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(54) Titre : COMPOSITION COMPRENANT DES GLYCOSAMINGLYCANES ET DES INHIBITEURS D'Hyaluronidase DESTINEE AU TRAITEMENT D'ARTICULATIONS ARTHRIQUES
(54) Title: COMPOSITION COMPRISING GLYCOSAMINOGYCANS AND HYALURONIDASE INHIBITORS FOR THE TREATMENT OF ARTHRITIC JOINTS

(57) Abrégé/Abstract:
A preferred embodiment of the present invention is directed to a composition and method for treating arthritis comprising one or more glycosaminoglycans in combination with one or more hyaluronidase inhibitor. In a more preferred embodiment the present invention is directed to a composition and method for treating arthritis comprising one or more glycosaminoglycans which would include at least hyaluronic acid in combination with one or more hyaluronidase inhibitors selected from the group consisting of heparan sulphate, dextran sulphate and xylose sulphate. In still a more preferred embodiment the present invention relates to a composition and method for treating arthritis comprising hyaluronic acid co-encapsulated with a hyaluronidase inhibitor in liposomes. Hyaluronic acid in the composition would confer the viscosupplement properties to the joint. The function of the hyaluronidase inhibitor would be to act as a preservative, and protect the hyaluronic acid from premature degradation in the joint. The liposomal encapsulation and delivery of the composition would serve as a slow release depot for the hyaluronic acid and the hyaluronidase inhibitor. This invention therefore provides a means of delivering stable and long lasting high molecular weight HA to the joint. The therapeutic effectiveness of the liposome co-encapsulated hyaluronic acid with the hyaluronidase inhibitor would be greater than simple injection of hyaluronic acid. The preferred method of treatment would be by intra-articular injection of an admixture of hyaluronic acid and a hyaluronidase inhibitor, optionally encapsulated in liposomes. The treatment is more effective than currently available treatments based on HA alone.
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COMPOSITION COMPRISING GLYUCOSAMINOGYCANS AND
HYALURONIDASE INHIBITORS FOR THE TREATMENT OF
ARTHRITE JOINTS

FIELD OF THE INVENTION

The invention broadly relates to a composition and method for the treatment of arthritic joints. More specifically the present invention relates to intrarticular delivery of a composition comprising at least one glycosaminoglycan, preferably hyaluronic acid, in combination with at least one compound that inhibits the action of at least one enzyme that breakdown glycosaminoglycan. Even more specifically the present invention relates to intrarticular delivery of a composition comprising at least one glycosaminoglycan, preferably hyaluronic acid, in combination with at least one hyaluronidase inhibitor, with encapsulation in liposomes as an option al emboideent. More preferably, the enzyme inhibitor is a inhibitor of enzymes that breakdown glycosaminoglycan. This invention therefore provides a means of delivering stable and long lasting high molecular weight glycosaminoglycan such as hyaluronic acid to the joint which is important for the treatment of arthritis.

The hyaluronidase inhibitor would be specific only for hyaluronidase, should we incorporate a broader statement to include other inhibitors of enzymes that breakdown Glycosaminoglycans.
BACKGROUND OF THE INVENTION

Glycosaminoglycans (GAGS) are biopolymers consisting of repeating polysaccharide units, and are present on the cell surface as well as in the extracellular matrix of animals. GAGS are long unbranched polysaccharides containing a repeating disaccharide unit. The disaccharide units contain either of two modified sugars, N-acetylgalactosamine or N-acetylglucosamine and a uronic acid such as glucuronate or iduronate. GAGS are highly negatively charged molecules, with extended conformation that imparts high viscosity to the solution. GAGS are located primarily on the surface of cells or in the extracellular matrix. Along with the high viscosity of GAGS comes low compressibility, which makes these molecules ideal for a lubricating fluids in the joints. At the same time, their rigidity provides structural integrity to cells and provides passageways between cells allowing for cell migration.

Common naturally occurring GAGS include, but are not limited to, chondroitin sulphate, keratan sulphate, heparin, heparan sulphate, , dermatan sulphate and hyaluronidate (commonly referred to as hyaluronic acid, HA)

Hyaluronic acid (HA) is a high molecular weight polysaccharide of N-acetyl glucosamine and glucuronic acid molecules that is naturally occurring in all mammals in a variety of tissue and some bacterial species. HA is unique among the GAGS in that it does not contain any sulfate and is not found covalently attached to proteins as a proteoglycan. HA polymers are very large with molecular weights of between about 50,000-10,000,000 Da, and can displace a large volume of water.

The chemical structure of hyaluronic acid is:

![Hyaluronic acid structure diagram]
The highest concentrations are found in connective tissue such as synovial membrane and synovial fluid. Hyaluronic acid can vary in molecular mass from 50,000-10,000,000Da and forms highly viscoelastic solutions. It is synthesized in the plasma membrane of fibroblasts and other cells by addition of sugars to the reducing end of the polymer, whereas the nonreducing end protrudes into the pericellular space. The polysaccharide is catabolized locally or carried by lymph to lymph nodes or the general circulation, from where it is cleared by the endothelial cells of the liver sinusoids. The overall turnover rate is surprisingly rapid for a connective tissue matrix component (t_{1/2} = 0.5 to a few days).

Methods to prepare pure samples of HA are well known in the art. For example, EP 0239335, US 4879375, US4141973 disclose methods to prepare highly pure fractions of hyaluronic acid, which purport to be non-inflammatory.

Hyaluronic acid is critical for the homeostasis of the joint, in part, because it provides the rheological properties (viscosity and elasticity) of the synovial fluid. It contributes to joint lubrication, buffers load transmission across articular surfaces, provides a renewed source of HA to joint tissues, and imparts anti-inflammatory properties to synovial fluid. In osteoarthritis, the molecular weight and concentration of HA in synovial fluid are diminished and this impairs the ability of synovial fluid to function effectively. The above observations have led to the development of viscosupplementation by means of intra-articular injections of hyaluronic acid for treatment of osteoarthritis of the knee. This treatment involves removal of pathologic osteoarthritic synovial fluid and replacement with HA-based products that restore the molecular weight and concentration of HA toward normal levels that can have beneficial therapeutic effects. Scientific publications describing the use of hyaluronic acid for treatment of articular conditions are well known in the art examples of which are Adams, 1993, 1996; Adams et al., 1995; Baker, 1997;
Balazs, 1968, 1982; Balazs & Denlinger, 1985, 1989, 1993; Balazs & Gibbs, 1970; Band et al., 1995; Denlinger, 1982, 1996; Dickson & Hosle, 1998; Estey, 1998; Gibbs et al., 1968; Moreland et al., 1993; Peyron, 1993a, 1993b, 1999; Rydell et al., 1970; Scale et al., 1994; Weiss et al., 1981; and Weiss & Balaz 1987. In the patent literature hyaluronic acid preparations for treatment of arthritic joints have been described. Examples of which are US 5914322, described in US 4801619.

Several preparations of HA, e.g. Hylalgan (Fidia S.p.A) and Synvisc (Genzyme Biosurgery), are commercially available as treatments applied via intra-articular injection into the diseased joint. Such treatments have been found to provide significant pain relief [1-5], by supplementing the synovial fluid with HA which is chemically and mechanically more closely representative of the HA found in young, healthy articular joints.

Although the use of such treatments were reported as early as 1974 [1], the mechanism of action remains poorly understood. While evidence supports several roles of HA within the joint such as viscosupplementation and lubrication [6], protection of the cartilage surfaces [6], and suppression of pain-stimulating mediators such as IL-1α [7-9], it is also known that HA molecules are removed from the joint over time through the process of enzymatic breakdown and lymphatic clearance [10-12]. Therefore the longer-term effects of such treatments are limited.

Attempts to increase the residence time of HA within the joint have largely focused on modifying the HA molecule by cross-linking [11] [US Patent 5827937, WO99/10385], and while this delays clearance of HA there is little evidence to suggest that any additional long-term benefits are derived from such treatments, and concerns remain associated with the altering of the molecular structure, and in some cases the presence of chemical cross-linking agents.

The current regiment for hyaluronic acid treatment typically requires three to five weekly injections to be administered. One potential adverse effect that could rise from repeated injections could be the risk of joint infection or inflammation.
The present invention relates to a composition and method for the treatment of arthritic joints which consists of a combination of glycosaminoglycans, preferably hyaluronic acid, and an inhibitor of enzymes that breakdown GAG's. An example of enzyme inhibitor would be a hyaluronidase inhibitor, which would increase the long-term efficacy of the treatment. In addition to the functions of the hyaluronic acid as described above, the enzyme inhibitor, as for example the hyaluronidase inhibitor would act as a preservative, and protect the hyaluronic acid from premature degradation in the joint. This invention therefore provides a means of delivering stable and long lasting high molecular weight HA to the joint.

Enzyme inhibitors are defined as any compound alone or in combination with other compounds, that inhibits the degradation of an enzyme responsible for the breakdown of GAG's. Hyaluronidase inhibitors are defined as including any class of compounds that have the ability to inhibit hyaluronic acid degrading enzyme hyaluronidase from degrading hyaluronic acid. Hyaluronidases are defined as including enzymes, which catalytically cleave the glycosidic bonds of hyaluronic acid. Examples of sulfated saccharides that are hyaluronidase inhibitors are heparan sulphate, dextran sulphate and xylose sulphate.

Cysteamine is another compound found to completely inhibit testicular hyaluronidase (US7255870). Acrylamidobenzoic acid derivatives, and (1,3,5,6-dioxo-1,3-propanediyl)diamino!bisbenzoic acid derivatives are other classes of compounds with hyaluronidase inhibitory activity (US5006548, US4755506). In addition several agents, such as sodium aurothiomalate (Myocrisin), anti-inflammatory agents such as glycyrrhizin, (Furuya et al., 1997), phenylbutazone and oxyphenbutazone, or the plant natural products like flavonoids luteolin, or apigenin, have been shown to be potent antagonists of hyaluronidase. A study, assessing the potential for intraarticular administration of protease inhibitors in patients with rheumatoid arthritis (RA), showed that with the individual approach to intraarticular
drug administration, the number of repeated punctures of the joints decreased by 18.8%, while the amount of glucocorticosteroid hormones administered was twice as reduced. (Matveikov et al., 1989).

Lipids are also present in joint synovial fluid, and certain phospholipids (in particular dipalmitoylphosphatidylcholine (DPPC)) have been implicated in the lubrication of cartilage surfaces [13-15] and shown to reduce osteoarthritic pain by intra-articular injection into the knee joint [16].

Liposomes, can be used to deliver HA and hyaluronidase inhibitor, are structures consisting of a membrane bilayer composed of phospholipids of biological or synthetic origin, usually spherical in shape, were first described in 1965 by Bangham and co-workers. Liposomes form naturally when phospholipids or lipids contact water and because liposomes have features of biological membranes, they can be engineered in the laboratory to contain a variety of biologically and therapeutic relevant complex molecules, including proteins. The phospholipid bilayer membrane of liposomes separates and protects entrapped materials in the inner aqueous core from the outside. Because of their relative ease of preparation and compatibility with a variety of complex molecules, liposomes have been widely used as carriers to deliver a variety of therapeutic and diagnostic agents useful in the treatment of cancers and fungal disease including amphotericin B and doxorubicin. A large number of publications and review on liposomal chemistry and formulations strategies have been published and are herein incorporated by reference. (Gregoriadis, 1988, 1992, WO0103669, WO0100247, WO0076476, WO 8500515).

Combinations of lipids and HA have been variously referenced in the literature. WO-A-91/12026 patented the combination of HA and phospholipid for the treatment of rheumatic joints. It was postulated that by combining HA and DPPC, both of which provide joint lubrication, improved lubrication could be imparted to the cartilage surfaces. A mixture of DPPC liposomes and HA has been
shown to remove reduce surgical adhesions post-operatively. In both of these cases the lipid component and the HA component are combined in mixture; therefore no effect on the residence time of the HA molecules would be expected.

Chemical interactions between lipids and HA have been described which show hexagonal shaped structures [18,19] or display acid amide bonding between the two ingredients (Aoki et. Al., US Patent 5,470,578, Antirheumatic Composition) Buttle et. Al. (WO 00/74662 A2, Arthritis Treatment) showed that catechins could be beneficial in the treatment of osteoarthritis and proposed their combination with HA. A liposomal delivery vehicle was mentioned for such a treatment; however, the method for achieving this was unclear as liposomes are generally less than 200 nm in diameter, while the diameter of HA molecules is typically around 200-300 nm [6]. None of the above prior art satisfactorily addresses the need for providing a beneficial longer-term pharmacological effect due to increased HA residence time in the joint. The present invention addresses this need.

SUMMARY OF THE INVENTION

A preferred embodiment of the present invention is directed to a composition and method for treating arthritis comprising one or more glycosaminoglycans in combination with one or more enzyme inhibitors, as for example a hyaluronidase inhibitor.

In a more preferred embodiment the present invention is directed to a composition and method for treating arthritis comprising one or more glycosaminoglycans which would include at least hyaluronic acid in combination with one or more enzyme inhibitors, as for example hyaluronidase inhibitors which may be selected from the group consisting of: heparan sulphate, dextran sulphate and xylose sulphate.
In still a more preferred embodiment the present invention relates to a composition and method for treating arthritis comprising hyaluronic acid co-encapsulated with an enzyme inhibitor, as for example a hyaluronidase inhibitor in liposomes. Hyaluronic acid in the composition would confer the viscosupplement properties to the joint. The function of the hyaluronidase inhibitor would be to act as a preservative, and protect the hyaluronic acid from premature degradation in the joint. The liposomal encapsulation and delivery of the composition would serve as a slow release depot for the hyaluronic acid and the hyaluronidase inhibitor. This invention therefore provides a means of delivering stable and long lasting high molecular weight HA to the joint. The therapeutic effectiveness of the liposome co-encapsulated hyaluronic acid with the hyaluronidase inhibitor would be greater than simple injection of hyaluronic acid.

The preferred method of treatment would be by intra-articular injection of an admixture of hyaluronic acid and a hyaluronidase inhibitor, optionally encapsulated in liposomes. It is expected that the treatment would be more effective than currently available treatments based on HA alone. Therefore one treatment option would involve intra-articular injections as used in current practise for HA. A preferred delivery method, however, would be by a single intra-articular injection into the diseased joint, thereby reducing the risk of adverse events associated with multiple intra-articular injections.

**DETAILED DESCRIPTION OF THE INVENTION**

It is believed that one skilled in the art can, based upon the description herein, utilize the present invention to its fullest extent. The following specific
embodiments are to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention belongs. Also, all publications, patent applications, patents, and other references mentioned throughout this application are herein expressly incorporated by reference.

Glycosaminoglycans (GAGS) are defined as biopolymers consisting of repeating polysaccharide units, and are present on the cell surface as well as in the extracellular matrix of animals. GAGS are long unbranched polysaccharides containing a repeating disaccharide unit. The disaccharide units contain either of two modified sugars, N-acetylgalactosamine or N-acetylg glucosamine and a uronic acid such as glucuronate or iduronate. GAGS are highly negatively charged molecules, with extended conformation that imparts high viscosity to the solution. GAGS are located primarily on the surface of cells or in the extracellular matrix. Along with the high viscosity of GAGS comes low compressibility, which makes these molecules ideal for a lubricating fluids in the joints. At the same time, their rigidity provides structural integrity to cells and provides passageways between cells allowing for cell migration.

Hyaluronic acid (HA) is defined as a high molecular weight polysaccharide of N-acetyl glucosamine and glucuronic acid molecules that is naturally occurring in all mammals in a variety of tissue and some bacterial species. For purposes of this applications HA includes any derivatives such as hyaluronan and Hyaluronic acid itself with H+ ion attached to the COO- group. And salts of hyaluronic acid whereby another positive ion replaces the H+ ion, as for example with NA+ which forms sodium hyaluronate. Also included in the definition is any physically or chemically cross-linked hyaluronic acid and derivatives. HA is unique among the GAGS in that it does not contain any sulfate and is not found covalently attached to proteins as
a proteoglycan. HA polymers are very large with molecular weights of between about 100,000-10,000,000, and can displace a large volume of water. For purposes of this invention a most preferred embodiment includes a non cross-linked hyaluronic acid with a molecular weight of 1-10Mda.

5 Enzyme inhibitor is defined as any compound which inhibits the action of enzymes that breakdown Glycosaminoglycosamine.

The optimum concentrations of Hyaluronidase (HAs) inhibitors to use in the formulations will depend on the chemical nature of the inhibitor compound. For non-peptide inhibitors a wide range of concentrations can be used from 10- to 0.01 microM. Phenylbutazone has been used at the dosage of 4.4mg/Kg of body weight. Glycyrhrhizin, can be used at concentrations ranging from 1-6 micro M since at 3 micro M, 50 % inhibition was observed in vitro. The hyaluronidase inhibitory activity of cysteamine had an IC50 value of 150 microg/ml. The flavonoid Apigenin inhibited hyaluronidase over a concentration range from 50-200micro M.

Hyaluronidase inhibitors are generally effective in the micro M range in in vitro cultures. These in vitro ranges can be to translated into the in vivo dose for formulations by those skills in the art.

Hyaluronidase inhibitors are defined as any class of compounds that have the ability to inhibit hyaluronic acid degrading enzyme hyaluronidase.

Hyaluronidases are defined as including enzymes, which catalytically cleave the glycosidic bonds of hyaluronic acid.

Liposomes are defined as small spheres whose walls are layers of phospholipids with water. As they form, liposomes entrap water and any water soluble solutes that are present. Because of this entrapping ability, they are useful as drug delivery systems. For purposes of the present invention a most preferred embodiment includes the use of a multilamellar vesicle. For purposes of this
invention a preferred embodiment includes any naturally occurring phospholipid and a most preferred embodiment includes dipalmitoylphosphatidylcholine (DPPC).

Intra-articular delivery is defined as a method whereby a treatment is delivered, directly or indirectly, into the synovial capsule of an articulating joint.
Examples

Example 1:

A. Evaluation of Efficacy in vitro

The efficacy of the above composition can be tested in in vitro experiments outlined below. Stability of the liposomal formulations of hyaluronic acid (HA) with hyaluronidase inhibitors can be evaluated in cell culture medium supplemented with hyaluronidase and phospholipase A2. Hyaluronic acid encapsulated in liposomes and non-encapsulated hyaluronic acid will also be evaluated in the same experiment and would serve as controls.

Serum free chondrocyte culture medium containing 0.1% BSA would be supplemented with hyaluronidase (bovine testes) and phospholipase A2 (PLA2, porcine pancreas) to make final concentrations of 0.5 mU/ml (Ann Rheum Dis 58 186-188 1999) and 5000 U/ml (J Rheumatol 12(2) 211-216 1085), respectively (to partly mimic in vivo osteoarthritic synovial fluid). Equal volumes of the cell culture medium (supplemented with hyaluronidase and phospholipase ) will be combined with liposomal formulation of HA with Hyaluronidase inhibitor) in different tubes. These tubes would be mixed and incubated for 0, 1, 2, 4 days, 2 weeks, 1 and 3 months at 37°C with gentle shaking. After the appropriate incubation periods, the medium containing various formulated products will be analyzed for determination of HA molecular weight distribution and by using fluorescent labelling of DPPC (label in bilayers), to identify level of encapsulation by overlaying GPC-UV and MALLS spectra. The Stability of the Liposomal Formulations of Hyaluronic acid (HA) can also be assessed in synovial fluid obtained from human osteoarthritic patients (Source of Hyaluronidase and Phospholipase A2). This experiment will
highlight the beneficial effect of co-incorporating hyaluronic acid and hyaluronidase inhibitors in liposomes for achieving long stable and long term delivery of hyaluronic acid to the joints.

B. Evaluation of efficacy in vivo

The optimum concentrations of HAase inhibitors to use in the formulations for humans would be expected to be as follows. For non-peptide inhibitors like BAY 12-9566 a wide range of concentrations are used from 10- to 0.01 microM. For phenybutazone in in vivo studies to determine the pharmacokinetics of the drug 4.4mg/Kg of body weight is used. For glycyrrhizin, 50% inhibition of bovine testis HAase activity is achieved with 3micro M in vitro. The hyaluronidase inhibitory activity of cysteamine has an IC50 value of 150microg/ml. The flavonoid Apigenin inhibites hyaluronidase over a concentration range from 50-200 microM.

THE FOLLOWING PUBLICATIONS AND PATENTS ARE HEREIN INCORPORATED BY REFERENCE

3. Adams, M.E. Viscosupplementation as articular therapy. In The Chemistry, Biology and Medical Applications of hyaluronan and its derivatives


[2] to [5] (To be added)


CLAIMS

What is claimed is:

1. A pharmaceutical composition useful for the treatment of arthritic joints comprising at least one glycosaminoglycan (GAG) and at least one enzyme inhibitor in an acceptable dosage.

2. The pharmaceutical composition of claim 1 wherein the enzyme inhibitor is a hyaluronidase inhibitor.

3. The composition of claim 1 wherein the glycosaminoglycan is selected from the group consisting of: chondroitin sulphate, keratinsulphate, heparin, heparin sulphate and dermatan sulphate.

4. The composition of claim 2 wherein the hyalluronidase inhibitor is selected from the group consisting of: xylose sulphate, cyteamine, a derivative of acrylamidobenzoic acid, a derivative of (1,3, -dioxo-1-3-prpadenyll) diiminobisbenzoic acid sodium aurothiomalate, glycyrrhizin, phenylbutazone, oxyphenbutazone, luteolin or apigenin.

5. The composition of claim 1 wherein the glycosaminoglycan is hyaluronic acid.

6. The composition of claim 1, in which the glycosaminoglycan is of greater than 500 kDa molecular weight

7. The composition of claim 1 in which the glycosaminoglycan is encapsulated within at least one liposome.
8. The composition of claim 2 in which the hyaluronidase inhibitor is encapsulated within at least one liposome.

9. The composition of claim 2 in which both the glycosaminoglycan and hyaluronidase inhibitor are encapsulated within one or more liposomes.

10. The composition of claim 4, in which the hyaluronic acid's concentration is greater than 1 mg/ml.

11. The composition of claim 2, in which at least 10% by volume of the hyaluronic acid is encapsulated in liposomes.

12. The composition of claim 1, in which the concentration of the hyaluronidase inhibitor is between xx and yy µg/ml.

13. The composition of claim 6, in which the liposome is made from a bilayer-forming phospholipid.

14. The composition of claim 12, in which the phospholipid is dipalmitoylphosphatidylcholine.

15. The composition of claim 6, in which the phospholipid concentration is greater than 10 mg/ml.

16. A liposomal delivery vehicle which encapsulates one or both components of the composition of claim 1.
17. A liposomal delivery vehicle according to claim 15, which is spherical or rod-
shaped in structure, and which has a diameter of greater than 0.1\(\mu\)m.

18. A method of treating arthritic joints, the method comprising the steps of: a) preparing the composition of claim 1 and b) administering the composition to a human in a pharmaceutically appropriate dosage.

19. The method according to claim 16, wherein the method of administering the composition is by intra-articular injection into the arthritic joint.

20. A method of manufacture the composition of claim 1, which consists of preparing the glycosaminoglycans and enzyme inhibitor as an admixture.