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(54) **Method of treating acute myocardial infarction**

Verfahren zur Behandlung von akutem Myokardinfarkt

Méthode de traitement de l'infarctus aigu du myocarde

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Description

BACKGROUND OF THE INVENTION

[0001] Despite the advance in various therapeutic means, acute myocardial infarction (AMI) is still the leading cause of mortality in the western world. Acute myocardial infarction refers to a common clinical condition that leads to necrosis of myocardial tissue. This condition is well known in the art and is characterized by the occurrence of pain, in most cases precordial, characteristic electrocardiographic changes and an increase in plasma levels of intracellular enzymes released by the necrotic cardiac tissue such as creatinine phosphokinase and α -hydroxybutyrate dehydrogenase. AMI may be accompanied by hypotension, circulatory failure, pulmonary edema and arrhythmia. In most cases, but not exclusively, AMI results from vascular injury and thrombosis in the coronary vessels, which causes these vessels to become occluded with subsequent impaired blood flow to the jeopardized myocardium (Fuster, V. et al., 1992, New Engl. J. Med., 326 : 242 and 310). In most cases, the time of the occlusion of the coronary vessel can be estimated from the medical history, the course of plasma levels of intracellular heart muscle enzymes and electrocardiographic changes.

[0002] The initiating event of many myocardial infarctions (heart attacks) is rupture of an atherosclerotic plaque. Such rupture may result in formation of a thrombus or blood clot in the coronary artery which supplies the infarct zone. The infarct zone or area, as it is commonly referred to, is an area of necrosis which results from an obstruction of blood circulation. The thrombus formed is composed of a combination of fibrin and blood platelets. The formation of a fibrin-platelet clot has serious clinical ramifications. The location, degree and duration of the occlusion caused by the fibrin-platelet clot determine the mass of the infarct zone and the extent of damage.

[0003] Myocardial infarction occurs generally with an abrupt decrease in coronary blood flow to the infarct zone that follows a thrombotic occlusion of a coronary artery. The occluded artery often has been narrowed previously by atherosclerosis, and the risk of recurrent myocardial infarction persists in many patients. Ultimately, the extent of myocardial damage caused by the coronary occlusion depends upon the "territory" supplied by the affected vessel, the degree of occlusion of the vessel, the amount of blood supplied by collateral vessels to the affected tissue, and the demand for oxygen of the myocardium whose blood supply has suddenly been limited (Pasternak, R. and Braunwald, E., 1994, Acute Myocardial Infarction, Harrison's Principles of Internal Medicine, 13 th Ed., pgs. 1066-77.)

[0004] Inflammation has been related both to the pathogenesis of acute myocardial infarctions and to the healing and repair following AMI. Myocardial ischemia prompts an inflammatory response. In addition, reperfusion, the mainstay of current acute therapy of AMI, also enhances inflammation. Reperfusion involves the rapid dissolution of the occluding thrombus and the restoration of blood flow to the area of the heart which has had its blood supply cut off. The presence of inflammatory cells in the ischemic myocardial tissues has traditionally been believed to represent the pathophysiological response to injury. However, experimental studies have shown that while crucial to healing, the influx of inflammatory cells into tissues, specifically macrophages which are phagocytic cells, results in tissue injury beyond that caused by ischemia alone.

[0005] Macrophages and other leukocytes infiltrate the myocardium soon after ischemia ensues. Macrophages secrete several cytokines, which stimulate fibroblast proliferation.

[0006] However, the activated macrophages also secrete cytokines and other mediators that promote myocardial damage. Accordingly, the influx of macrophages into the myocardium increases myocardial necrosis and expands the zone of infarct. Thus, although the acute phase of inflammation is a necessary response for the healing process, persistent activation is in fact harmful to the infarct area as well as the area surrounding it, the so-called 'peri-infarct zone'.

[0007] The inflammatory response that follows myocardial ischemia is critical in determining the severity of the resultant damage caused by the activated macrophages. Plasma levels of inflammatory chemotactic factors (macrophage chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 α (MIP-1 α), have been shown to correlate with subsequent heart failure and left ventricular dysfunction (See, for example, Parissis, J. T. et al., 2002, J. Interferon Cytokine Res., 22 (2) : 223-9). Peripheral monocytosis (an elevated number of monocytes) at two and three days after AMI is associated with left ventricular dysfunction and left ventricular aneurysm, suggesting a possible role of monocytes in the development of left ventricular remodeling after reperfused AMI (Maekawa, Y. et al., 2002, J. A7n. Coll. Cardiol., 39 (2): 241-6). Left ventricular remodeling after acute myocardial infarction is the process of infarct expansions followed by progressive left ventricular dilation and is associated with an adverse clinical outcome. Furthermore, plasma levels of macrophage chemoattractant protein-1 (MCP-1) are elevated in patients with acute myocardial infarction. MCP-1 is induced by myocardial ischemia/reperfusion injury and neutralization of this chemokine significantly reduced infarct size.

[0008] Suppression of the inflammatory response by nonspecific anti-inflammatory composites after coronary occlusion, in several coronary occlusion/reperfusion models, was shown to reduce the infarct area (See, for example, Squadrito, F. et al., 1997, Eur. J. Pharmacol. ; 335: 185-92; Libby, P. et al., 1973, J. Clin. Invest, 3: 599-607 ; Spath J. A. et al., 1974, Circ. Res., 35: 44-51). However, these nonspecific regimens are associated with adverse effects, such as interference with scar formation and healing; and, leading in some patients, to the development of aneurysm and rupture of the ventricular wall. As such, these regimens are precluded from clinical use. On the other hand, animals deficient in

the anti-inflammatory cytokine interleukin- 10, that suppress macrophage function, were shown to suffer from increased infarct size and myocardial necrosis in a coronary occlusion model (Yang, Z. et al., 2000, Circulation, 101: 1019- 1026.)

[0009] A major therapeutic goal of modern cardiology is to design strategies aimed at minimizing myocardial necrosis and optimizing cardiac repair following myocardial infarction.

[0010] One object of the invention is to describe methods which minimize the deleterious effects produced by an abrupt decrease in myocardial blood flow. It is another object of the invention to describe treatments that limit damage to the myocardium and the infarct area following acute myocardial infarction.

SUMMARY OF THE INVENTION

[0011] The present invention relates to the use of a formulation comprising an encapsulated agent, an embedded agent or a particulate agent having a size in the range of 0.03 to 1.0 μm , for the preparation of a medicament to improve remodeling following an acute myocardial infarction, and wherein the agent is selected from the group consisting of bisphosphonate, gallium, gold, selenium, gadolinium, silica, mithramycin, paclitaxel, sirolimus, everolimus, and combinations of two or more. The present invention also relates to a pharmaceutical composition for use in a treatment of acute myocardial infarction, wherein the composition suppresses the inflammatory response following acute myocardial infarction, thereby improving remodeling following the acute myocardial infarction, wherein the composition comprises an encapsulated bisphosphonate, an embedded bisphosphonate or a particulate bisphosphonate having a size in the range of 0.03 to 1.0 μm , together with a pharmaceutically acceptable carrier or diluent.

[0012] In accordance with the present invention, a method is provided to treat acute myocardial infarction. More particularly, the present invention relates to a method of minimizing myocardial necrosis, reducing the final zone of infarct and improving cardiac repair and outcome following acute myocardial infarction.

[0013] The present invention relates to a method of treating myocardial infarction by administering to an individual an effective amount of a formulation which inhibits and/or depletes phagocytic cells with high specificity, thereby suppressing the inflammatory response that occurs during and following acute myocardial infarction. The formulation comprises an agent which is an intra-cellular inhibitor that is released within the targeted phagocytic cells, specifically macrophages/monocytes, and inhibits and/or destroys the macrophages and/or monocytes, thereby reducing the final zone of infarct and improving cardiac repair and myocardial remodeling. Since macrophages and monocytes possess the unique ability to phagocytose large bodies, the agent is formulated into a specific size so that it can enter cells via phagocytosis. Thus, the specifically sized formulation selectively targets monocytes/macrophages. The formulation may comprise an encapsulated agent, an embedded agent or a particulate agent, wherein the formulation is of a specific size, such that it can primarily enter cells via phagocytosis.

[0014] US2002/0187184 A1 discloses a method of treating or preventing restenosis comprising the administration of an effective amount of an active ingredient comprising a bisphosphonate particle or a bisphosphonate particulate. The bisphosphonate may be encapsulated, embedded or adsorbed within the particle, dispersed uniformly in the polymer matrix, adsorbed on the particle surface, or in combination of any of these forms. The particles include liposomes or inert polymeric particles such as microcapsules, nanocapsules, nanoparticles, nanospheres, or microparticles. This document is limited to the treatment of restenosis in its disclosure. In particular the disclosed invention relates to the decreasing of the thickening of the inner blood vessel lining that results from stimulation and proliferation of smooth muscle cell or other cell migration and proliferation, and from extracellular matrix accumulation, following various angioplasty procedures.

[0015] In one embodiment, the present invention relates to a method of treating myocardial infarction by administering to an individual an effective amount of a formulation comprising an encapsulated agent. The agent is encapsulated in a suitable carrier of a specific dimension. The formulation specifically targets phagocytic cells by virtue of its properties, such as, for example, size, which allow the formulation to be taken-up primarily by phagocytosis.

[0016] Once the formulation is taken-up by the phagocytic cells, the encapsulated agent is released and the agent is able to inhibit the activity of and/or destroy the phagocytic cells.

[0017] In a further embodiment, the present invention relates to a method of treating acute myocardial infarction by administering to an individual an effective amount of a formulation comprising an embedded agent. The agent is embedded in a suitable carrier of a specific dimension. The formulation specifically targets phagocytic cells by virtue of its properties, such as, for example, size, which allow the formulation to be taken-up primarily by phagocytosis. Once inside the phagocytic cells the embedded agent is released and the agent acts intra-cellularly to inactivate and/or destroy the cells.

[0018] The present invention also relates to a method of treating acute myocardial infarction and reducing the zone of infarct by administering to an individual an effective amount of a formulation comprising a particulate agent. The formulation specifically targets phagocytic cells by virtue of its properties, such as, for example, size, which allow the formulation to be taken-up primarily by phagocytosis. Once inside the phagocytic cells the agent acts intra-cellularly to inactivate and/or destroy the cells.

[0019] In a further embodiment, the present invention includes a pharmaceutical composition comprising a formulation

selected from the group consisting of an encapsulated agent, an embedded agent, and a particulate agent together with a pharmaceutically acceptable carrier, stabilizer or diluent for the treatment of myocardial infarction.

[0020] The formulation of present invention is in the size range of 0.03-1.0 microns. However, depending on the type of agent and/or the carrier used, the preferred ranges include, but are not limited to, 0.1-0.5 microns, 0.1-0.3 microns and 0.1 to 0.18.

DESCRIPTION OF THE FIGURES

[0021]

Figure 1 illustrates the effect of liposomal alendronate treatment on the infarct area after transient coronary artery occlusion in rabbits. The results present the area of the infarcted zone as a % of the left ventricular area supplied by the occluded artery and at risk for subsequent infarction.

Figure 2 illustrates the effect of liposomal alendronate treatment on myocardial morphometry after reversible coronary occlusion in rabbits.

Figure 3 illustrates the reduction in macrophage infiltration following treatment with liposomal alendronate after reversible coronary occlusion in rabbits.

DETAILED DESCRIPTION OF THE INVENTION

[0022] The present invention relates to formulations and methods for treating myocardial infarction. More particularly, the present invention includes a method of treating myocardial infarction by administering to an individual, an effective amount of an agent known to deplete, inactivate or inhibit blood monocytes and tissue macrophages. The agent is formulated such that it can primarily enter a cell via phagocytosis. For example, the agent may be encapsulated in a liposome of a specific size, embedded in a nanoparticle of a specific size, or formulated into particulate form, such as, for example, in aggregates of a specific size. The agent, when formulated into a particular size, specifically targets and is efficiently engulfed by way of phagocytosis by the macrophages and monocytes. Accordingly, the formulation does not target and thus does not affect non-phagocytic cells. Once inside the macrophages and/or monocytes, the agent is released and inactivates or destroys the cells. Depletion and/or inhibition of blood monocytes and tissue macrophages suppresses the inflammatory response following acute myocardial infarction. As a result, the final zone of infarct is reduced and myocardial remodeling is improved. Reduced infarct zone and proper remodeling correlates with decreased left ventricular dysfunction, decreased morbidity and decreased mortality.

[0023] The present invention encompasses an agent which is formulated so that it can primarily enter a cell via phagocytosis and selectively target macrophage and monocytes without affecting other non-phagocytic cells. Once inside the phagocytic cells, the agent is released and inhibits and/or depletes the monocytes and/or macrophages for treatment of myocardial infarction, reduction in the final zone of infarct and improvement of cardiac repair and outcome following acute myocardial infarction. The formulations may comprise an encapsulated agent, an embedded agent, or an agent in particulate form, all of a specific dimension, which allows up-take primarily via phagocytosis.

[0024] In one embodiment, the formulation comprises the agent encapsulated in a carrier of a specific size, hereinafter referred to as an "encapsulated agent". The term "encapsulated agent" includes an agent which is encapsulated within a carrier such as, for example, a liposome.

[0025] In a further embodiment, the formulation comprises the agent embedded in a carrier of a specific size hereinafter referred to as an "embedded agent". The term "embedded agent" includes an agent which is embedded, enclosed, and/or adsorbed within a carrier, dispersed in the carrier matrix, adsorbed or linked on the carrier surface, or in combination of any of these forms. The carrier includes many forms, such as, for example, microparticles, nanoparticles, nanospheres, microspheres, microcapsules, or nanocapsules (e.g., M. Donbrow in: Microencapsulation and Nanoparticles in Medicine and Pharmacy, CRC Press, Boca Raton, FL, 347, 1991). The term carrier includes both polymeric and non-polymeric preparations. In addition, suspending compounds and stabilizers may also be used with the encapsulated and/or embedded agent formulations.

[0026] In a further embodiment, the formulation comprises an agent in particulate form, hereinafter referred to as a "particulate agent". A "particulate agent" dosage form includes any insoluble suspended or dispersed particulate form of the agent of a specific dimension which is not encapsulated, entrapped or adsorbed within a carrier. Particulate agent formulations include, but are not limited to, suspended or dispersed colloids, aggregates, flocculates, insoluble salts, insoluble complexes, and polymeric chains of an agent. Such particulates may also be aggregates of the polymerized agent. Typically, "insoluble" refers to a solubility of one (1) part of an agent in more than ten-thousand (10,000) parts of a solvent; the solvent, in this case, being blood (water). In addition, suspending agents and stabilizers may be used with

the particulate agent formulation.

[0027] The formulation of the present invention, for example, the encapsulated agent, embedded agent or the particulate agent, suppresses the inflammatory response by transiently depleting and/or inactivating cells that are important triggers in the inflammatory response, namely macrophages and/or monocytes. The encapsulated agent, embedded agent and/or the particulate agent are taken-up, by way of phagocytosis, very efficiently by the macrophages and monocytes, and to some extent by other cells with phagocytic activity such as fibroblasts. In contrast, non-phagocytic cells are incapable of taking up the formulation due to the large dimension and/or other physiochemical properties of the formulation.

[0028] Once inside the macrophages, the structure of the encapsulated, embedded or particulate agent (e. g. , liposome, microparticle, nanoparticle, aggregates) is disrupted and the agent is released intra-cellularly, thereby inhibiting the activity of, disabling and/or killing the monocytes/macrophages. Since macrophages and monocytes, in their normal state, are recruited to the infarcted area and promote myocardial damage beyond that caused by ischemia alone, monocyte/macrophage inhibition and/or depletion attenuates the myocardial damage. After being taken-up by the monocytes/macrophages, the agent has a sustained inhibitory activity on the monocytes/macrophages. This sustained activity is sufficient to modulate myocardial damage. Thus, prolonged release of the agent is not required in order to sustain inhibition.

[0029] Accordingly, the method of treating myocardial infarction by inhibiting monocytes/macrophages, such as, for example, by the use of an encapsulated agent, an embedded agent or a particulate agent, is preferably a systemic therapy, in that the formulation targets the circulating monocytes and macrophages.

[0030] Furthermore, the formulation of the present invention not only retains the agent for a sufficient time so that the agent is not released in the body fluids, but also efficiently discharges the drug within the target cell. The agent is formulated into an encapsulated/embedded agent or a particulate agent because, in many instances, the agent in its free form is ineffective since it does not specifically target phagocytic cells.

[0031] Encapsulating/embedding the agent in carrier particles of a specific size or formulating the agent into particulates, e. g. aggregates, of a specific size allows the formulations to be taken-up primarily and efficiently by macrophages and monocytes through phagocytosis.

[0032] The formulation, comprising an encapsulated agent, embedded agent or a particulate agent, is specifically sized so as to be taken-up by the macrophage and monocytes.

[0033] The encapsulated, embedded, or particulate agent is in the size range of 0.03-1.0 microns. However, depending on the type of agent and/or the carrier used, the preferred ranges include, but are not limited to, 0.1-0.5 microns, 0.1-0.3 microns and 0.1 to 0.18 microns.

[0034] The agent includes any substance that once released within the targeted macrophages/monocytes inhibits and/or destroys the macrophages and monocytes to minimize myocardial necrosis and reduce the infarcted area. In accordance with the present invention, the agent comprises an intra-cellular inhibitor, deactivator, toxin, arresting substance and/or cytostatic/cytotoxic substance. That is, the agent includes any compound that once released within the targeted macrophages/monocytes inhibits, destroys, arrests, modifies and/or alters the macrophages and monocytes. The agent includes not only monomer, but also polymeric chains of the agent. One preferred class of agents are bisphosphonates. Free bisphosphonates, due to their affinity to bone and due to their inability to cross cellular membranes, have virtually no effect on the systemic inflammatory response. In contrast, bisphosphonates, when encapsulated in liposomes of a specific size, embedded in microparticles or nanoparticles of specific dimensions or when in a particulate formulation, such as, for example, in aggregates of a specific size, are specifically targeted to, and efficiently taken-up by way of phagocytosis, by the macrophages and monocytes. In contrast, non-phagocytic cells are incapable of taking-up the encapsulated bisphosphonates, embedded bisphosphonates and particulate bisphosphonates.

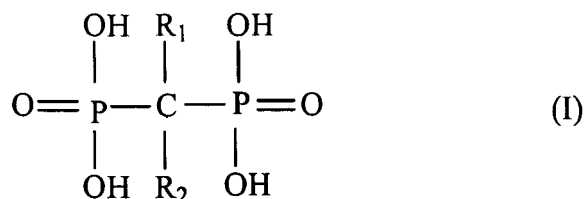
[0035] While the following detailed description often relates to a preferred embodiment of the present invention, ie., the use of an encapsulated bisphosphonate, specifically, liposomal alendronate, it will be understood by the skilled practitioner in the art that any agent as claimed having a size range of 0.03 to 1.0 μm such that it can primarily enter a cell via phagocytosis, that can effectively deplete and/or inactivate monocytes/macrophages to minimize myocardial necrosis and improve cardiac repair following acute myocardial infarction, can be employed without departing from the scope of the invention. For instance, gallium and gold are inactivators of monocytes and macrophages and can be used as the agent of the present invention to treat acute myocardial infarction. Other agents useful in the present invention include, but are not limited to, selenium, gadolinium, silica, mithramycin, paclitaxel, sirolimus, and everolimus. Any intra-cellular inhibitor may be formulated as an encapsulated/embedded agent or a particulate agent of a specific size. Moreover, a combination of two or more inhibitors may be formulated into one dosage form for an improved effect.

[0036] In accordance with the present invention, a preferred class of agents are bisphosphonates. Bisphosphonates (formerly called diphosphonates) are compounds characterized by two C-P bonds. If the two bonds are located on the same carbon atom (P-C-P) they are termed geminal bisphosphonates. The bisphosphonates are analogs of the endogenous inorganic pyrophosphate which is involved in the regulation of bone formation and resorption.

[0037] The term bisphosphonates is generally used for geminal and non-geminal bisphosphonates. The bisphospho-

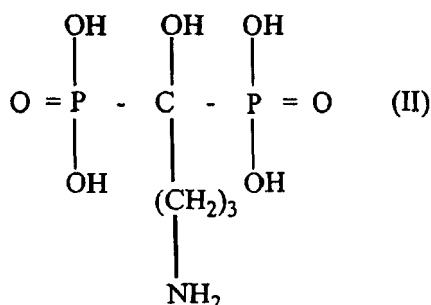
nates may at times form polymeric chains. Bisphosphonates act on bone because of their affinity for bone mineral and also because they are potent inhibitors of bone resorption and ectopic calcification. Bisphosphonates have been clinically used mainly as (a) antiosteolytic agents in patients with increased bone destruction, especially Paget's disease, tumor bone disease and osteoporosis ; (b) skeletal markers for diagnostic purposes (linked to ^{99m}Tc) ; (c) inhibitors of calcification in patients with ectopic calcification and ossification, and (d) antitartar agents added to toothpaste (Fleisch, H. , 1997, in: Bisphosphonates in bone disease. Parthenon Publishing Group Inc., 184-186). Furthermore, being highly hydrophilic and negatively charged, bisphosphonates in their free form are almost entirely incapable of crossing cellular membranes.

[0038] The bisphosphonates, when encapsulated in liposomes or embedded in carrier particles of specific dimensions, or when in a particulate dosage form, such as, for example, in aggregates of a specific size, can be used for the treatment of myocardial infarction. The term bisphosphonate as used herein, denotes both geminal and non-geminal bisphosphonates. A preferred agent, a bisphosphonate, has the following formula (I) :



wherein R_1 is H, OH or a halogen atom; and R_2 is halogen ; linear or branched C_1 - C_{10} alkyl or C_2 - C_{10} alkenyl optionally substituted by heteroaryl or heterocyclyl C_1 - C_{10} alkylamino or C_3 - C_8 cycloalkylamino where the amino may be a primary, secondary or tertiary amine; -NHY where Y is hydrogen, C_3 - C_8 cycloalkyl, aryl or heteroaryl; or R_2 is -SZ where Z is chlorosubstituted phenyl or pyridinyl.

[0039] One example of a preferred agent is the bisphosphonate, alendronate, having the following formula (II):



[0040] Additional bisphosphonates having activities similar to that of alendronate are also preferred in accordance with the invention. Such bisphosphonates may be selected on the basis of their ability to mimic the biological activity of alendronate. This includes, for example: in vitro activity in inhibiting activity of phagocytic cells, e. g. macrophages and fibroblasts; inhibition of secretion of IL-1 and/or IL-6 and/or TNF- α from macrophages; and in vivo activity, e. g. the ability of the tested formulations to deplete or disable blood monocytes in an animal model or in humans or to treat myocardial infarction and reduce the zone of infarct in an experimental animal model such as, for example, the rabbit acute myocardial infarction model described in Example 1 below.

[0041] Additional bisphosphonates applicable in the present invention, include, but are not limited to, clodronate, tiludronate, 3-(N, N-dimethylamino)-1-hydroxypropane-1, 1-diphosphonic acid, e. g. dimethyl-APD ; 1-hydroxy-ethylidene-1, 1-bisphosphonic acid, e. g. etidronate; 1-hydroxy-3 (methylpentylamino) -propylidene-bisphosphonic acid, (ibandronic acid), e. g. ibandronate; 6-amino-1-hydroxyhexane-1, 1-diphosphonic acid, e. g. amino-hexyl-BP; 3- (N- methyl-N-pentylamino)-1-hydroxypropane-1, 1-diphosphonic acid, e. g. methyl-pentyl-APD; 1- hydroxy-2- (imidazol-1-yl) ethane-1, 1-diphosphonic acid, e. g. zoledronic acid; 1-hydroxy-2- (3- pyridyl) ethane-1, 1-diphosphonic acid (risedronic acid), e. g. risedronate; 3- [N- (2-phenylthioethyl)- N-methylamino]-1-hydroxypropane-1, 1-bisphosphonic acid; 1-hydroxy-3- (pyrrolidin-1- yl) propane-1, 1-bisphosphonic acid, 1- (N-phenylaminothiocarbonyl) methane-1, 1-diphosphonic acid, e. g. FR 78844 (Fujisawa); 5-benzoyl-3,4-dihydro-2H-pyrazole-3, 3-diphosphonic acid tetraethyl ester, e. g. U81581 (Upjohn); and 1-hydroxy-2-(imidazo [1, 2-a] pyridin-3-yl) ethane-1, 1- diphosphonic acid, e. g. YM 529.

[0042] The term "effective amount" denotes an amount of the formulation which is effective in achieving the desired therapeutic result, namely treatment of myocardial infarction to minimize myocardial necrosis and improve cardiac repair. The decrease in number and activity of activated macrophages and monocytes reduces the zone of infarct and improves

remodeling.

[0043] The effective amount may depend on a number of factors including, but not limited to: weight and gender of the treated individual; the mode of administration of the formulation (namely whether it is administered systemically or directly to the site); the therapeutic regime (e. g. whether the formulation is administered once daily, several times a day, once every few days, or in a single dose); clinical indicators of inflammation; clinical factors influencing the rate of development of myocardial necrosis such as diabetes, smoking, hypercholesterolemia, pro-inflammatory states, renal diseases; and on the dosage form of the composition. The artisan, by routine experimentation, should have no substantial difficulties in determining the effective amount in each case.

[0044] The formulation used in accordance with the invention may be formulated into pharmaceutical compositions by any of the conventional techniques known in the art (see, for example, Alfonso, G. et al. , 1995, in: The Science and Practice of Pharmacy, Mack Publishing, Easton PA, 19th ed.). The formulations may be prepared in forms suitable for injection, instillation or implantation in the body, such as, for example, suspensions of the nanoparticles.

[0045] In addition, the pharmaceutical compositions of the invention may be formulated with appropriate pharmaceutical additives for parenteral dosage forms. The preferred administration form in each case depends on the desired delivery mode, which is usually that which is the most physiologically compatible with the patient's condition and with the other therapeutic treatments which the patient currently receives.

[0046] The formulations may be administered by any route which effectively transports the formulation to the appropriate or desirable site of action. Preferred modes of administration include intravenous (IV) and intra-arterial (IA) (particularly suitable for on-line administration).

[0047] Other suitable modes of administration include intramuscular (IM), subcutaneous (SC), and intraperitoneal (IP). Such administration may be bolus injections or infusions. Another mode of administration may be by perivascular delivery. The formulation may be administered directly or after dilution. Combinations of any of the above routes of administration may also be used in accordance with the invention.

[0048] The dosage of the formulation to be used also depends on the specific activity of the agent selected, the mode of administration (e. g. systemic administration or local delivery), the form of the formulation (e. g. encapsulated agent, embedded agent, or particulate agent), the size of the formulation, and other factors as known per se. In one embodiment of the invention, the agent is encapsulated in liposomes. The liposomes may be prepared by any of the methods known in the art (regarding liposome preparation methods, see Mönkkönen, J. et al., 1994, J. Drug Target, 2: 299-308, and Mönkkönen, J. et al., 1993, Calcif Tissue Int., 53: 139-145). The liposomes may be positively charged, neutral or negatively charged, negatively charged liposomes being currently preferred, and may be single or multilamellar. Suitable liposomes in accordance with the invention are preferably non-toxic liposomes such as, for example, those prepared from phosphatidyl-choline phosphoglycerol, and cholesterol, e. g. as described below. The diameter of the liposomes used preferably range from 100 to 500 nm. However, other size ranges suitable for macrophage/monocyte up-take may also be used.

[0049] In a further embodiment, the agent may be embedded in nanoparticles. Nanoparticles are 30-1000 nm diameter, spherical or non-spherical polymeric particles. The agent may be embedded in the nanoparticle, dispersed uniformly or non-uniformly in the polymer matrix, adsorbed on the surface, or in combination of any of these forms. It is the submicron nature of this compositional form, which makes it efficient in therapeutic applications. The submicron size facilitates specific uptake by phagocytic cells such as monocytes and macrophages. In a preferred embodiment, the polymer used for fabricating nanoparticles is the biocompatible and biodegradable, poly (DL-lactide-co-glycolide) polymer (PLGA). However, additional polymers which may be used for fabricating the nanoparticles include, but are not limited to, PLA (polylactic acid), and their copolymers, polyanhydrides, polyalkyl-cyanoacrylates (such as polyisobutylcyanoacrylate), polyethyleneglycols, polyethyleneoxides and their derivatives, chitosan, albumin, gelatin and the like. The size of the nanoparticle used to encapsulate the agent depends on the method of preparation and the mode of administration. Preferably, the nanoparticles range in size from 70-500 nm. However, depending on preparation and sterilization techniques, the more preferred ranges include, but are not limited to, 100-300 nm and 100-180 nm.

[0050] The pharmaceutical carrier or diluent used in the formulation of the invention may be any one of the conventional solid or liquid or semi-solid carriers known in the art. A solid carrier, for example, may be lactose, sucrose, gelatins, and other carbohydrates. A liquid carrier, for example, may be biocompatible oil suitable for injection such as peanut oil, water or mixtures of biocompatible liquids, or a biocompatible viscous carrier such as a polyethylene or gelatin gel.

[0051] The composition of the formulation used for injection may be selected from emulsions, suspensions, colloidal solutions containing suitable additives, and additional suitable compositions known to the skilled artisan.

[0052] In accordance with a preferred embodiment of the invention, the formulation is administered during an acute myocardial infarction or as early as possible after acute myocardial infarction occurs. However, for preventive purposes, the formulation may be administered prior to the onset of a myocardial infarction to those individuals who are at a high risk of a myocardial infarction. In addition, the formulation may also be administered prior to or after reperfusion to significantly attenuate myocardial injury. The formulation may also be administered prior to or during a procedure where an acute myocardial infarction is probable. For example, the formulation may be administered prior to a percutaneous

transluminal coronary angioplasty (PTCA). In addition, the formulation may be administered to the individual either alone or in combination with other kinds of treatments.

[0053] In a further embodiment, the formulation may be administered to patients at risk of an impending myocardial infarction, to those with unstable coronary syndromes, or to those with myocardial ischemia.

[0054] In conclusion, modulation of the inflammatory response by specifically targeting monocytes and macrophages may reduce necrosis and improve cardiac repair and function after acute myocardial infarction.

EXAMPLE(S)

[0055] The following examples as set forth herein are meant to illustrate and exemplify the various aspects of carrying out the present invention and are not intended to limit the invention in any way.

EXAMPLE 1: Effect of Liposomal Alendronate on the Zone of Infarct

[0056] The effects of treatment with encapsulated bisphosphonates on the zone of infarct were studied in a rabbit AMI model. Eight New Zealand White male rabbits, 2.5-3.5 kg B. W., were fed normal chow and water ad libitum. The rabbits were anesthetized by Ketamine/Xylazine (35mg/kg; 5 mg/kg) and Isoflurane. The experiment was performed with respiratory support given by intubation and mechanical ventilation with isoflurane in balance oxygen, and continuous echocardiogram (ECG) and arterial blood pressure (catheter in ear artery) monitoring. The rabbits were randomly administered saline (control) or liposomal alendronate (3 mg/kg, i. v.). Thoracotomy was performed through the left 4th intercostal space, followed by pericardiotomy and creation of a pericardial cradle. The left main coronary artery was identified and a large branch was encircled by a 5-0 silk suture and a snare. Thereafter, the snare was tightened for 30 minutes. Ischemia was verified by ECG changes (ST-T segment elevation), changes of segment coloration and hypokinesia. After thirty minutes, the snare was released and resumption of blood flow was confirmed. The suture was left in place, released, and the chest cavity was closed in layers. Buprenex was administered to the rabbits for analgesia for 2-3 additional days. Following euthanasia with Pentotal, the rabbits were sacrificed after 7 days and the hearts were harvested. The coronary arteries were perfused through the ascending aorta with saline, followed by tightening of the suture on the previously occluded coronary artery and perfusion of the coronary arteries with 0.5% Evans blue solution (Sigma). The hearts were then frozen at -20 C for 24 hours and cut into transverse sections 2 mm apart. Slices of the hearts were incubated for 30 minutes in tritrazolium chloride (TTC, 1%, Sigma), fixed in 10% natural buffered formalin, and then photographed and processed by digital planimetry (photoshop). The left ventricular area unstained by Evans blue was defined as the area at risk and the area not stained by TTC (white) was defined as the area of infarct.

[0057] The results of liposomal alendronate on the final zone or area of infarct are shown in Figure 1. The results are presented as percentage of infarcted zone out of the area at risk. As illustrated, the area or zone of infarct was 42.5% in the control group and 29.56% in the group treated with liposomal alendronate. The data in Figure 1 are expressed as mean SD, n=4/group, p < 0.05. Accordingly, liposomal alendronate was effective in reducing the zone of infarct. No adverse effects were observed in the treatment group.

[0058] The variation in myocardial morphometry is illustrated in Figure 2. The control rabbits have a distorted myocardial morphometry while the rabbits treated with liposomal alendronate exhibit a more normal morphometry.

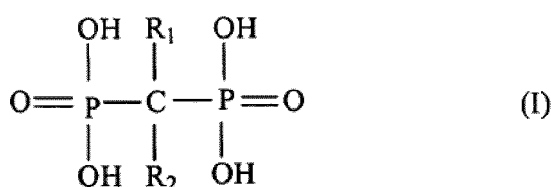
[0059] In addition, the effect of liposomal alendronate on blood monocytes was also determined. Monocyte suppression was ascertained using FACS analysis. At 48 hours after injection with liposomal alendronate, the blood monocyte population was reduced by 75-95%.

[0060] Similarly, Figure 3 illustrates the reduction in macrophage infiltration in rabbits treated with liposomal alendronate. The reduction in macrophage infiltration was ascertained by immunostaining for RAM11+ macrophages in representative sections of rabbit's hearts from the control group and those treated with liposomal alendronate.

Claims

1. Use of a formulation comprising an encapsulated agent, an embedded agent or a particulate agent having a size in the range of 0.03 to 1.0 μm , for the preparation of a medicament to improve remodeling following an acute myocardial infarction, and wherein the agent is selected from the group consisting of bisphosphonate, gallium, gold, selenium, gadolinium, silica, mithramycin, paclitaxel, sirolimus, everolimus, and combinations of two or more thereof.
2. Use according to claim 1, wherein the embedding in said embedded agent comprises embedding, enclosing, and/or adsorbing within a carrier, dispersing in the carrier matrix, adsorbing or linking on the carrier surface, or in combination of any of these forms, wherein carrier includes microparticles, nanoparticles, nanospheres, microspheres, microcapsules, or nanocapsules.

3. Use according to claim 1, wherein said encapsulated agent is encapsulated in liposomes.
4. Use according to any one of claims 1 to 3, wherein the formulation inactivates or destroys macrophages or monocytes.
5. Use according to any one of claims 1 to 3, wherein the formulation depletes blood_monocytes or tissue macrophages.
6. Use according to any one of claims 1 to 3 wherein the size of the encapsulated agent, the embedded agent, or the particulate agent is from 0.1 to 0.5 μm .
7. Use according to any one of claims 1 to 3, wherein the size of the encapsulated agent, the embedded agent, or the particulate agent is from 0.1 to 0.3 μm .
8. Use according to any one of claims 1 to 3, wherein the size of the encapsulated agent, the embedded agent, or the particulate agent is from 0.1 to 0.18 μm .
9. Use according to any one of claims 1 to 3, wherein the formulation can primarily enter the macrophage or monocyte via phagocytosis.
10. Use according to any one of claims 1 to 3, wherein the bisphosphonate is selected from the group consisting of clodronate, etidronate, tiludronate, pamidronate, alendronate and risendronate.
11. Use according to claim 2, wherein the agent is embedded in a carrier selected from the group consisting of micro-particles, nanoparticles, microspheres, and nanospheres.
12. Use according to claim 1, wherein the particulate is selected from the group consisting of flocculates, colloids, polymer chains, insoluble salts, and insoluble complexes.
13. Use according to claim 4, wherein inhibition of said monocytes or macrophages occurs through phagocytosis of the formulation.
14. Use according to claim 5, wherein depletion of said monocytes or macrophages occurs through phagocytosis of the formulation.
15. Use according to any one of claims 1, 2, or 3, wherein said agent has a formula(I):

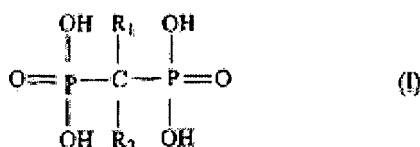


wherein R_1 is H, OH or halogen group ; and

R_2 is halogen; linear or branched C_1 - C_{10} alkyl or C_2 - C_{10} alkenyl, optionally substituted by heteroaryl or heterocycl C_1 - C_{10} alkylamino or C_3 - C_8 cycloalkylamino, where the amino may be a primary, secondary or tertiary amine; -NHY where Y is hydrogen, C_3 - C_8 cycloalkyl, aryl or heteroaryl ; or -SZ, where Z is chlorosubstituted phenyl or pyridinyl.

16. Use according to any one of claims 1, 2, or 3, wherein the formulation is administered following an acute myocardial infarction.
17. Use according to any one of claims 1, 2, or 3, wherein the formulation is administered during an acute myocardial infarction.
18. Use according to any one of claims 1, 2, or 3, wherein the formulation is administered prior to the anticipated onset of an acute myocardial infarction.
19. Use according to any one of claims 1, 2, or 3, wherein the formulation is administered during reperfusion.

20. Use according to any one of claims 1, 2, or 3, wherein the formulation is administered prior to or during a procedure where an acute myocardial infarction is probable.
21. Use according to claim 20, wherein the procedure is a percutaneous coronary angioplasty.
22. A pharmaceutical composition for use in a treatment of acute myocardial infarction, wherein the composition suppresses the inflammatory response following acute myocardial infarction, thereby improving remodeling following the acute myocardial infarction, wherein the composition comprises an encapsulated bisphosphonate, an embedded bisphosphonate or a particulate bisphosphonate having a size in the range of 0.03 to 1.0 μm , together with a pharmaceutically acceptable carrier or diluent.
23. A pharmaceutical composition for use according to claim 22, wherein the composition comprises an embedded bisphosphonate wherein the embedded bisphosphonate is a bisphosphonate that is embedded, enclosed, and/or adsorbed within a carrier, dispersed in the carrier matrix, adsorbed or linked on the carrier surface, or in combination of any of these forms, wherein carrier includes microparticles, nanoparticles, nanospheres, microspheres, microcapsules, or nanocapsules.
24. A pharmaceutical composition for use according to claim 23, wherein the bisphosphonate is embedded in a carrier selected from the group consisting of microparticles, nanoparticles, microspheres, and nanospheres.
25. A pharmaceutical composition for use according to claim 22, wherein the bisphosphonate is encapsulated in liposomes.
26. A pharmaceutical composition for use according to claim 22, wherein the particulate bisphosphonate is selected from the group consisting of flocculates, colloids, polymer chains, insoluble salts, and insoluble complexes.
27. A pharmaceutical composition for use according to any one of claims 22 to 26 for intravenous (i.v.), intramuscular (i.m.), intra-arterial (i.a.), or subcutaneous (s.c.) administration.
28. A pharmaceutical composition for use according to any one of claims 22 to 26 wherein said bisphosphonate has the general formula (I):



wherein R_1 is H, OH or halogen group ; and

R_2 is halogen; linear or branched $\text{C}_1\text{-C}_{10}$ alkyl or $\text{C}_2\text{-C}_{10}$ alkenyl, optionally substituted by heteroaryl or heterocyclyl $\text{C}_1\text{-C}_{10}$ alkylamino or $\text{C}_3\text{-C}_8$ cycloalkylamino, where the amino may be a primary, secondary or tertiary amine; $-\text{NH}\text{Y}$ where Y is hydrogen, $\text{C}_3\text{-C}_8$ cycloalkyl, aryl or heteroaryl ; or $-\text{SZ}$, where Z is chlorosubstituted phenyl or pyridinyl.

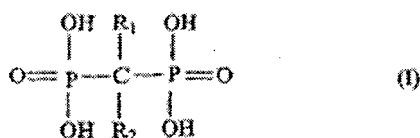
29. A pharmaceutical composition for use according to any one of claims 22 to 26 wherein said bisphosphonate is clodronate, etidronate, tiludronate, pamidronate, or alendronate.

Patentansprüche

1. Verwendung einer Rezeptur, die ein gekapseltes Agens, ein eingebettetes Agens oder ein Partikelagens mit einer Größe zwischen 0,03 und 1,0 μm aufweist, zur Herstellung eines Medikaments, um das Remodellieren nach einem akuten Herzinfarkt zu verbessern, und wobei das Agens aus der Gruppe ausgewählt ist, die aus einem Bisphosphonat, Gallium, Gold, Selen, Gadolinium, Kieselsäure, Mithramycin, Paclitaxel, Sirolimus, Everolimus und Kombinationen von zweien oder mehreren davon besteht.
2. Verwendung nach Anspruch 1, wobei das Einbetten bei dem eingebetteten Agens ein Einbetten, Umschließen und/oder Adsorbieren in einem Träger, Lösen in der Trägermatrix, Adsorbieren oder Anbinden auf der Trägerober-

fläche, oder eine Kombination aus jeder dieser Formen umfasst, wobei der Träger Mikropartikel, Nanopartikel, Nanokugeln, Mikrokugeln, Mikrokapseln oder Nanokapseln umfasst.

3. Verwendung nach Anspruch 1, wobei das gekapselte Agens in Liposomen gekapselt ist.
4. Verwendung nach einem der Ansprüche 1 bis 3, wobei die Rezeptur Makrophagen oder Monozyten inaktiviert oder zerstört.
5. Verwendung nach einem der Ansprüche 1 bis 3, wobei die Rezeptur Blutmonozyten oder Gewebemakrophagen dezimiert.
6. Verwendung nach einem der Ansprüche 1 bis 3, wobei die Größe des gekapselten Agens, des eingebetteten Agens oder des Partikelagens 0,1 bis 0,5 μm beträgt.
7. Verwendung nach einem der Ansprüche 1 bis 3, wobei die Größe des gekapselten Agens, des eingebetteten Agens oder des Partikelagens 0,1 bis 0,3 μm beträgt.
8. Verwendung nach einem der Ansprüche 1 bis 3, wobei die Größe des gekapselten Agens, des eingebetteten Agens oder des Partikelagens 0,1 bis 0,18 μm beträgt.
9. Verwendung nach einem der Ansprüche 1 bis 3, wobei die Rezeptur in die Makrophage oder den Monozyten primär über Phagozytose eindringen kann.
10. Verwendung nach einem der Ansprüche 1 bis 3, wobei das Biphosphonat aus der Gruppe ausgewählt ist, die aus Clodronat, Etidronat, Tiludronat, Pamidronat, Alendronat und Risendronat besteht.
11. Verwendung nach Anspruch 2, wobei das Agens in einen Träger eingebettet ist, der aus der Gruppe ausgewählt ist, die aus Mikropartikeln, Nanopartikeln, Mikrokugeln und Nanokugeln besteht.
12. Verwendung nach Anspruch 1, wobei die Partikel aus der Gruppe ausgewählt sind, die aus Ausflockungen, Kolloiden, Polymerketten, unlöslichen Salzen und unlöslichen Komplexen besteht.
13. Verwendung nach Anspruch 12, wobei das Hemmen der Monozyten oder Makrophagen mittels Phagozytose der Rezeptur stattfindet.
14. Verwendung nach Anspruch 13, wobei das Dezimieren der Monozyten oder Makrophagen mittels Phagozytose der Rezeptur stattfindet.
15. Verwendung nach einem der Ansprüche 1, 2 oder 3, wobei das Agens eine Formel (I) aufweist:

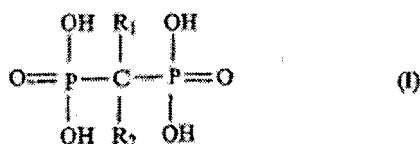


wobei R_1 H, OH oder eine Halogengruppe ist; und

R_2 ein Halogen, lineares oder verzweigtes C_1 - C_{10} -Alkyl oder C_2 - C_{10} -Alkenyl ist, das optional durch Heteroaryl oder Heterocyclyl C_1 - C_{10} -Alkylamino oder C_3 - C_8 -Cycloalkylamino substituiert ist, wobei das Amino ein primäres, sekundäres oder tertiäres Amin sein kann; -NHY, wobei Y Wasserstoff, C_3 - C_8 -Cycloalkyl, Aryl oder Heteroaryl ist; oder -SZ, wobei Z chloresubstituiertes Phenyl oder Pyridinyl ist.

16. Verwendung nach einem der Ansprüche 1, 2 oder 3, wobei die Rezeptur nach einem akuten Herzinfarkt verabreicht wird.
17. Verwendung nach einem der Ansprüche 1, 2 oder 3, wobei die Rezeptur während eines akuten Herzinfarkts verabreicht wird.

18. Verwendung nach einem der Ansprüche 1, 2 oder 3, wobei die Rezeptur vor dem erwarteten Einsetzen eines akuten Herzinfarkts verabreicht wird.
19. Verwendung nach einem der Ansprüche 1, 2 oder 3, wobei die Rezeptur während einer Reperfusion verabreicht wird.
20. Verwendung nach einem der Ansprüche 1, 2 oder 3, wobei die Rezeptur vor oder während einer Prozedur verabreicht wird, bei der ein akuter Herzinfarkt wahrscheinlich ist.
21. Verwendung nach Anspruch 20, wobei die Prozedur eine perkutane Koronarangioplastie ist.
22. Pharmazeutische Rezeptur zur Verwendung bei einer Behandlung eines akuten Herzinfarkts, wobei die Rezeptur die Entzündungsantwort unterdrückt, die auf einen akuten Herzinfarkt folgt, wodurch das Remodellieren nach dem akuten Herzinfarkt verbessert wird, wobei die Rezeptur ein gekapseltes Biphosphonat, ein eingebettetes Biphosphonat oder ein Partikelbiphosphonat mit einer Größe zwischen 0,03 und 1,0 μm , zusammen mit einem pharmazeutisch unbedenklichen Träger oder Verdünner enthält.
23. Pharmazeutische Rezeptur zur Verwendung nach Anspruch 22, wobei die Rezeptur ein eingebettetes Biphosphonat enthält, wobei das eingebettete Biphosphonat ein Biphosphonat ist, das in einen Träger eingebettet, eingeschlossen und/oder adsorbiert ist, in der Trägermatrix gelöst ist, auf der Trägersoberfläche adsorbiert oder angebunden ist, oder in Kombination dieser Formen, wobei der Träger Mikropartikel, Nanopartikel, Nanokugeln, Mikrokugeln, Mikrokapseln oder Nanokapseln umfasst.
24. Pharmazeutische Rezeptur zur Verwendung nach Anspruch 23, wobei das Biphosphonat in einen Träger eingebettet ist, der aus der Gruppe ausgewählt ist, die aus Mikropartikeln, Nanopartikeln, Mikrokugeln und Nanokugeln besteht.
25. Pharmazeutische Rezeptur zur Verwendung nach Anspruch 22, wobei das Biphosphonat in Liposomen gekapselt ist.
26. Pharmazeutische Rezeptur zur Verwendung nach Anspruch 22, wobei das Partikelbiphosphonat aus der Gruppe ausgewählt ist, die aus Ausflockungen, Kolloiden, Polymerketten, unlöslichen Salzen und unlöslichen Komplexen besteht.
27. Pharmazeutische Rezeptur zur Verwendung nach einem der Ansprüche 22 bis 26 zur intravenösen (i.v.), intramuskulären (i.m.), intraarteriellen (i.a.) oder subkutanen (s.c.) Verabreichung.
28. Pharmazeutische Rezeptur zur Verwendung nach einem der Ansprüche 22 bis 26, wobei das Biphosphonat die allgemeine Formel (I) aufweist:



wobei R_1 H, OH oder eine Halogengruppe ist; und

R_2 ein Halogen, lineares oder verzweigtes C_1 - C_{10} -Alkyl oder C_2 - C_{10} -Alkenyl ist, das optional durch Heteroaryl oder Heterocyclyl C_1 - C_{10} -Alkylamino oder C_3 - C_8 -Cycloalkylamino substituiert ist, wobei das Amino ein primäres, sekundäres oder tertiäres Amin sein kann; -NHY, wobei Y Wasserstoff, C_3 - C_8 -Cycloalkyl, Aryl oder Heteroaryl ist; oder -SZ, wobei Z chloresubstituiertes Phenyl oder Pyridinyl ist.

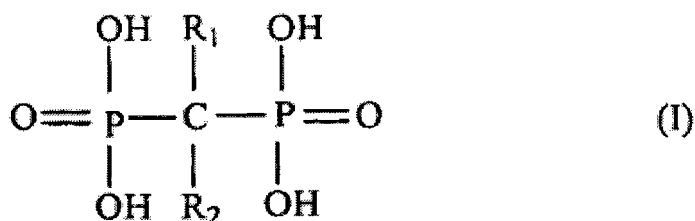
29. Pharmazeutische Rezeptur zur Verwendung nach einem der Ansprüche 22 bis 26, wobei das Biphosphonat Clodronat, Etidronat, Tiludronat, Pamidronat oder Alendronat ist.

Revendications

1. Utilisation d'une formulation comprenant un agent encapsulé, un agent incorporé ou un agent particulaire ayant une taille située dans la plage de 0,03 à 1,0 μm , pour la préparation d'un médicament destiné à améliorer le remodelage à la suite d'un infarctus aigu du myocarde, et dans laquelle l'agent est choisi dans le groupe constitué

de bisphosphonate, gallium, or, sélénium, gadolinium, silice, mithramycine, paclitaxel, sirolimus, évérolimus, et des combinaisons de deux d'entre eux ou plus.

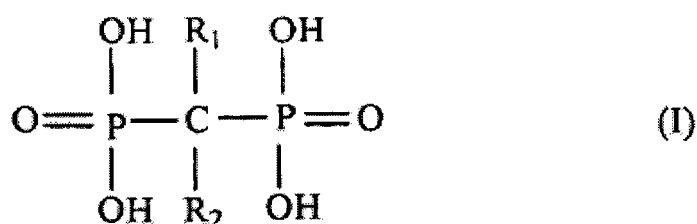
2. Utilisation selon la revendication 1, dans laquelle l'incorporation dans ledit agent incorporé comprend l'incorporation, l'inclusion, et/ou l'adsorption au sein d'un support, la dispersion dans la matrice d'un support, l'adsorption ou la liaison sur la surface d'un support, ou en combinaison de l'une quelconque de ces formes, dans laquelle le support comprend des microparticules, des nanoparticules, des nanosphères, des microsphères, des microcapsules, ou des nanocapsules.
3. Utilisation selon la revendication 1, dans laquelle ledit agent encapsulé est encapsulé dans des liposomes.
4. Utilisation selon l'une quelconque des revendications 1 à 3, dans laquelle la formulation inactive ou détruit les macrophages ou les monocytes.
5. Utilisation selon l'une quelconque des revendications 1 à 3, dans laquelle la formulation appauvrit les monocytes sanguins ou les macrophages tissulaires.
6. Utilisation selon l'une quelconque des revendications 1 à 3, dans laquelle la taille de l'agent encapsulé, de l'agent incorporé, ou de l'agent particulaire est de 0,1 à 0,5 μm .
7. Utilisation selon l'une quelconque des revendications 1 à 3, dans laquelle la taille de l'agent encapsulé, de l'agent incorporé, ou de l'agent particulaire est de 0,1 à 0,3 μm .
8. Utilisation selon l'une quelconque des revendications 1 à 3, dans laquelle la taille de l'agent encapsulé, de l'agent incorporé, ou de l'agent particulaire est de 0,1 à 0,18 μm .
9. Utilisation selon l'une quelconque des revendications 1 à 3, dans laquelle la formulation peut pénétrer principalement dans le macrophage ou le monocyte par phagocytose.
10. Utilisation selon l'une quelconque des revendications 1 à 3, dans laquelle le bisphosphonate est choisi dans le groupe constitué de clodronate, étidronate, tiludronate, pamidronate, alendronate et risédronate.
11. Utilisation selon la revendication 2, dans laquelle l'agent est incorporé dans un support choisi dans le groupe constitué de microparticules, nanoparticules, microsphères, et nanosphères.
12. Utilisation selon la revendication 1, dans laquelle la matière particulaire est choisie dans le groupe constitué de floculats, colloïdes, chaînes polymères, sels insolubles, et complexes insolubles.
13. Utilisation selon la revendication 4, dans laquelle l'inhibition desdits monocytes ou macrophages se produit grâce à la phagocytose de la formulation.
14. Utilisation selon la revendication 5, dans laquelle l'appauvrissement desdits monocytes ou macrophages se produit grâce à la phagocytose de la formulation.
15. Utilisation selon l'une quelconque des revendications 1, 2, ou 3, dans laquelle ledit agent a la formule (I) :



dans laquelle R_1 représente H, OH, ou un atome d'halogène ; et R_2 représente un atome d'halogène ; un groupe alkyle en C_1 à C_{10} ou alcényle en C_2 à C_{10} linéaire ou ramifié, éventuellement substitué par un groupe hétéroaryle ou hétérocyclyle alkyl en C_1 à C_{10} -amino ou cycloalkyl en

C₃ à C₈-amino, où le radical amino peut être une amine primaire, secondaire ou tertiaire ; -NHY où Y représente un atome d'hydrogène, un groupe cycloalkyle en C₃ à C₈, aryle ou hétéroaryle ; ou -SZ, où Z représente un groupe phényle ou pyridinyle chloro-substitué.

16. Utilisation selon l'une quelconque des revendications 1, 2, ou 3, dans laquelle la formulation est administrée à la suite d'un infarctus aigu du myocarde.
17. Utilisation selon l'une quelconque des revendications 1, 2, ou 3, dans laquelle la formulation est administrée durant un infarctus aigu du myocarde.
18. Utilisation selon l'une quelconque des revendications 1, 2, ou 3, dans laquelle la formulation est administrée avant l'apparition anticipée d'un infarctus aigu du myocarde.
19. Utilisation selon l'une quelconque des revendications 1, 2, ou 3, dans laquelle la formulation est administrée durant la reperfusion.
20. Utilisation selon l'une quelconque des revendications 1, 2, ou 3, dans laquelle la formulation est administrée avant ou durant une procédure où un infarctus aigu du myocarde est probable.
21. Utilisation selon la revendication 20, dans laquelle la procédure est une angioplastie coronarienne percutanée.
22. Composition pharmaceutique pour une utilisation dans un traitement de l'infarctus aigu du myocarde, dans laquelle la composition supprime la réponse inflammatoire à la suite d'un infarctus aigu du myocarde, améliorant de cette façon le remodelage à la suite de l'infarctus aigu du myocarde, dans laquelle la composition comprend un bisphosphonate encapsulé, un bisphosphonate incorporé ou un bisphosphonate particulaire ayant une taille située dans la plage de 0,03 à 1,0 µm, conjointement avec un support ou un diluant pharmaceutiquement acceptable.
23. Composition pharmaceutique pour une utilisation selon la revendication 22, dans laquelle la composition comprend un bisphosphonate incorporé dans laquelle le bisphosphonate incorporé est un bisphosphonate qui est incorporé, inclus, et/ou adsorbé au sein d'un support, dispersé dans la matrice d'un support, adsorbé ou lié sur la surface d'un support, ou en combinaison de l'une quelconque de ces formes, dans laquelle le support comprend des microparticules, des nanoparticules, des nanosphères, des microsphères, des microcapsules, ou des nanocapsules.
24. Composition pharmaceutique pour une utilisation selon la revendication 23, dans laquelle le bisphosphonate est incorporé dans un support choisi dans le groupe constitué de microparticules, nanoparticules, microsphères, et nanosphères.
25. Composition pharmaceutique pour une utilisation selon la revendication 22, dans laquelle le bisphosphonate est encapsulé dans des liposomes.
26. Composition pharmaceutique pour une utilisation selon la revendication 22, dans laquelle le bisphosphonate particulaire est choisi dans le groupe constitué de floculats, colloïdes, chaînes polymères, sels insolubles, et complexes insolubles.
27. Composition pharmaceutique pour une utilisation selon l'une quelconque des revendications 22 à 26 pour une administration intraveineuse (i.v.), intramusculaire (i.m.), intra-artérielle (i.a.), ou sous-cutanée (s.c.).
28. Composition pharmaceutique pour une utilisation selon l'une quelconque des revendications 22 à 26, dans laquelle ledit bisphosphonate a la formule générale (I) :



dans laquelle R_1 représente H, OH, ou un atome d'halogène ; et
 R_2 représente un atome d'halogène ; un groupe alkyle en C_1 à C_{10} ou alcényle en C_2 à C_{10} linéaire ou ramifié,
 éventuellement substitué par un groupe hétéroaryle ou hétérocyclyle alkyl en C_1 à C_{10} -amino ou cycloalkyl en
 C_3 à C_8 -amino, où le radical amino peut être une amine primaire, secondaire ou tertiaire ; -NHY où Y représente
 un atome d'hydrogène, un groupe cycloalkyle en C_3 à C_8 , aryle ou hétéroaryle ; ou -SZ, où Z représente un
 groupe phényle ou pyridinyle chloro-substitué.

29. Composition pharmaceutique pour une utilisation selon l'une quelconque des revendications 22 à 26, dans laquelle
 ledit bisphosphonate est le clodronate, l'etidronate, le tiludronate, le pamidronate, ou l'alendronate.

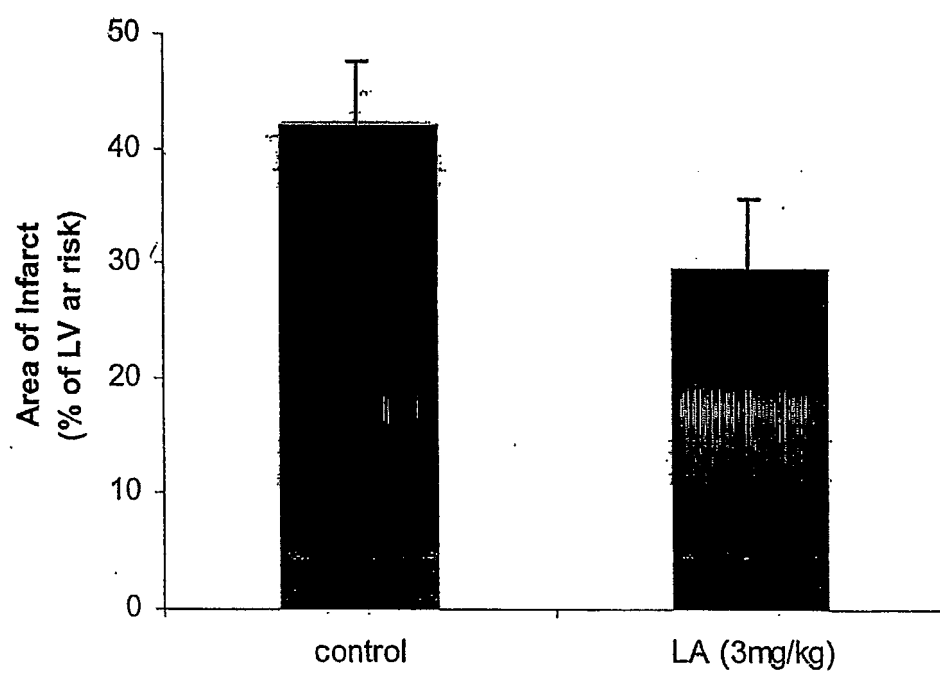


FIG. 1

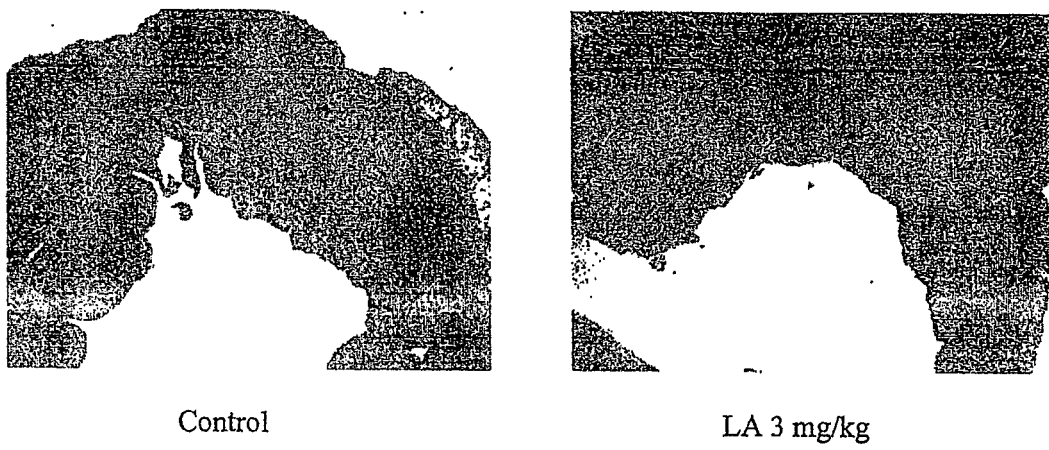


FIG. 2

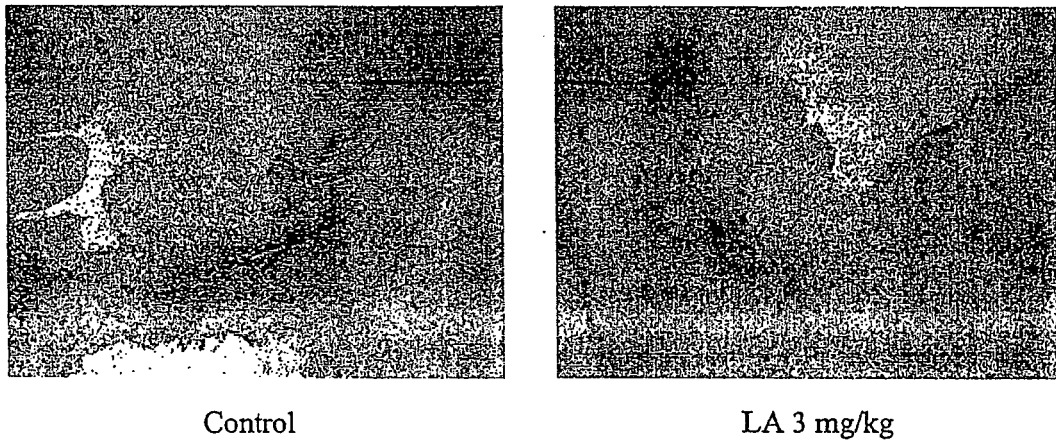


FIG. 3

REFERENCES CITED IN THE DESCRIPTION

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