutical research. In the literature there is discussion, for example, of alleles of the apoE genes which both represent risk factors for the development of coronary heart disease and are associated with the development of Alzheimer's disease (Rubinsztein, D. C. and Easton, D. F.; Apolipoprotein E genetic variation and Alzheimer's disease. a meta-analysis; Dement. Geriatr. Cogn. Disord., 1999; 10 (3): pp. 199-209; Nakayama S. and Kuzuhara S.; Apolipoprotein E phenotypes in healthy normal controls and demented subjects with Alzheimer's disease and vascular dementia in Mie Prefecture of Japan; Psychiatry Clin. Neurosci. 1999; 53 (6): pp. 643-648; Fullerton S. M., Strittmatter W. J. and Matthew W. D.; Peripheral sensory nerve defects in apolipoprotein E knockout mice; Exp. Neurol. 1998; 153 (1): pp. 156-163). ApoE is a constituent of the very low density lipoprotein (VLDL) which is produced in the liver, and of the chylomicrons which are synthesized in the intestine. ApoE mediates high-affinity binding of the chylomicrons and of VLDL to specific receptors on cells. This enables said particles to be metabolized and taken up into the corresponding cells, resulting in prevention of the accumulation of cholesterol-richer remnants and ppTRL in the plasma. Homozygous inactivation of the apoE genes, as is the case in apoE-knockout mice, results in apoE being undetectable in the serum of these animals. Development of the animals after birth is initially normal but they show disturbances of lipoprotein and lipid metabolism, which may be associated for example with plasma cholesterol levels which are elevated up to five-fold. In addition, these animals spontaneously develop manifestations of neuronal degeneration and atherosclerotic lesions. This is similar to the case of humans having an apoE variant which is able to bind only weakly or not at all to cellular receptors. However, ApoE is additionally involved in the regulation of the immune system, the regeneration of nerve cells and the differentiation of muscles (Masliah E, Mallory M, Ge N, Alford M, Veinbergs I, Roses A D Neurodegeneration in the central nervous system of apoE-deficient mice. Exp. Neurol. 1995; 136 (2): 107-122; Masliah E, Samuel W, Veinbergs I, Mallory M, Mante M, Saitoh T "Neurodegeneration and cognitive impairment in apoE-deficient mice is ameliorated by infusion of recombinant apoE" Brain Res 1997; 751(2):307-314; Chen Y, Lomnitski L, Michaelson D M, Shohami E "Motor and cognitive deficits in apolipoprotein E-deficient mice after closed head injury" Neuroscience 1997: 1255-1262; Fullerton S M, Strittmatter W J, Matthew W D. "Peripheral sensory nerve defects in apolipoprotein E knockout mice" Exp Neurol 1998; 153 (1): 156-63; Mato M, Ookawara S, Mashiko T, Sakamoto A, Mato T K, Maeda N, Kodama T Anat Rec 1999; 256 (2): 165-176 "Regional difference of lipid distribution in brain of apolipoprotein E deficient mice").

[0005] The pathological consequences of disturbances of lipoprotein or lipid metabolism are accordingly not confined just to atherosclerosis. The apoE-knockout mouse is therefore suitable as animal model for investigating the effects of pharmaceuticals multifactorially on lipoprotein and lipid metabolism, atherosclerosis and damage to the nervous system with the aim of intervening in these multifaceted pathological processes.

[0006] In recent literature there are also descriptions of an important part played by, in particular, ppTRL and its degradation products in diabetes (Howard, B. V.; Insulin resistance and lipid metabolism; Am. J. Cardiol., 1999; 84 (1A): pp. 28J-32J; Mero, N., Malmstrom, R., Steiner, G., Taskinen, M., Syvanne, M.; Postprandial metabolism of apolipoprotein B-48- and B-100-containing particles in type 2 diabetes mellitus: relations to angiographically verified severity of coronary artery disease. Atherosclerosis, 2000; 150 (1): pp. 167-177). It is therefore of great importance to find possible ways of reducing the ppTRL levels in blood plasma.

[0007] It has now been found, surprisingly, that MTP inhibitors diminish ppTRL in the plasma, e.g. after lipid loading. The invention therefore relates to the use of MTP inhibitors for diminishing or reducing ppTRL in plasma. The lowering of the ppTRL by inhibition of MTP has a beneficial effect on morbidity and mortality, especially in relation to neurodegenerative and cardiovascular disorders. MTP inhibitors are therefore suitable for beneficially influencing these disease processes.

[0008] It has further been found, surprisingly, that the reduction in ppTRL, especially after intake of fatty food, occurs even with dosages of the MTP inhibitor with which no significant or only a slight reducing effect on the serum triglyceride or the serum cholesterol concentration is seen in the fasting state (about 12 hours after the last food intake). In the same way there is substantially no effect in this case on the LDL particles which originate from the liver and which, in humans, are exclusively ApoB-100-associated lipoprotein particles. A slight effect is intended to be regarded in this connection as a reduction in the plasma triglyceride or the plasma cholesterol concentration or a

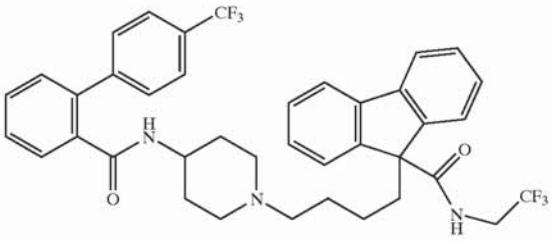
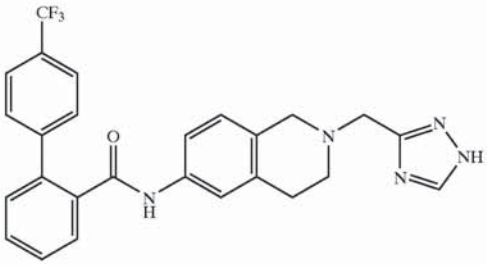
reduction in the ApoB-100-associated lipoproteins of less than 20%, preferably less than 10% or below. "Fasting plasma levels" means that measurements must not take place in postprandial plasma or serum, that is to say after intake of lipid-containing food, but in the fasting plasma or serum obtained about 12 hours after the last food intake.

[0009] Because of the effect on ppTRL, the MTP inhibitors can also be employed for inhibiting or diminishing intestinal cholesterol absorption.

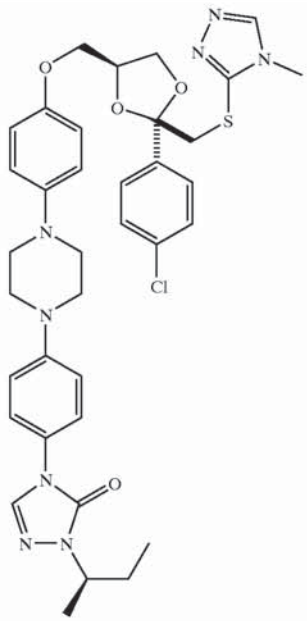
[0010] Surprisingly, deliberate reduction in plasma ppTRL with a low dosage of an MTP inhibitor is itself sufficient to extend the survival of the patients, in conjunction with improved tolerability. Since disturbances of lipoprotein or lipid metabolism may, as explained above, lead to multifaceted degenerative disorders, the reduction in ppTRL makes an important therapeutic contribution to the treatment of such complex pathological states.

[0011] MTP inhibitors are described in the following documents, for example: Wetterau et al. Science 282, 751 (1998), J Lipid Res 37, 1468 (1996), Bristol-Myers-Squibb: EP-A-584 446, EP-A-643 057, WO 96/26205, WO 97/26240, WO 91/43255, WO 97/43257, WO 98/27979, U.S. Pat. No. 5,760,246, U.S. Pat. No. 5,827,875, WO 99/21564; Pfizer: WO 96/40 640, WO 98/23593, EP-A 887 345, WO 97/41111; Glaxo-Wellcome: WO 98/16526, WO 98/47877, WO 98/56790; Janssen: WO 96/13499, WO 96/33193; Novartis: WO 00/05201; Meji Seika Kaisha: WO 98/54135, Japan Tobacco: WO 99/31085; Advanced Medicine: WO 99/63929. In the following documents of Bayer A G, substances which inhibit the release of ApoB-100-associated lipoproteins are described, these substances being MTP inhbitors: EP-A 716 082, EP-A 719 763, EP-A 705 831, EP-A 753 517, EP-A 765 878, EP-A 764 647, EP-A 779 279, EP-A 779 276, EP-A 799 828, EP-A 802 198, EP-A 802 186, EP-A 802 188, EP-A 802 192, EP-A 802 197. The disclosure of the aforementioned documents disclosing MTP inhibitors is incorporated herein in its entirety by reference.

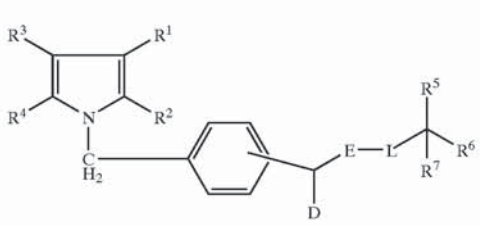
[0012] Some examples of MTP inhibitors described therein are listed below:

Structure/systematic name (test number)	Described in
 N-(2,2,2-Trifluoroethyl)-9-{4-[4-({[4'-(trifluoromethyl)-1,1'-biphenyl-2-yl]carbonyl}amino)-1-piperidinyl]butyl}-9H-fluorene-9-carboxamide (BMS201038)	EP-A 643 057, Wetterau et al., Science 282, 751 (1998)
 N-[2-(1H-1,2,4-Triazol-3-ylmethyl)-1,2,3,4-tetrahydro-6-isoquinolinyl]-4'-(trifluoromethyl)-1,1'-biphenyl-2-carboxamide	WO 97/41111 (Pfizer)

-continued

Structure/systematic name (test number)	Described in
 4-[4-(4-{4-[((2S,4S)-2-(4-Chlorophenyl)-2-{[(4-methyl-4H-1,2,4-triazol-3-yl)sulfanyl]methyl}-1,3-dioxolan-4-yl)methoxy]phenyl}-1-piperazinyl)phenyl]-2-[(1R)-1-methylpropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (R103757)	WO 96/13499 (Janssen Int. NV)

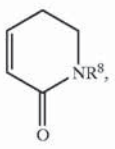
[0013] Preferred MTP inhibitors which can be used according to the invention are: compounds of the general formula (A1)



(A1)

[0014] in which

[0015] R^1 and R^2 together form, with inclusion of the double bond connecting them, a phenyl or pyridyl ring or a ring of the formula



[0016] in which

[0017] R^8 is hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

[0018] R^3 and R^4 together form, with inclusion of the double bond connecting them, a phenyl ring or a 4- to 8-membered cycloalkene or oxocycloalkene residue, where all ring systems mentioned under R^1/R^2 and R^3/R^4 optionally have up to 3 identical or different halogen, trifluoromethyl, carboxyl, hydroxyl substituents, straight-chain or branched alkoxy or alkoxycarbonyl substituents each having up to 6 carbon atoms, or straight-chain or branched alkyl substituents which have up to 6 carbon atoms and which in turn may be substituted by hydroxyl or by straight-chain or branched alkoxy having up to 4 carbon atoms,

[0019] D is hydrogen, cycloalkyl having 4 to 12 carbon atoms or is straight-chain or branched alkyl having up to 12 carbon atoms,

[0020] E is the —CO— or —CS— group,

[0021] L is an oxygen or sulfur atom or is a group of the formula $—NR^9$,

[0022] in which

[0023] R^9 is hydrogen or straight-chain or branched alkyl which has up to 6 carbon atoms and which is optionally substituted by hydroxyl or phenyl,

[0024] R^5 is phenyl or is a 5- to 7-membered saturated or unsaturated heterocycle having up to 3 heteroatoms from the series S, N and/or O, where the rings optionally have up to 3 identical or different nitro, carboxyl, halogen, cyano substituents or straight-chain or branched alkenyl or alkoxycarbonyl substituents each having up to 6 carbon atoms or straight-chain or branched alkyl substituents which have up to 6 carbon atoms and which are optionally substituted by hydroxyl, carboxyl or by straight-chain or branched alkoxy or alkoxycarbonyl each having up to 6 carbon atoms, and/or the rings are optionally substituted by a group of the formula —OR^{10} or —$NR^{11}R^{12}$,

[0025] in which

[0026] R^{10} is hydrogen or straight-chain or branched alkyl or alkenyl each having up to 6 carbon atoms,

[0027] R^{11} and R^{12} are identical or different and are phenyl, hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms, or straight-chain or branched acyl which has up to 8 carbon atoms and which is optionally substituted by a group of the formula —$NR^{13}R^{14}$,

[0028] in which

[0029] R^{13} and R^{14} are identical or different and are hydrogen or straight-chain or branched acyl having up to 8 carbon atoms,

[0030] R^6 is hydrogen, carboxyl or is straight-chain or branched alkoxycarbonyl having up to 5 carbon atoms, or is straight-chain or branched alkyl which has up to 6 carbon atoms and which is optionally substituted by hydroxyl or by a group of the formula —O—CO—R^{15},

[0031] in which

[0032] R^{15} is phenyl which optionally has up to 3 identical or different halogen, hydroxyl substituents or straight-chain or branched alkyl substituents having up to 5 carbon atoms, or straight-chain or branched alkyl or alkenyl which each have up to 22 carbon atoms and which are optionally substituted by a group of the formula —OR^{16},

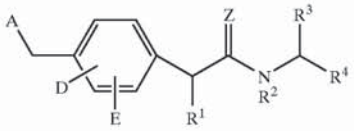
[0033] in which

[0034] R^{16} is hydrogen, benzyl, triphenylmethyl or straight-chain or branched acyl having up to 6 carbon atoms,

[0035] R^7 is hydrogen or

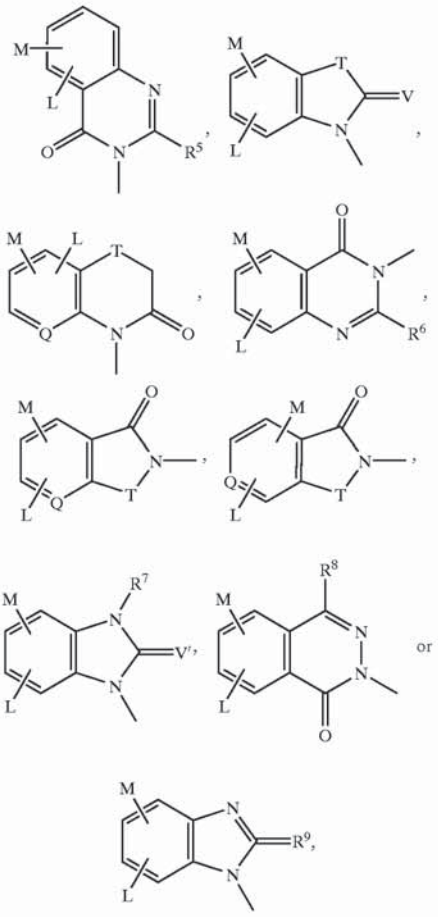
[0036] R^6 and R^7 together are the group of the formula =O,

[0037] or of the general formula (A2)



[0038] in which

[0039] A is a radical of the formula



[0040] in which

[0041] L and M are identical or different and are hydrogen, halogen, trifluoromethyl, carboxyl, cycloalkyl having 3 to 6 carbon atoms, hydroxyl, phenyl or straight-chain or branched alkyl, alkoxycarbonyl or alkoxy each having up to 6 carbon atoms,

[0042] Q is a nitrogen atom or the —CH group,

[0043] T is a group of the formula —SO_2 or —CO or an oxygen or sulfur atom,

[0044] V is an oxygen or sulfur atom,

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