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DIRECCIÓN DE NUEVAS CREACIONES

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Abogado(a)/Señor(a)
ALICIA LLOREDA RICAURTE

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Patente de Invención	X			Patente de Modelo de Utilidad	
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No. Solicitud Internacional	PCT/GB2009/050353				
Fecha de Presentación Internacional	09/04/2009				

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	10-134179-00000-0000	28/Octubre/2010
Reivindicaciones:	10-134179-00009-0000	12/Marzo/2013
Prioridad:	US61043491	09/Abril/2008

2. Análisis de la Prioridad

Se acepta la reivindicación de Prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486). Y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título de la solicitud: “DEPÓSITO FARMACÉUTICO QUE COMPRENDE N-{5-[(CICLOPROPILAMINO)CARBONIL]-2-METILFENIL}-3-FLUORO-4-(PIRIDIN-2-ILMETOXI) BENZAMIDA”

El problema técnico se refiere a la necesidad de proporcionar una composición de liberación lenta que logre una alta concentración en el área de la inyección,

mientras que la concentración sanguínea es baja, y sea útil para tratar inflamación y dolor de las articulaciones (como artritis reumatoide, osteoartritis y gota), para solucionar este problema la solicitud presenta un depósito farmacéutico que comprende micropartículas o nanopartículas de N-{5-[(ciclopropilamino)carbonil]-2-metilfenil}-3-fluoro-4-(piridin-2-ilmetoxi)benzamida, o una sal farmacéuticamente aceptable de la misma, y un copolímero biodegradable de ácido láctico-ácido glicólico.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A61K 9/16

4. De la Solicitud de Patente

De acuerdo con lo establecido en el numeral 1.2.2.2 del Capítulo Primero del Título X de la Circular Única para efectos del examen de patentabilidad, se tendrá en cuenta la tasa pagada por el solicitante al momento de comenzar el examen para las reivindicaciones adicionales; esto es que cuando la solicitud contenga más de diez (10) reivindicaciones y no se haya pagado la tasa complementaria, sólo se estudiarán las cubiertas por la tasa pagada.

5. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de presentación de la solicitud de prioridad invocada, es decir el 09 de abril de 2008.

Consultadas las fuentes de información con que se cuenta, se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación
D1	WO2005061465	"Amide derivatives bearing a cyclopropylaminoacarbonil substituent useful as cytokine inhibitors"	07/Julio/2005
D3	Advanced Drug Delivery Reviews	"Intraarticular drug delivery in osteoarthritis"	23/Febrero/2006

El documento D1¹ divulga compuestos de la Fórmula (I), en la que Qa es heteroarilo y está sustituido con halógeno R1 y R2 son cada uno hidrógeno y Qb es fenilo o heteroarilo, y Qb puede tener opcionalmente 1 o 2 sustituyentes seleccionados de hidroxilo, halógeno y alquilo (C₁₋₆), o una sal farmacéuticamente aceptable de los mismos. Entre estos derivados de amida se incluye el compuesto N-{5-[(ciclopropilamino)carbonil]-2-metilfenil}-3-fluoro-4-(piridin-2-ilmetoxi)benzamida (Pág. 72, Ej. 43), que inhibe la producción de citoquinas tales como IL y TNF, lo cual lo hace útil para tratar inflamación y dolor de las articulaciones (como artritis reumatoide, osteoartritis y gota). Las composiciones pueden estar en una forma apropiada para uso oral, tópico, por inhalación o para administración parenteral (por ejemplo para dosificación intravenosa, subcutánea o intramuscular, como una solución estéril acuosa u oleosa) (Pág. 29, líneas 10 a 17). El documento D1 divulga también procesos para su preparación, composiciones farmacéuticas que los contienen y su uso en el tratamiento de enfermedades o condiciones médicas mediadas por citoquinas.

El documento D3² divulga que la encapsulación con PLGA puede aumentar fuertemente la eficacia terapéutica del compuesto activo en el tratamiento intraarticular de osteoartritis (OA). Este documento informa sobre la preparación

¹ [http://worldwide.espacenet.com/searchResults?](http://worldwide.espacenet.com/searchResults?compact=false&PN=WO2005061465&ST=advanced&locale=en_EP&DB=EPODOC)

[compact=false&PN=WO2005061465&ST=advanced&locale=en_EP&DB=EPODOC](http://worldwide.espacenet.com/searchResults?compact=false&PN=WO2005061465&ST=advanced&locale=en_EP&DB=EPODOC)

² Intraarticular drug delivery in osteoarthritis. Advanced Drug Delivery Reviews 58 (2006) 226– 242. <http://www.med.nyu.edu/pmr/residency/resources/injections%20and%20procedures/intra-art%20drugs%20in%20OA.pdf>

de nano partículas de PLGA encapsulando moléculas bioactivas para liberación sostenida e inyección intraarticular (IA). Varios glucocorticoides y formulaciones de ácido hialurónico (HA), que están actualmente disponibles en el mercado para el tratamiento de IA, proporcionan alivio del dolor a corto plazo. Las drogas orales disponibles para el tratamiento sintomático también tienen deficiencias, en particular los efectos secundarios. Por lo tanto, para lograr la exposición a largo plazo de la droga, se presentan formulaciones tales como las suspensiones y los hidrogeles y también nuevos enfoques como las formulaciones basadas en nano o micropartículas. Este documento informa que numerosas publicaciones describen el uso de nano o micropartículas hechas de polímeros biodegradables como unos medios para controlar la liberación de los compuestos activos después de la inyección IA. Agrega que la albúmina y el PLGA (poli(ácido láctico-co-glicólico)) han sido usados preferiblemente, para este propósito, como polímeros biocompatibles y biodegradables. Por ejemplo las investigaciones de Ratcliffe et. al. mostraron que las micropartículas de tamaño inferior a 6 μm son tomadas por los macrófagos sinoviales. Después de la inyección IA de radio-micropartículas de albúmina marcada mostraron tiempos de residencia de varias semanas en la articulación (Págs. 237, 238, 241 y 242).

6. Examen de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

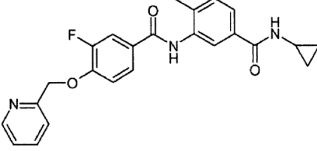
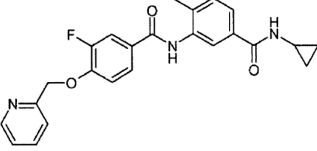
En el presente caso, el depósito reclamado en la solicitud no tiene nivel inventivo, teniendo en cuenta que la reivindicación 1 se refiere a: *“Un depósito farmacéutico que comprende micropartículas o nanopartículas de N-{5-[(ciclopropilamino)carbonil]-2-metilfenil}-3-fluoro-4-(piridin-2-ilmetoxi)benzamida, o una sal farmacéuticamente aceptable de la misma, y un copolímero biodegradable de ácido láctico-ácido glicólico.”* (Pág. 10 del radicado 10-134179-00009-0000).

La tabla 1 presenta la comparación entre las características técnicas esenciales de la solicitud estudiada, mencionadas en la reivindicación 1, y las reveladas en los documentos D1 y D3 que representan el estado de la técnica.

El documento D1, considerado el estado de la técnica más cercano a la invención definida en la reivindicación 1, divulga compuestos de la Fórmula (I), en la que Qa es heteroarilo y está sustituido con halógeno R1 y R2 son cada uno hidrógeno y Qb es fenilo o heteroarilo, y Qb puede tener opcionalmente 1 o 2 sustituyentes seleccionados de hidroxilo, halógeno y alquilo (C_{1-6}), o una sal farmacéuticamente aceptable de los mismos. Entre estos derivados de amida se incluye el compuesto N-{5-[(ciclopropilamino)carbonil]-2-metilfenil}-3-fluoro-4-(piridin-2-ilmetoxi)benzamida, que inhibe la producción de citoquinas tales como IL y TNF, lo cual lo hace útil para tratar inflamación y dolor de las articulaciones (como artritis reumatoide, osteoartritis y gota).

La diferencia entre la invención, definida en la reivindicación 1, y las composiciones del documento D1 consiste en que el compuesto activo está encapsulado en micropartículas o nanopartículas del copolímero biodegradable de ácido láctico-ácido glicólico (tal como PLGA).

Tabla 1

Características esenciales	D1	D3
Reiv 1		
Depósito	Composición	Depósito
micropartículas o nanopartículas de:		micropartículas o nanopartículas de:
		Glucocorticoides Ácido hialurónico Diclofenac Condroitina Capsaicina Icatibant Anakinra etc.
	(Pág. 72, Ej. 43)	(Págs. 237, 238, 241 y 242)
copolímero biodegradable de ácido láctico-ácido glicólico	portador farmacéuticamente aceptable	copolímero biodegradable de ácido láctico-ácido glicólico
	(Reiv 11)	(Pág. 238)
Efecto:	Efecto:	Efecto:
Contra artritis reumatoide, osteoartritis y gota	Contra artritis reumatoide, osteoartritis y gota	Contra artritis reumatoide, osteoartritis
	(Pág. 1, línea 29)	(Págs. 237, 238, 241 y 242)
Liberación prolongada		Liberación prolongada
		(Págs. 237, 238, 241 y 242)

El efecto observado por el hecho de encapsular el compuesto activo en micropartículas o nanopartículas del copolímero biodegradable de ácido láctico-ácido glicólico es que luego de la inyección en el líquido sinovial, el compuesto activo logra una alta concentración en el área de la inyección, mientras que la concentración sanguínea es baja (Pág. 17 de la descripción).

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular así: cómo modificar la composición conocida en el documento D1 para proporcionar una composición de liberación lenta que logre una alta concentración en el área de la inyección, mientras que la concentración sanguínea es baja, y sea útil para tratar inflamación y dolor de las articulaciones (como en artritis reumatoide, osteoartritis y gota).

El documento D3 divulga que la encapsulación con PLGA puede aumentar fuertemente la eficacia terapéutica del compuesto activo en el tratamiento intraarticular de osteoartritis (OA). Este documento informa sobre la preparación de nano partículas de PLGA encapsulando moléculas bioactivas para liberación sostenida e inyección intraarticular (IA). Varios glucocorticoides y formulaciones de ácido hialurónico (HA), que están actualmente disponibles en el mercado para el tratamiento de IA, proporcionan alivio del dolor a corto plazo. Las drogas orales disponibles para el tratamiento sintomático también tienen deficiencias, en particular los efectos secundarios. Por lo tanto, para lograr la exposición a largo plazo de la droga, se presentan formulaciones tales como las suspensiones y los hidrogeles y también nuevos enfoques como las formulaciones basadas en nano o micropartículas. Este documento informa que numerosas publicaciones describen el uso de nano o micropartículas hechas de polímeros biodegradables como unos medios para controlar la liberación de los compuestos activos después de la inyección IA. Agrega que la albúmina y el PLGA (poli(ácido láctico-co-glicólico)) han sido usados preferiblemente, para este propósito, como polímeros biocompatibles y biodegradables. Por ejemplo las investigaciones de Ratcliffe et. al. mostraron que las micropartículas de tamaño inferior a 6 µm son tomadas por los macrófagos sinoviales. Después de la inyección IA de radio-micropartículas de albúmina marcada mostraron tiempos de residencia de varias semanas en la articulación (Págs. 237, 238, 241 y 242).

En consecuencia, la persona normalmente conocedora de la materia, encapsularía el compuesto activo que se da a conocer en el documento D1 en micropartículas o nanopartículas del copolímero biodegradable de ácido láctico-ácido glicólico (tal como PLGA, según enseña el documento D2), logrando de esta forma una composición de liberación lenta que alcance una alta concentración en el área de la inyección, mientras que la concentración sanguínea es baja, y sea útil para tratar inflamación y dolor de las articulaciones (como artritis reumatoide, osteoartritis y gota). Por lo cual la reivindicación 1 de la solicitud se considera obvia.

Dado que las reivindicaciones dependientes 2 a 10 no presentan alguna característica adicional que conceda nivel inventivo al objeto de la reivindicación independiente, se considera que tampoco tienen nivel inventivo.

7. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO2005061465	1 – 10	Nivel Inventivo
D2	Advanced Drug Delivery Reviews	1 – 10	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir del día siguiente de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante de sesenta (60) días para dar respuesta a este requerimiento y presentarla por escrito.

Finalmente, se le recuerda al solicitante que si como respuesta a este requerimiento llegara a modificar el capítulo reivindicatorio y éste contenga más de diez (10) reivindicaciones, no pagará la tasa de modificación voluntaria pero sí la correspondiente al pago por reivindicación adicional.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha 2014-01-21

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Abstract

Osteoarthritis (OA) is a primarily non-inflammatory, degenerative joint disease characterized by progressive loss of articular cartilage, subchondral bone sclerosis, osteophyte formation, changes in the synovial membrane, and an increased volume of synovial fluid with reduced viscosity and hence changed lubrication properties. As OA is the most common type of arthritis and a leading cause of disability, there is a largely unmet medical need for disease-modifying and symptomatic treatment. Due to the localized nature of the disease, intraarticular (IA) drug injection is an attractive treatment approach for OA. The various glucocorticoid and hyaluronic acid (HA) formulations, which are currently available on the market for IA treatment, provide only short-term pain relief or/and often do not provide adequate pain relief. The available oral drugs for symptomatic treatment also have shortcomings, most notably side effects. Therefore, there is still a large unmet need for novel OA drugs, which provide effective long-term pain relief and/or have disease-modifying properties. To achieve long-term drug exposure, different established formulations such as suspensions and hydrogels, and also novel approaches such as lipid based formulations and nano- or microparticles are currently in development. The development of novel drugs in combination with new formulations for IA treatment of OA, represents a promising approach in this challenging area of research.

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Keywords: Osteoarthritis; Intraarticular; Sustained release; Hyaluronic acid; Glucocorticoid[☆] This review is part of the *Advanced Drug Delivery Reviews* theme issue on “Drug Delivery in Degenerative Joint Disease”, Vol. 58/2, 2006.

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1. Introduction

Osteoarthritis (OA) is the most common form of arthritis, with a prevalence after the age of 65 years of about 60% in men and 70% in women [1]. Current treatment options for OA are limited. They include symptomatic treatment with simple analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) or intra-articular (IA) injected glucocorticoids and hyaluronic acid (HA) preparations. Non-pharmacological measures range from physical exercise and weight loss to joint lavage, and eventually surgical joint replacement.

There are major unmet needs in OA treatment, for disease-modifying OA drugs (DMOADs), which are

not available yet, and also for efficacious pain treatments with long-lasting effects. Furthermore, there is a significant unmet need for OA treatments which do not have any major side effects, due to the chronic nature of the disease often requiring treatment of extended duration. The currently available systemic drugs for relief of OA pain, e.g., the non-selective NSAIDs and selective cyclooxygenase 2 (COX-2) inhibitors, are effective in the early-mid stages of OA, but often fail to provide adequate pain relief as the joint deteriorates. In addition, NSAIDs cause gastrointestinal complications in a significant number of patients, and the COX-2 inhibitors have recently raised concerns regarding cardiovascular side effects/risks, resulting in the with-

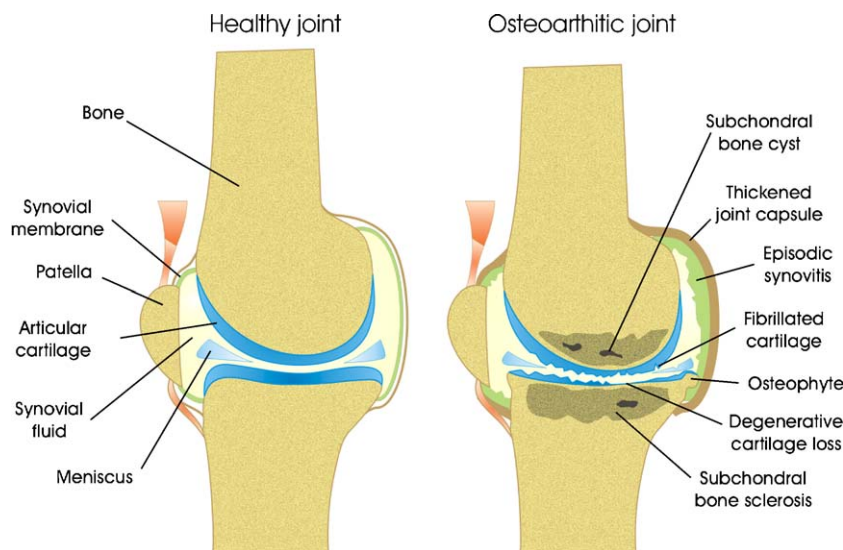


Fig. 1. Comparison of systematic cross sections of a healthy (left) and an OA joint (right).

drawal of the COX-2 inhibitors Vioxx® and Bextra® from the US market [2,3]. Unlike other joint diseases, OA is locally restricted to one or a few joints, which provides a unique opportunity for local IA treatment without the risk of systemic side effects. Here we describe the currently available IA treatment options for OA and suggest approaches for the development of future IA treatments for OA. A major improvement that should be targeted in future IA treatment is a longer duration of action, since it is desirable to limit the number of IA injections per year due to the discomfort/pain associated with administration, as well as the possible risk of infection. This highlights the need for IA drug delivery formulations which provide sustained release of the drug from a depot over a period of several weeks. In this article we review the currently available formulations for IA drug delivery and present new evolving technologies to obtain sustained release formulation for IA drug treatment.

2. Anatomy and physiology of the joint and characteristics of osteoarthritis (OA)

2.1. Anatomy and physiology of joints

Joints can be considered as organs with the primary role of providing stability and mobility to the skeleton.

They are complex structures and their components are evolutionary adaptations to the different mechanical and biological conditions under which they function in the body. Joints can be classified based on the amount of motion they allow into synarthroses, amphiarthroses and diarthroses, with diarthrodial or synovial joints being freely movable and including most of the joints of the extremities [4].

Synovial joints are most frequently affected by OA. They are held together by a fibrous capsule and accessory ligaments. The inner surface of the capsule is lined by the synovium. The articular surfaces are covered by hyaline cartilage, and contact is facilitated by synovial fluid (SF) acting as a lubricant [4]. The structure of synovial joints is exemplified by the knee joint (Fig. 1).

2.1.1. Synovium

The synovium consists of two layers, the inner layer or intima, and a deep layer or subintima. Within the intima are the synovial lining cells of type A or B. Type A synoviocytes, which comprise approximately one third of the synovial membrane cells, are macrophages which process and clear debris within the membrane. Type B synoviocytes are the most prevalent cell. They closely resemble fibroblasts and synthesize hyaluronic acid (HA), a very long glycosaminoglycan. The subintimal layer is composed of

adipose, fibrous, or areolar tissue. The extracellular matrix (ECM) of the synovium consists of large numbers of collagen bundles. Collagens types VI, III, I and V, hyaluronan, fibronectin and the proteoglycans decorin and biglycan have been identified in the synovium [4,5].

The synovium has several functions, which are critical to normal joint homeostasis: while its ECM provides hydraulic resistance, it also allows an ultrafiltrate of plasma to pass across its capillary walls, through the ECM, and into the joint cavity. The ultrafiltrate and HA synthesized by type B synovio-cytes form the SF, which is essential for the preservation of the low coefficient of friction between the surfaces of articular cartilage and provides the nutrients

necessary for chondrocyte metabolism. This function of the SF is very important since the cartilage has no blood supply of its own [5]. The synovium contains the key components of the joint's immune system providing cell-mediated and humoral immunity, and an intricate system of capillaries and lymphatics within the synovium clears the joint of unwanted particles. Finally, the synovium has an extensive neural network with two different neural systems, one somatic and the other autonomic, which provide nociceptive feedback and control synovial blood flow [4].

2.1.2. Synovial fluid

SF is a clear, viscous liquid in diarthrodial joints. The composition of SF (Table 1) is almost identical to

Table 1

Composition of human synovial fluid in normal and OA conditions and human plasma composition for comparison [4,8,54–57]

Parameter	Synovial fluid		Plasma
	Normal	Osteoarthritic	Normal
<i>Physical parameters</i>			
Volume (ml/knee for SF or ml/kg body weight for plasma)	0.5–2.0	>3.5	39–44
Viscosity (mPa s)	>300 (thixotropic fluid)	<300	1.4
Osmolarity (mOsm/l)	~296	Unchanged	~290
pH	7.4	Unchanged	7.4
<i>Cellular components</i>			
Erythrocytes (cells $\times 10^9$ /l)	<2	n.d.a. ^a	4900 ^b
Leukocytes (cells $\times 10^9$ /l)	<0.2	<3	7.0 ^b
Monocytes/macrophages (% of leukocytes)	~60	n.d.a. ^a	6.1 ^b
Lymphocytes (% of leukocytes)	~30	n.d.a. ^a	35 ^b
Neutrophils (% of leukocytes)	~10 (<25)	<25	52 ^b
<i>Biochemical parameters</i>			
Total protein (g/100ml)	1.0–3.0	1.5–3.5	6.5–8.0
Albumin (g/100ml)	0.8–1.3	Unchanged	3.5–4.5
Immunoglobulin (percent of plasma concentration)	~50	Unchanged	100
α_2 -Macroglobuline (mg/100ml)	31	n.d.a. ^a	270
Hyaluronic acid (g/100ml)	0.35	<0.22	4.2×10^{-6}
Lubricin (g/100ml)	0.005	n.d.a. ^a	n.d.a. ^a
Glucose (mg/100ml)	66	Unchanged	91
Urea (mg/100ml)	4.0	Unchanged	4.0
Lactate (mg/100ml)	9–16.2	<37.8	9–16
Calcium (mg/100ml)	4.8–9.6	Unchanged	10
Chloride (mM)	107.4	Unchanged	110
Sodium (mM)	145	Unchanged	142
Potassium (mM)	4.0	Unchanged	5
Iron (μ mol/kg)	5.19	n.d.a. ^a	n.d.a. ^a
Zinc (μ mol/kg)	2.69	Unchanged	n.d.a. ^a
Copper (μ mol/kg)	4.33	Unchanged	n.d.a. ^a

^a No data available.

^b In blood.

that of plasma with the exception of the large polymers like fibrinogen or larger globulins, which are reduced or not found at all in SF due to the sieving action of the synovial capillary walls. Small molecules (molecular weight <10,000 Da) are in equilibrium in plasma and SF, as are small solutes and electrolytes. The concentration of glucose in SF is lower than in plasma since it is utilized by the articular cartilage chondrocytes [5]. SF can be distinguished from plasma by the presence of HA (concentration 0.35 g/100 ml) and lubricin (concentration approximately 0.005 g/100 ml). These two molecules are the major determinants of SF viscosity and are of key importance for one of its main functions, which is to act as lubricant of the joint surfaces. HA is extremely viscous. SF forms a thin viscous film over the surface of the synovium and articular cartilage in the joint space and at low shear rates this provides an effective hydrodynamic lubricant. At high loads HA is not an effective lubricant. Here lubricin, which interacts with surface-active phospholipids (SAPLs), seems to have an important role [6,7]. Furthermore, HA in the SF also bonds the opposing surfaces of the joints to each other. This creates tensile strength with little or no shear strength and enables opposing surfaces to slide freely across each other but limits their distraction [8].

The volume of SF in normal human joints is quite small with approximately 0.5–2.0 ml [4,5]. SF undergoes continuous turnover by trans-synovial flow into synovial lymph vessels. As a result, water and protein in the SF are replaced within a period of 2 h or less. The turnover of HA is considerably slower with complete replacement of HA within about 38 h [5]. In inflamed joints, more SF is produced (up to 100 ml in joints of rheumatoid arthritis patients) with low viscosity due to a reduction in HA concentration and molecular weight [9]. Interestingly, the entry of proteins into SF can be up to three times the normal level in patients with rheumatoid arthritis (RA) and the clearance can be much greater. In OA patients such pronounced changes are usually not observed [8].

2.1.3. Cartilage

Hyaline cartilage is a unique biological material that forms the articular surface of the joints and is to a large extent responsible for the almost frictionless movement of the articulating surfaces on each other. Articular cartilage is highly molded to the bone ends

and its thickness normally ranges from 1 to 5 mm. It is composed of chondrocytes which are embedded in an extracellular matrix consisting of 80% water, a collagen type II network and proteoglycans [10]. The collagen network confers tensile strength to the cartilage, while strongly hydrophilic proteoglycans such as aggrecan absorb the water and thereby provide cartilage with the ability to resist compression and distribute load. Since articular cartilages are both avascular and alymphatic, nutrients from the SF must be able to diffuse through the dense cartilage matrix to reach the chondrocytes during repetitive loading of the joint [4].

A layer of calcified cartilage exists at the interface between articular cartilage and its underlying (subchondral) bone. Articular cartilage and calcified cartilage are separated from the bone by the so-called tidemark, which may act as a limit to calcification. Calcified cartilage consists of type II collagen fibrils, which are heavily encrusted with hydroxyapatite and contains chondrocytes which are metabolically inactive. The deep surface of the calcified cartilage merges with the endplate of the underlying bone [7].

In some joints, including the knee, an articular meniscus is also present in the joint cavity. The meniscus is a fibrocartilaginous, wedge-shaped structure that partially covers the articulating surfaces of the bone and absorbs shock by correcting the incongruence of the opposed surfaces [10].

2.1.4. Bone

Although, at the tissue level, the bone located in the subchondral plate and the cancellous bone that supports it are indistinguishable from bone in other sites, the organization of subchondral bone is specific. The subchondral bone plate is thinner than cortical bone in most sites and contains haversian systems which run in parallel to the joint rather than in parallel to the long axis of the bone. The major plates in the supporting cancellous bone are arranged at right angles to the predominating stresses. These unique structural features make the subchondral bone approximately 10 times more deformable than the cortical bone shaft [7].

2.2. The OA joint

OA is characterized by the loss of articular cartilage, which is probably initiated as a focal lesion

and may progressively enlarge to involve specific compartments, inducing alterations in articular surfaces by producing changes in loading. Cartilage degeneration is first observed at the articular surface in the form of fibrillation (Fig. 1). Fissures are initially more in parallel to the articular surface, later they penetrate the damaged cartilage, eventually reaching subchondral bone. Chondrocyte cloning is observed early, but is confined to more superficial sites. Progressive loss of articular cartilage thickness, starting at the surface, is then observed [11].

Earliest changes in the cartilage matrix composition feature proteoglycan loss as well as enhanced synthesis of proteoglycans. This is followed by a phase of increased matrix turnover, with net depletion of cartilage proteoglycans and collagens. Finally, severe damage to and loss of the collagen network are observed [12].

A multitude of cytokines, growth factors and proteases drive the cartilage breakdown. The matrix metalloproteinases (MMPs) play a principal role in the cleavage of cartilage macromolecules including type II collagen and the cartilage proteoglycan aggrecan. The degradation products of matrix molecules may themselves stimulate degradation, establishing a positive feedback loop. Cellular responses in this loop involve the production of cytokines such as IL-1, which is known to stimulate degradation and works in an autocrine and paracrine fashion. The synthetic processes observed throughout the development of OA are probably regulated by the growth factors IGF-1 and TGF β . Anti-inflammatory and modulatory cytokines also seem to contribute to cartilage anabolism [11]. The expression of type X collagen by hypertrophic chondrocytes and the mineralization which are observed in OA seem to recapitulate the processes which occur during endochondral ossification.

While OA is a relatively non-inflammatory condition compared to RA, there is evidence of a limited, non-erosive synovitis in OA joints (Fig. 1). This synovitis is characterized by hyperplasia and enlargement of synovial lining cells and by the presence of lymphocytes and mononuclear cells. The degree of synovitis may influence the development and progression of the pathologic changes [11].

In OA, bone remodeling and new bone formation are observed in two places, in the form of osteophytes at the margins of the articular cartilage and in the

subchondral bone, directly beneath the weight-bearing surface (Fig. 1). Osteophytes are protuberances into the joint space. They consist in large part of bone that merges imperceptibly with the other cortical and cancellous tissue of the subchondral bone. The osteophyte is capped by a layer of cartilage. In advanced lesions, the landmarks are obliterated because the osteophytic surface itself undergoes degeneration, and fibrous tissue may cover the marginal portions of the osteophyte [13]. The sclerosis of subchondral bone, which is associated with OA, represents an increase in bony structure through thickening of the subchondral plate, advancement of the tidemark, and thinning of the overlying articular cartilage. These changes are deleterious to the function of the joint and the health of the overlying cartilage [7].

In OA, blood vessels can penetrate the subchondral bone plate and the calcified cartilage. The calcified cartilage can then act as a source of endochondral calcification, remodeling the subchondral plate and creating a new tidemark. After substantial remodeling in OA the tidemark may be duplicated or even appear as multiple lines.

2.2.1. Characteristics and epidemiology of OA

OA usually has a slow and insidious onset. Clinically, OA manifests in the form of gradual development of joint pain, joint stiffness and crepitus with motion, joint effusions, and limitation of movement in the joints [14–16]. Risk factors for the development and progression of OA include local biomechanical factors like obesity, joint injury, joint deformity, and extensive sport participation, as well as systemic factors including age, gender, ethnic characteristics, bone density, and estrogen deficiency.

OA is the most common type of arthritis and a leading cause of disability in the USA, Europe and Japan. The estimated total prevalence of radiographic OA in these countries ranges from 36% to 48% of the population. The estimated number of total prevalent cases in the USA, Europe and Japan in 2002 of 300 million is expected to grow by 1.1–1.2% per year due to the growing proportion of older age groups and an increase in risk factors for OA, primarily obesity and an inactive life style [14].

It is the hallmark of OA that it affects only one single or a few joints. The joints most frequently affected by OA, based on radiographic evidence in

Caucasian populations, are the knees (33% prevalence) followed by the hands (29.5%), feet (20.8%) and the hips (4.7%) [17]. These prevalence estimates illustrate that OA most frequently affects joints which are easily accessible for IA injection, like the knee, hand and foot joints, and that a huge patient population is amenable to IA treatment.

3. Rationale for the intraarticular (IA) treatment of OA

OA, unlike many other diseases, is amenable to local IA treatment as well as systemic treatment. While most efforts so far have concentrated on the development of systemic treatments, such agents bear considerable risk of systemic adverse events as the cardiovascular events and gastrointestinal side effects observed for most NSAIDs and COX-2 inhibitors for the treatment of joint pain have demonstrated [2,3]. The chronic nature of the disease requires the development of drugs suitable for chronic systemic treatment with minimal side effects, which is a challenging goal. Local drug application, i.e., the injection of drugs directly into the affected joint, is an option for the treatment of OA which is already frequently used and has the potential to deliver the desired profile.

3.1. IA injection: general and technical considerations

A major fear in the use of IA injections is the risk of introducing infection. Careful sterile technique and avoidance of injection through inflamed skin are essential for avoiding joint infections. The use of fresh materials and disinfection of the site prior to injection help to further reduce the risk of infections [18]. The incidence of sepsis can be further reduced by the use of glucocorticoids or hyaluronic acid preparations packaged in sterile pre-filled syringes [19], so that critical handling steps for the preparation of the medication, like transfer of the formulation from a vial or an ampoule into a syringe, are not required.

Although IA injection is widely practiced, some recent studies have called into question the ability of physicians to accurately localize such injections, finding that almost a third of knee injections are

inaccurate [20]. This finding emphasizes the importance of proper needle placement. Attempts to improve accuracy using radiographic or ultrasound techniques have been studied but as yet have not been widely adopted for most peripheral joints (e.g., the knee, hand and shoulder). For deeper joints such as the hip, imaging is crucial and many techniques have been described [20].

Aspiration of SF at the time of injection is generally recommended for several reasons: it is associated with improved accuracy of injection, it prevents the tissue cylinder formed when the syringe penetrates the tissue from entering the joint space, and it allows the use of collected SF for diagnostic purposes. It has been observed that aspiration of SF at the time of injection in patients with joint effusions can lead to an increase in the magnitude of response. This effect might be due to the fact that aspiration diminishes the dilution factor of the injected treatment, thereby increasing the efficacy of the treatment, and/or that simple aspiration of SF in patients with effusion per se can lead to an improvement of pain [18,19].

Based on clinical studies in arthritis, a 24-h post-injection rest is recommended. Post-injection rest increases the residence time of the applied substance in the joint and increases the response to therapy [19].

3.2. Pros and cons of IA OA treatment

The local nature of OA makes IA drug injection an attractive treatment approach as the drug can be applied directly into the affected joint, minimizing systemic side effects. Furthermore, the joints which are frequently affected by OA, like the knee, hand and foot joints are well suited for IA injection. Interestingly, also a strong beneficial response of IA placebo injections, ranging from 36% to 86%, has been described [19].

Direct delivery of the drug to the affected joint also offers the possibility to achieve appropriate drug concentrations at the site of action by applying low amounts of drug. In addition, IA injection also makes it possible to develop drugs which have good efficacy, but low oral bioavailability, which is an issue for many of the novel drug candidates in development.

An obvious disadvantage of IA injections is the discomfort and pain they may cause and the possible

risk of infection. Therefore, the number of IA injections per year should be reduced to a minimum. This is a major challenge in IA drug delivery, considering that, based on the physiology of joints, residence times of IA injected drugs are very short due to rapid uptake of the drugs by the circulation. Drugs are cleared from SF by lymph drainage, which is largely dependent on the size of the molecule. The clearance of albumin from SF in knees of OA patients was about 0.04 ml/min, corresponding to a turnover of about 1 h. In other studies the residence time of NSAIDs in SF was shown to be as short as 1–5 h [21]. This emphasizes the need for the development of sustained release formulations, which support the continuous release of the drug from a depot in the joint space over a period of several weeks or months.

4. Current IA treatments for OA

When reviewing drug reference manuals like PDR (Physician's Desk Reference) in the US or the "Rote Liste" in Germany [22] one finds that mainly glucocorticoids and hyaluronic acid are available as IA injection formulations for the treatment of OA (Table 2).

4.1. Glucocorticoid injections

4.1.1. Efficacy

Glucocorticoid injections are widely used for symptomatic treatment of peripheral OA joints, especially the knee joint. From randomized controlled trials in OA patients there is evidence that IA steroids are effective, but their benefit over placebo may be

Table 2
Selection of IA injection formulations available in Germany [22]

Active ingredient	Available concentrations	Formulation
<i>Glucocorticoid solutions</i>		
Betamethasone hydrogenphosphate, disodium	5.3 mg/ml	1 or 5 ml solution in an ampoule
Dexamethasone hydrogenphosphate, disodium	4.37 or 5.26 mg/ml	1, 2, 5, or 10 ml solution in an ampoule
Prednisolon hydrogenphosphate, disodium	33.6 mg/ml	1 ml solution in an ampoule
<i>Glucocorticoid suspensions</i>		
Betamethasone dihydrogenphosphate, disodium plus Betamethasone acetate	4 mg/ml plus 3 mg/ml	1 ml suspension in an ampoule
Betamethasone dihydrogenphosphate, disodium plus Betamethasone dipropionate	2.63 mg/ml plus 6.43 mg/ml	1 or 2 ml suspension in an ampoule or in a pre-filled syringe
Dexamethasone acetate plus Lidocain-HCl	5 or 10 mg/ml plus 30 or 60 mg/ml	1 or 2 ml suspension in an ampoule
Prednisolon acetate	10, 25, or 50 mg/ml	1 ml suspension in an ampoule
Rimexolone	40 mg	Dry powder ^a in a vial
Triamcinolone acetonide	10 or 40 mg/ml	1 ml suspension in an ampoule
Triamcinolone diacetonide	25 or 40 mg/ml	1 ml suspension in an ampoule
Triamcinolone hexacetonide	5 or 10 mg/ml	0.5, 1, or 1.5 ml suspension in an ampoule
<i>Glucocorticoid emulsion</i>		
Dexamethasone-21-palmitate	4 mg/ml	1 ml emulsion in an ampoule
<i>Hyaluronic acid solutions</i>		
Hyaluronic acid, sodium salt (fermentative or from cockcombs)	5, 10, or 15 mg/ml	1, 2, or 2.5 ml solution in a pre-filled syringe
Cross-linked hyaluronic acid (hylan)	8 mg/ml	2 ml solution in a pre-filled syringe
<i>Homoeopathic solutions</i>		
Mixture of standardized regulation factors of animal origin, according to homoeopathic manufacturing procedures	See "Rote Liste"	2 ml solution in an ampoule

^a For preparation of a suspension by addition of water for injection.

relatively short-lived, lasting from 1 to 4 weeks [19]. The evidence of efficacy has been graded as 1B (best evidence being 1A, worst 4) by a task force for the EULAR Standing Committee for Clinical Trials [23]. The American College of Rheumatology (ACR) Subcommittee on OA recommends glucocorticoid injections as an effective short-term method of decreasing pain and increasing quadriceps strength.

4.1.2. Overview of glucocorticoid preparations for IA treatment

There is a broad range of glucocorticoid formulations available for IA injection (Table 2). They are either solution or suspension formulations with a typical injection volume of 1 or 2 ml. The suspensions consist of crystals with particle sizes typically below 10 μm . To enhance the convenience and safety of the application, especially with respect to aseptic handling, several of these formulations are available in ready-to-use pre-filled syringes.

Whether a glucocorticoid is available as a solution or suspension formulation basically depends on the aqueous solubility of the compound. IA solution formulations are available for the comparatively well soluble glucocorticoids, e.g., betamethasone dihydrogenphosphate. Besides the active ingredient, these solutions contain isotonicizing agents, such as sodium chloride, mannitol, or sorbitol, and water for injection as solvent. Some of these solutions additionally contain pH modifiers, such as sodium hydroxide, sodium hydrogenphosphate, hydrochloric acid, or citric acid; surfactants, such as polysorbate 80; sodium edetate as stabilizer (synergistic anti-oxidative agent); propylene glycol or polyethylene glycol as cosolvent; and/or antimicrobial agents, like benzyl alcohol, methyl- and propyl-4-hydroxybenzoate, or cetylpyridinium chloride.

In contrast, glucocorticoids with poor aqueous solubility, like triamcinolone acetonide and rimexolone, are available as suspension formulations. Besides the excipients mentioned above, the suspension formulations additionally contain stabilizers, such as carmellose sodium, hypromellose or gelatine, to avoid or reduce the sedimentation of the suspension as far as possible, and to allow for a fast and reliable re-dispersion of the suspension prior to application. It is essential that the crystals in the suspension formulations maintain their particle size. An uncon-

trolled growth of crystals bears the risk of poor biocompatibility of the suspension formulation upon IA injection.

In some cases and probably due to stability reasons, the formulations are available as a dry powder which has to be re-dispersed by addition of the dispersing medium (e.g., water for injection). For all suspension formulations, it is essential that they are re-dispersed directly before the application, and that the resulting suspension appears homogenous.

In case of Lipotalon[®]—a liposome formulation—the active ingredient is a modified dexamethasone: dexamethasone-21-palmitate. Due to the covalent addition of the fatty acid chain, the solubility of the dexamethasone derivative is reduced, thereby enabling the inclusion of the compound into a liposome formulation from which it is slowly released following IA injection. The liposome formulation contains soy bean oil as lipid phase, egg yolk phospholipids, and glycerol and water in the aqueous phase. Due to the sensitive balance of the liposomal formulation, a mixture with other drug products, which is occasionally described for other products, is not recommended [24].

4.1.3. Pharmacokinetics of IA glucocorticoids

Fast clearance of dissolved injected steroids from the SF has been long recognized. Occasional side effects of IA corticoid injections, e.g., facial flushing, temporarily disturbance of diabetes, arterial hypertension and immunosuppression, have been observed and were attributed to the systemic availability of the corticoids following IA injection [20].

The pharmacokinetics of glucocorticoid formulations following IA injection were investigated by Derendorf et al. [25,26]. The studies demonstrated that the residence time of poorly soluble glucocorticoids applied as suspension formulations (e.g., rimexolone, triamcinolone acetonide) in the knee joint is longer than for the soluble glucocorticoids applied as solution formulations (e.g., betamethasone hydrogenphosphate, disodium) [25,26]. This is due to the fact that the dissolved molecules rapidly undergo clearance from the knee joint, while the solid particles of suspension formulations need to dissolve prior to being cleared from the joint. Thus, the residence time of an IA injected compound in the knee joint mainly depends on its solubility and dissolution rate.

The duration of action of glucocorticoids is prolonged relative to their short residence time in SF, which is probably due to their mechanism of action: IA injected glucocorticoids in solution can pass the cell membrane directly and bind to their receptors in the cytoplasm. The hormone-receptor complex then migrates to the nucleus, where it regulates the transcription of pro-inflammatory and pain mediators [27] and thus exhibits its effects beyond the half-life of the compound alone.

4.1.4. Side effects

Side effects of steroid injections are infrequent. The incidence of infection is low and is clearly less with the use of glucocorticoid packaged in pre-filled syringes. The incidence of post-injection flares, which begin 6–12 h after injection and resolve spontaneously in 1 to 3 days, is unclear. The underlying mechanism may be a mild synovitis due to a reaction to the crystalline steroid suspensions.

Early studies reported the possibility of marked destructive cartilage changes resulting from excessive IA use of steroids. In 1995, ACR guidelines recommended that injection of corticosteroids in a given knee joint not be performed more than three or four times in a given year. However, based on recent studies this risk of cartilage degradation seems minimal [19].

Recent findings suggest that chondrolysis occurs during OA flares, defined by episodes of exacerbation of pain with synovial effusion. Since IA glucocorticoids may be particularly indicated and efficient in the treatment of inflammatory flares and to reduce joint effusion, it is now recommended that steroids be used for the short-term treatment of disease flares, i.e., exacerbation of pain accompanied by effusion [19].

4.2. Hyaluronic acid (HA) injections

4.2.1. Possible mechanisms of action of HA in OA

Hyaluronic acid (HA) is a high molecular weight polysaccharide of *N*-acetyl glucosamine and glucuronic acid building blocks. It is produced by synovio-cytes, fibroblasts and chondrocytes, and represents a main constituent of SF and hyaline cartilage. In articular cartilage, HA provides a backbone for the attachment of aggrecan side chains by link proteins. This HA–aggrecan complex interacts with water and

type II collagen fibers to form the extracellular matrix of articular cartilage.

Native HA has a molecular weight of 4–10 million Da and forms an extensive network at concentrations over 0.3 mg/ml in aqueous solutions [9,28–30]. In joint fluid, the high concentration of HA (approximately 0.35 g/100 ml) (Table 1) is responsible for the viscoelastic properties of SF.

The viscoelasticity of HA is crucial for the maintenance of joint homeostasis. Since HA behaves as a viscous liquid at low shear rates and as an elastic solid at high shear rates, SF acts as a viscous lubricant during low impact movements of the joint and as an elastic shock absorber during high impact movement. HA also has barrier and exclusion effects that limit the movement of cells and large molecules through normal SF [9]. In joints affected by OA, the molecular weight and concentration of HA are diminished. This low HA concentration may be attributed both to reduced synthesis of HA and also increased volume of SF. This adversely affects the ability of SF to lubricate and protect articular tissues, and to absorb joint loads, which contributes to further progression of OA [9].

The concept of viscosupplementation suggests that IA injection of HA could help restore the viscoelasticity of the SF, but HA has also been demonstrated to have a multiplicity of biological actions on cells in vitro. For example, it inhibits prostaglandin E_2 synthesis induced by interleukin (IL)-1 in human OA synovial cells, and influences leukocyte adherence, proliferation, migration and phagocytosis (reviewed by Brandt et al. [30]). These anti-inflammatory effects of HA can be expected to have an indirect anti-nociceptive effect. Besides HA seems to have direct anti-nociceptive effects. For example there is evidence for inhibition of PGE_2 and bradykinin synthesis in joint tissues by HA, entrapment of endogenous pain substances by HA and decreased activation of joint pain fibers secondary to coating of their receptor endings with viscous HA (reviewed by Marshall [9]).

Chondroprotective effects of HA were observed in vitro, e.g., that it stimulates production of tissue inhibitors of matrix metalloproteinases (TIMP-1) by chondrocytes, inhibits neutrophil-mediated cartilage degradation and attenuates IL-1 induced matrix degeneration and chondrocyte cytotoxicity [9]. In several studies HA enhanced PG synthesis and decreased PG breakdown and release from cartilage

matrix [31]. Furthermore, it was shown to normalize endogenous HA synthesis by synoviocytes [32].

4.2.2. Overview of HA products for IA injection

Several HA preparations are currently available. They are hydrogel formulations of HA in water for injection and may contain additional excipients, such as sodium chloride for isotonicization and sodium hydrogenphosphate for pH adjustment.

Most of these formulations contain HA of a comparatively low molecular weight (0.5–1.5 million Da), while one formulation (Synvisc®) contains cross-linked HA (hylan) with 6–7 million Da molecular weight, the latter being close to the molecular weight of native HA.

So far, differences in half-life of low molecular weight HA and hylan were demonstrated only in animal studies. Rabbit studies demonstrated that the injected hylan is cleared from the joint by 28 days after the last injection [9].

The low molecular weight HA can be obtained from fermentation (e.g., *Streptococcus equi*) or by isolation, e.g., from cockcombs.

In contrast to the IA application of glucocorticoid formulations, the dosing regimen of HA formulations is different for different preparations. For the cross-linked HA preparation (Synvisc®) up to 3 injections in weekly intervals are recommended. A repetition of this treatment cycle is not recommended earlier than 4 weeks after the last injection and with not more than 6 injections per 6 months [22]. For low molecular weight HA preparations, up to 5 injections in weekly intervals are recommended [22].

4.2.3. Evidence for symptomatic and disease-modifying efficacy of HA injections

A large number of clinical trials have been conducted with different HA preparations over the past 25 years. The majority of these studies have provided evidence that the HA preparations are more effective than placebo in reducing pain associated with OA. A recently published meta-analysis of 20 blinded, placebo-controlled randomized studies confirms the symptomatic efficacy and showed that older patients (>65 years) and patients with endstage disease are less likely to benefit from IA HA injections [33].

HA acts as a slow acting symptomatic drug with a delayed onset of efficacy at 2 to 5 weeks after injection

and a long-lived benefit on pain, which may persist until 6 to 12 months. Depending on the HA preparation, a course of 3 to 5 weekly injections is recommended. A new treatment cycle is usually proposed when symptoms reappear [19].

For the high molecular weight hylan (Synvisc®) compared to the lower weight HA preparations, superior viscoelastic properties and prolonged half-life in the joint space have been postulated [28,34]. Some evidence from pre-clinical and clinical studies suggests that the greater the viscoelasticity of the HA preparation, the greater the effectiveness of the treatment [35]. However, the available clinical study results do not prove a significant superiority in efficacy for hylan [33].

When comparing hylan with various steroids, Ayral [19] found 3 randomized controlled trials reporting similar benefits of HA and steroids at 1 month, but with superiority of HA thereafter. Therefore, Ayral recommends that fast-acting but short-lived steroids and the delayed but long-acting HAs should be considered as complementary therapies.

Three randomized controlled trials comparing HAs with NSAIDs found that the benefit obtained with HA was similar to that of NSAIDs for pain, and with fewer gastrointestinal side effects [19].

There has been much debate whether HA also has structure-modifying effects. Recently Goldberg and Buckwalter [36] reviewed the available evidence. While effects of HA on cultured cells suggest that HA promotes joint repair and inhibits destruction (see 4.2.1), studies in OA animal models evaluating potential structure-modifying effects in the OA joint produced conflicting results [30,36]. Studies in dogs and rabbits which had undergone anterior cruciate ligament transection (ACLT) or partial meniscectomy suggested that HA injections reduced gross cartilage damage and abnormalities in cartilage biochemistry, or even produced pronounced tissue repair. In contrast, injection of HA into sheep joints subjected to meniscectomy resulted in significantly more extensive osteophytosis and cartilage fibrillation and in reduction in proteoglycan synthesis. A striking reduction in proteoglycan concentration in cartilage was also observed in dogs with ACLT which were prophylactically treated with a series of HA injections. These findings raised concerns that HA treatment could accelerate joint damage in OA.

Recently, results have become available from a number of clinical studies suggesting a possible structure-modifying effect of HA in human OA as reviewed by Ayral [19] and Goldberg and Buckwalter [36]. Arthroscopy, microarthroscopic assessment and/or histological analysis of biopsy samples in four studies showed that HA injections reduced the deterioration in structural parameters or improved the grading and/or extension of the cartilage lesions. In one study the HA group also scored higher for quality of life and reduced NSAID use during the study period [37]. In a 1-year study, HA injection reduced the need for IA glucocorticoid injections [38]. However, these preliminary studies require further larger prospective placebo-controlled, double-blind trials to confirm the hypothesis that HA could be a structure-modifying agent [19].

IA injection of HAs is one of the best tolerated treatments for OA of the knee. A comprehensive review of available data shows that the incidence of adverse events is low after local injections of HA. The only adverse effects of significance are transient local reactions in the injected joint, which are typically benign and short lived [35].

4.2.4. Other IA treatments, e.g., local anesthetics, NSAIDs and morphines

Local anesthetics, e.g., lidocaine, are used by some clinicians for IA injection either alone or in combination with glucocorticoids. Lidocaine can itself have some mild anti-inflammatory effect during its relatively short half-life of 1.5 h [18]. When mixing lidocaine with glucocorticoids, the prompt effect of the local anesthetic providing temporary relief of symptoms can help confirm proper placement of the injection and support that the site injected was the source of the pain. Relief is temporary and this is not recommended for sole therapy [18].

Jones and Doherty [20] have reviewed the results of studies with a variety of other agents which have been injected IA. For the NSAIDs phenylbutazone and tenoxicam some benefit was observed upon IA injection in studies with small groups of knee OA patients. However, IA indoprofen failed to demonstrate any additional benefit in hip joint distensions.

Interestingly IA morphine provided significantly more prolonged pain relief compared to intravenous morphine plus IA saline placebo in a small study with

knee OA patients and a parallel study comparing IA dexamethasone, IA morphine and saline placebo both the morphine and dexamethasone groups demonstrated similar reduction in pain over a period of 7 days [20]. Similarly, the 5-HT blocker tropisetron has demonstrated benefit in OA in a small pilot study. It remains to be seen whether IA injection of opiates or 5-HT blockers will become a more widespread therapy for OA pain.

Ogotein, a bovine Cu–Zn superoxide dismutase, has been subject to a number of clinical trials, which indicate that ogotein may be of symptomatic benefit in knee OA. Its mechanism of action in OA is unclear, but it is thought that the drug will inhibit phagocytic response to hydroxyapatite crystals as well as ameliorate the effect of hypoxic–reperfusion injury. Twelve fortnightly injections of ogotein in patients with knee OA were superior to placebo in decreasing pain and improving function, but the effects were slow in onset occurring only at 8–14 weeks [20].

5. Future of IA OA treatment

5.1. Current and future approaches for IA formulations

The formulations for IA application which are currently available (Table 2) mainly focus on glucocorticoids and hyaluronic acid products. Most of them are solution or suspension formulations. As discussed earlier, the release profile of the glucocorticoid formulations mainly depends on the physicochemical characteristics (solubility, particle size and associated dissolution rate) of the compound.

For new compounds, innovative formulations may be required to design the release profile of the compound in the joint according to the therapeutic needs. Typically, a sustained release of the compound from the formulation is preferable to allow for a prolonged presence of active ingredient in the joint—ideally over several weeks or months—and thus, a reduction of injection frequency.

5.1.1. Requirements for IA formulations

Formulations for IA application have to comply with most of the requirements that also apply to other injection formulations, i.e., they need to be sterile and

compatible with the physiological conditions at the application site (e.g., knee joint, SF).

The sterility of solution formulations can be achieved by autoclaving (if all components of the formulation are sufficiently resistant to thermal stress) or sterile filtration, while for other formulations, the manufacturing processes required for ensuring a sterile product may be more complex. For example, sterile filtration is not feasible for formulations containing particles (suspensions), semi-solid or solid formulations.

For compatibility of the formulation with the physiological conditions at the site of injection, the characteristics of the SF (Table 1) have to be taken into consideration. Therefore, most of the available formulations are isotonic. The pH of the available formulations is either close to the pH of SF (i.e., pH 7.4) or slightly lower, but not below pH ~5.5, to allow for optimum stability of the active ingredient, while minimizing possible side effects of non-physiological pH values such as activation of proteolytic enzymes, e.g., cathepsins. The excipients used for IA injection are also present in other injection formulations, e.g., for intramuscular or subcutaneous application. The use of excipients which have not yet been used in commercial IA products needs to be assessed very thoroughly.

5.1.2. Liposomes

The only liposomal formulation available for IA injection so far is Lipotalon® (manufactured by Merckle, Germany), containing dexamethasone-21-palmitate as active ingredient.

The description of increased anti-inflammatory activity and prolonged duration of action of cortisol palmitate dates back to an article by Dingle et al. from the 1970s [39]. They showed an improved residence time of the palmitic acid-derivative of cortisol in the liposomes as compared to free cortisol. López-García and colleagues tested a liposomal formulation of triamcinolone acetonide-palmitate in a rabbit model. Also in this case, the increased activity as compared to free triamcinolone acetonide was attributed to a prolonged residence in the joint following injection of the liposome formulation [40]. Investigations with radioactive-labeled methotrexate indicated that the liposomes accumulate in the synovial membrane and slowly release the active compound [41]. Another

advantage attributed to liposomal application of glucocorticoids is a reduced incidence of inflammatory reactions which are occasionally reported for crystalline suspension formulations of glucocorticoids [42].

The feasibility and the potential benefits of liposomal formulations for IA application of a new compound need to be evaluated on a case-by-case basis.

5.1.3. Hydrogels

The HA preparations which are currently available can be classified as hydrogels. They are colloidal dispersions of macromolecular HA in water or aqueous solutions containing further dissolved ingredients such as sodium chloride. The formation of a hydrogel structure by HA increases the viscosity of these preparations as compared to aqueous solutions of small molecules, such as the glucocorticoids. They need to be injected slowly and carefully with a needle of sufficient diameter to avoid any additional stress to the joint. The higher viscosity of the HA formulations is another reason for their availability in pre-filled syringes: it avoids the need for further handling steps prior to application.

Besides the HA formulations, so far no hydrogels are in use as carriers for IA drug delivery.

5.1.4. Micro- and nanoparticles

Numerous publications describe the use of micro- or nanoparticles made of biodegradable polymers as a means for controlled release of compounds following IA injection [43–51]. Albumin and poly(lactic-co-glycolic acid) (PLGA) have preferably been used as biocompatible and biodegradable polymers for this purpose. While a range of polymer-based controlled release products are available for subcutaneous injection of different active ingredients, no such system has been launched so far for IA application.

Besides the need to design a biocompatible system, the release profile of the encapsulated compound needs to be reproducible and independent of the force load of the joint.

According to investigations by Ratcliffe et al., microparticles of a size below 6 µm are taken up by synovial macrophages. Following IA injection, radioactive-labeled albumin microparticles showed a residence times of several weeks in the joint [45].

However, the release of lipophilic low molecular weight compounds (e.g., prednisolone, triamcinolone) was also demonstrated from larger albumin microparticles ($\sim 23\mu\text{m}$) [50].

The use of PLGA microparticles for the release of diclofenac sodium enabled a release over several days, but with no positive effect in a rabbit arthritis model [47]. In contrast, the efficacy of IA PLGA nanoparticles (300–490 nm) loaded with betamethasone phosphate for about 6 weeks was shown in another study [43]. In this study, also the uptake of the nanoparticles by synovial macrophages was demonstrated. A further study with fluorescence-labeled PLGA micro- and nanoparticles demonstrated that microparticles ($\sim 30\mu\text{m}$) were not taken up by phagocytosis in contrast to the nanoparticles [44].

For the release of macromolecular and well soluble compounds, microparticles produced by complex coacervation of gelatine and chondroitine sulfate were used. The manufacturing procedure required neither the use of organic solvents nor increased temperatures. Compared to the typical manufacturing procedures for PLGA micro- and nanoparticles, this may be beneficial especially for peptide and protein drugs [48].

Further polymer-based explorative approaches for cartilage therapy and related strategies for controlled release of compound comprise the use of polymer microparticles and hydrogels based on various materials, such as collagen, fibrin, chitosan and hyaluronan [49].

5.2. Candidate drugs and drug targets for symptomatic and disease-modifying IA treatment

There is still a large unmet medical need for novel drugs for IA injection, which provide efficient long-term pain relief. Candidates for future IA symptomatic treatments are for example oral drugs with proven analgesic effects, which could be formulated to achieve sustained release into the joint. Furthermore, some of the analgesics with novel mechanisms of action which are currently in development, are ideal candidates for IA treatment, because they are not orally bioavailable or have severe side effects when applied systemically.

One example is the development of capsaicin in a special formulation for IA injection (www.algorx.com). Capsaicin, the active ingredient in hot chilli peppers, activates neurons which transmit pain signals

to the brain. At high concentrations capsaicin causes a temporary degradation of pain-sensing endings and thereby prevents neurons from transmitting pain, which is expected to cause long-lasting pain relief. Injection of capsaicin directly into the limited joint space is expected to yield high local concentrations of capsaicin at the site of action and low systemic distribution. Phase II clinical trials with IA capsaicin for the treatment of knee OA are currently ongoing.

Another example is the decapeptide Icatibant (HOE140), a specific and potent bradykinin B2 receptor antagonist, which is not suitable for oral treatment due to its peptidic nature. In a first proof-of-mechanism study in patients with knee OA a single IA injection of HOE140 provided greater pain relief than placebo and was well tolerated. A Phase IIa trial for symptomatic effects in OA is currently ongoing [52].

Despite a large medical need, no disease-modifying OA drug (DMOAD) is currently available. IA application will enable the development of novel disease-modifying small chemical molecules and biologicals, which would not be tolerated when applied systemically or would be much less effective.

An example is the IA injection of the protein drug anakinra in a recently conducted small safety study in patients with painful knee OA [53]. Anakinra is a recombinant form of IL-1 receptor antagonist (IL-1Ra) and acts as a competitive antagonist of IL-1, which is a key mediator of cartilage degrading processes and induction of pain in OA. Previously, anakinra had provided significant symptomatic improvement and slowed the radiographic progression in clinical trials with rheumatoid arthritis patients upon daily subcutaneous administration. The safety study in knee OA patients showed that anakinra is well tolerated in patients with painful knee OA. Long-term benefit on pain in the responders may suggest a therapeutic effect, but remains speculative since there was no control arm in this study. A long-term randomized placebo-controlled study will be required to determine the efficacy of IA anakinra for pain relief and improvement of joint structure, which was not assessed in this study.

Due to the short half-life of most IA injected molecules in SF and the discomfort and risk of infection associated with IA injections, novel IA treatments for OA can only be developed in conjunction with appropriate sustained release formulations.

6. Conclusions

In joints affected by OA many physiologic parameters are changed. This leads to chronic degeneration of the joint and the development of pain, the symptom which is most disabling for the patient. The currently available IA treatments for OA provide pain relief to some extent and there are indications of additional structural benefits from IA application of HA hydrogel preparations. However, there remains a large unmet need for a disease-modifying treatment as well as for more effective long-term pain relief.

Currently, different compounds and biologics, which could provide better pain relief or even a disease-modifying effect are in development. Longer lasting release of compounds is a challenge for IA formulation development. Different approaches e.g., hydrogels, nano- or microparticles and liposomes, to obtain a sustained release product are under investigation. These sustained release formulations may be beneficial both for newly developed OA drugs and for already available treatments by increasing the duration of drug release to the joint space and consequently reducing the required injection frequency. The development of novel drugs in combination with new sustained release formulations is a promising approach to obtain efficacious treatments for OA.

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