What Should We Consider for Choosing Cross-linked HLA ?

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전 진 만

Contents

Contents

Pharmacologic Algorithms for Knee OA

2019 ESCEO		2019 OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL
• SYSADOAs • Paracetamol • Topical NSAIDs	**First line Treatments**	• Topical NSAIDs
• Non selective NSAID (± PPI) • COX-2 Inhibitor • IA corticosteroids • **IA hyaluronic acid**	**Stage 2 Treatments**	• Non selective NSAIDs (± PPI) • COX-2 Inhibitor • IA corticosteroids
• Short-term, weak opioids • Duloxetine	**Stage 3 Treatments**	• **IA hyaluronic acid**

ESCEO, European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis; OARSI, Osteoarthritis Research Society International; SYSADOA, symptomatic slow acting drugs of OA; NSAID, non-steroidal anti-Inflammatory drug; PPI, proton-pump inhibitors; COX-2, cyclooxygenase-2; IA, intra-articular

Arden NK et al., Nat Rev Rheumatol. 2021 Jan;17(1):59-66.

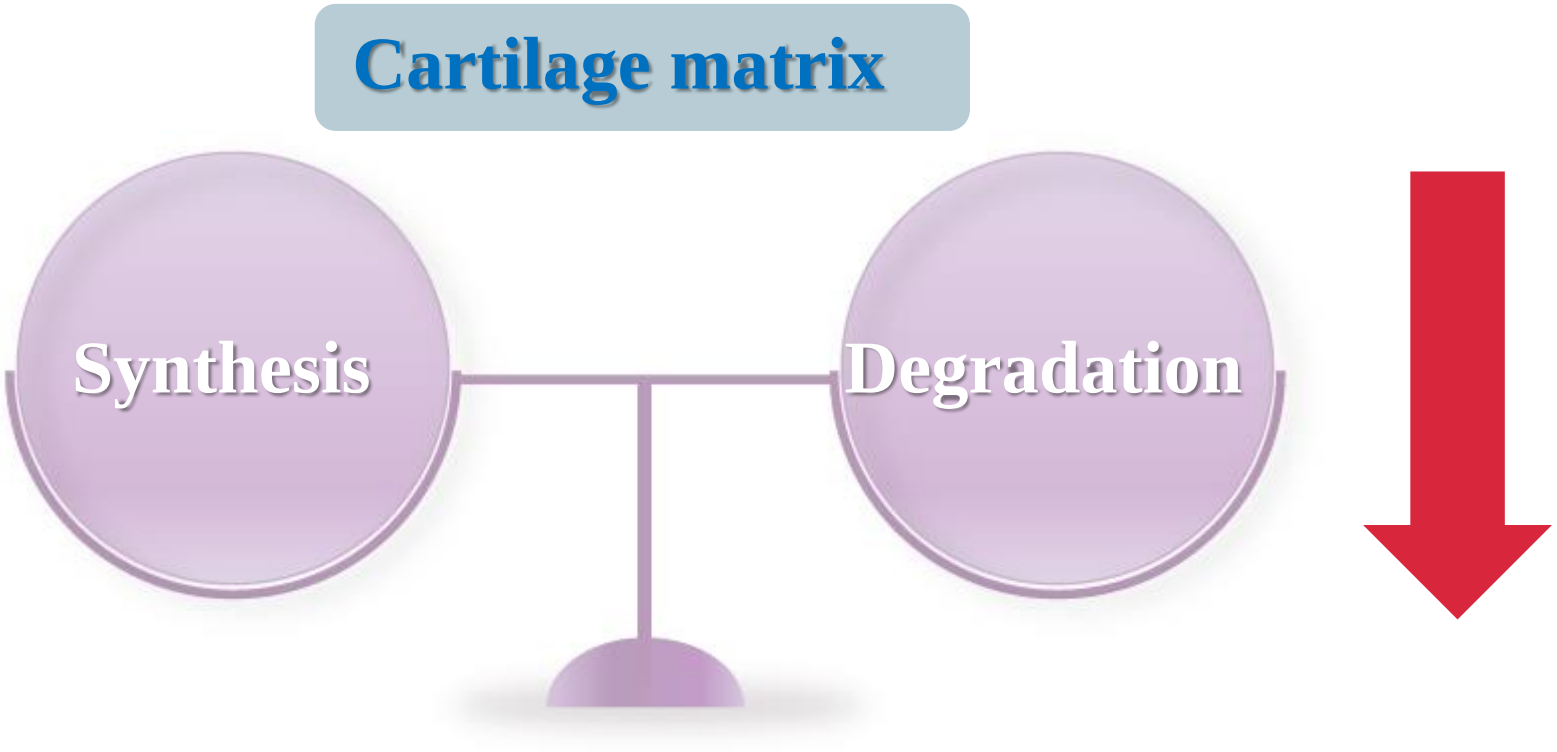
Changes for IAHA Recommendation in OARSI

Patients	Recommendation of IA hyaluronic acid	
	2014	2019
Knee OA *without* comorbidities	**Uncertain**	**Conditional Recommend (Level 2 (low))**
Knee OA *with* comorbidities (GI, CV, frailty)		**Conditional Recommend (Level 1B (high))**

OARSI, Osteoarthritis Research Society International; SYSADOA, symptomatic slow acting drugs of OA;
GI, gastrointestinal; CV, cardiovascular

McAlindon TE et al., Osteoarthritis Cartilage. 2014 Mar;22(3):363-88; Bannuru RR et al., Osteoarthritis Cartilage. 2019 Nov;27(11):1578-1589

Knee osteoarthritis

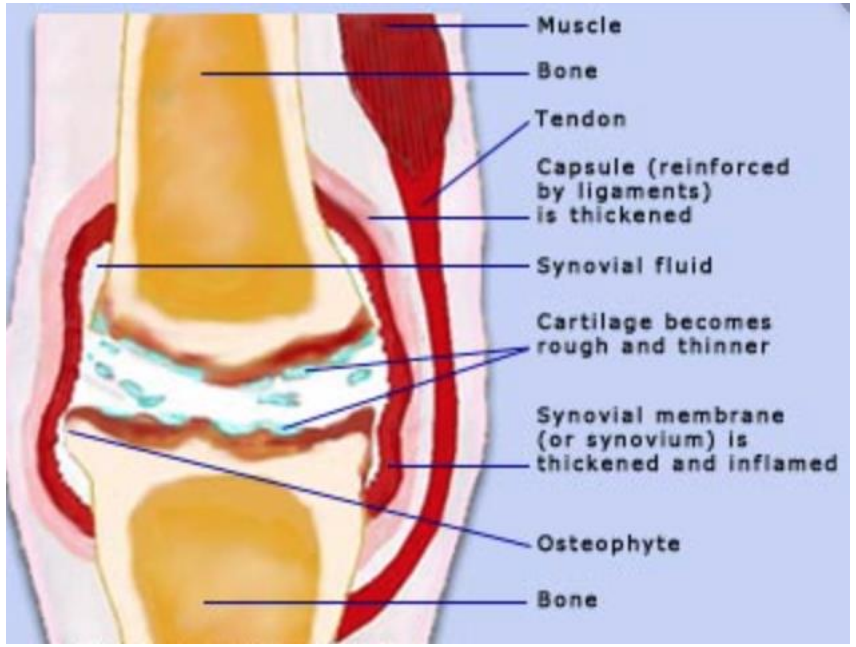


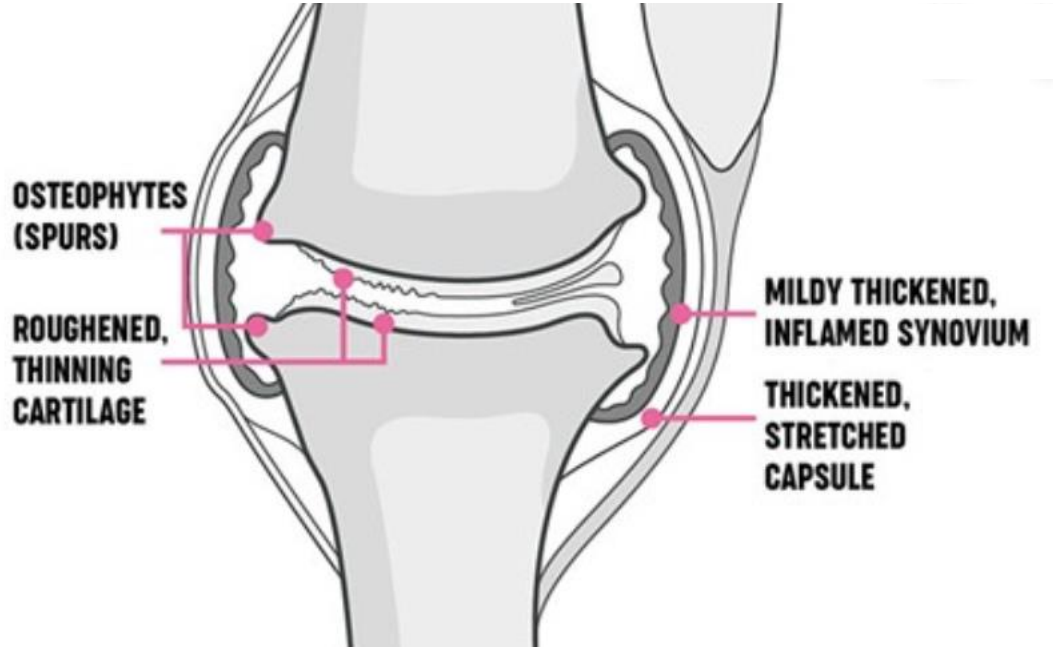
Loss of articular cartilage

Knee osteoarthritis

Loss of articular cartilage

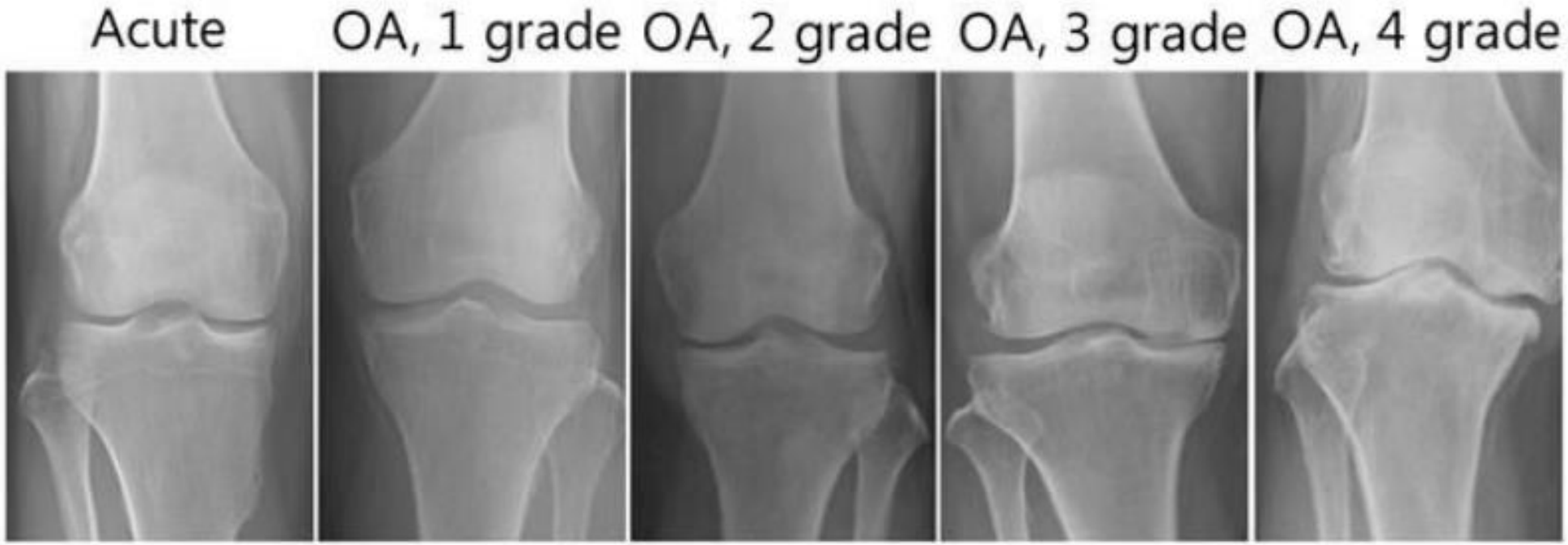
Subchondral bone remodeling
Osteophyte formation
Inflammation of synovial membrane





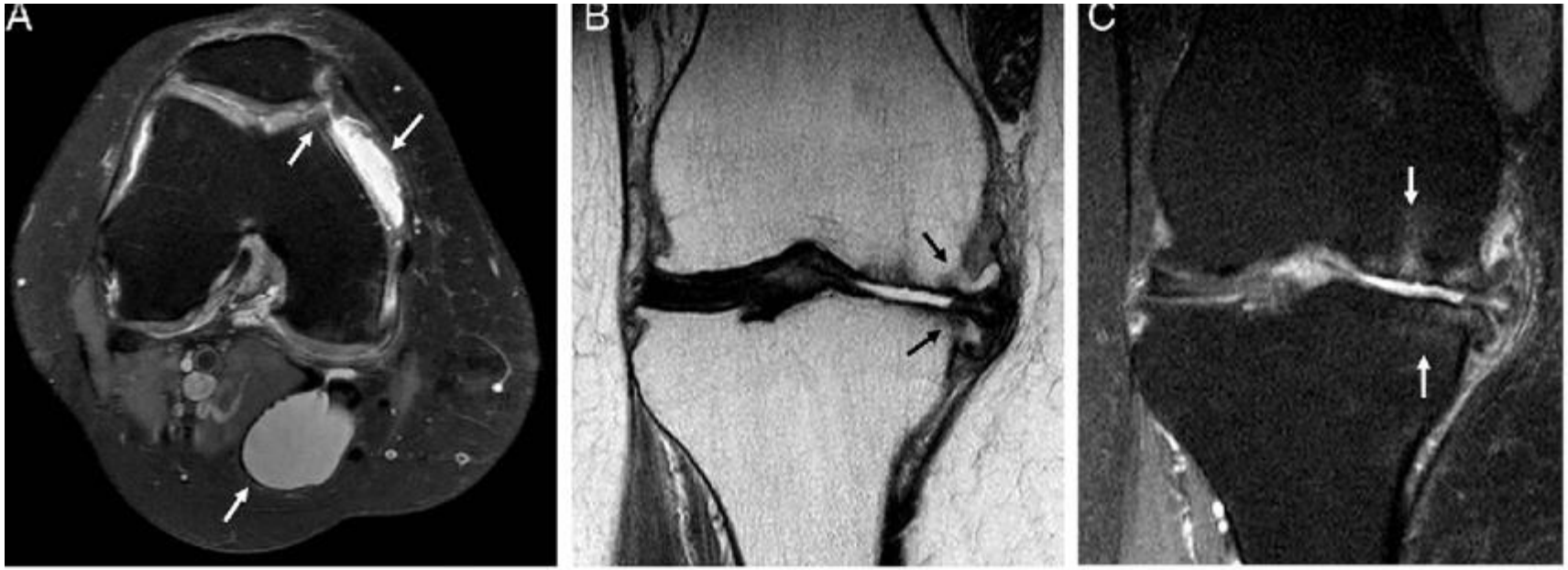
Knee osteoarthritis

Loss of articular cartilage

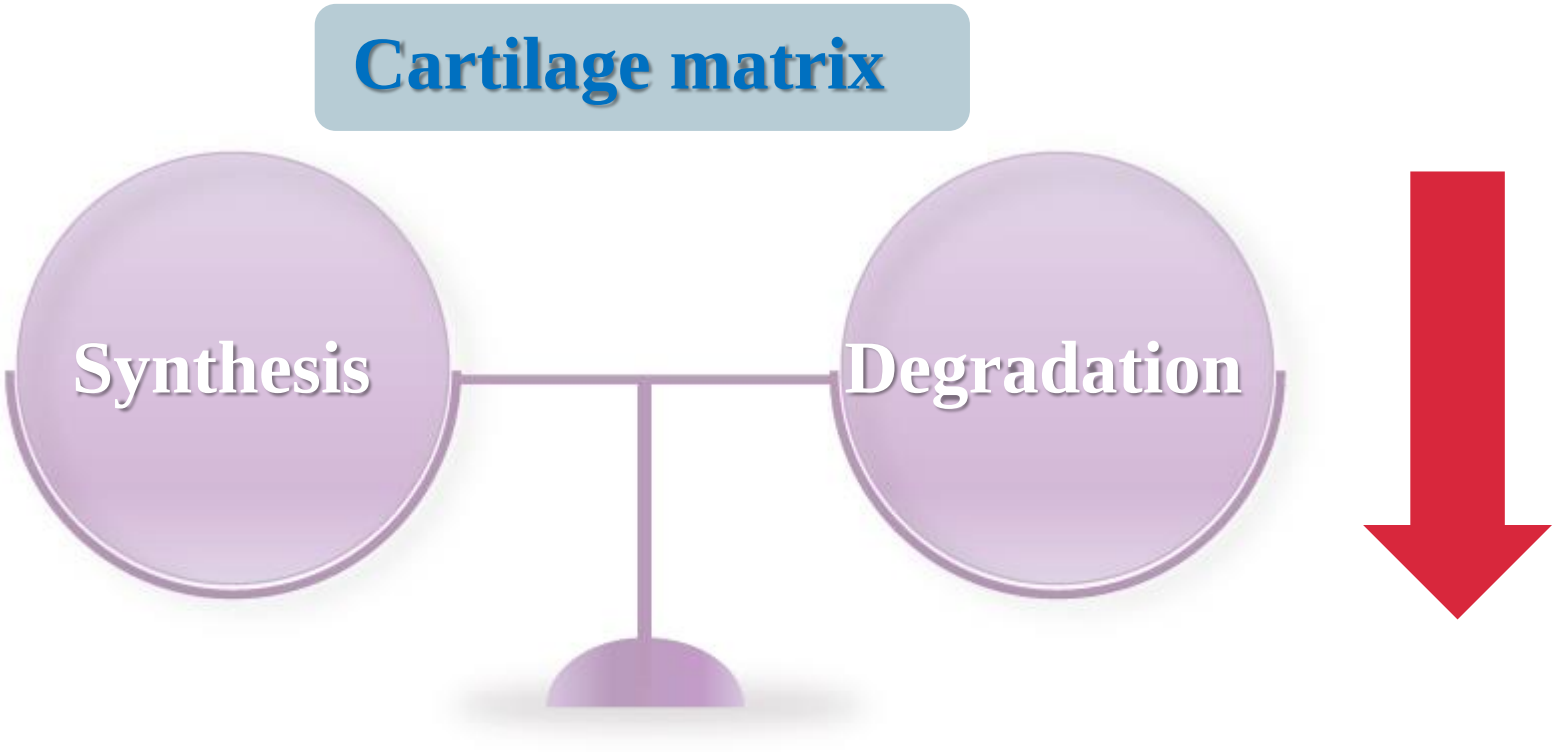


Knee osteoarthritis

Loss of articular cartilage

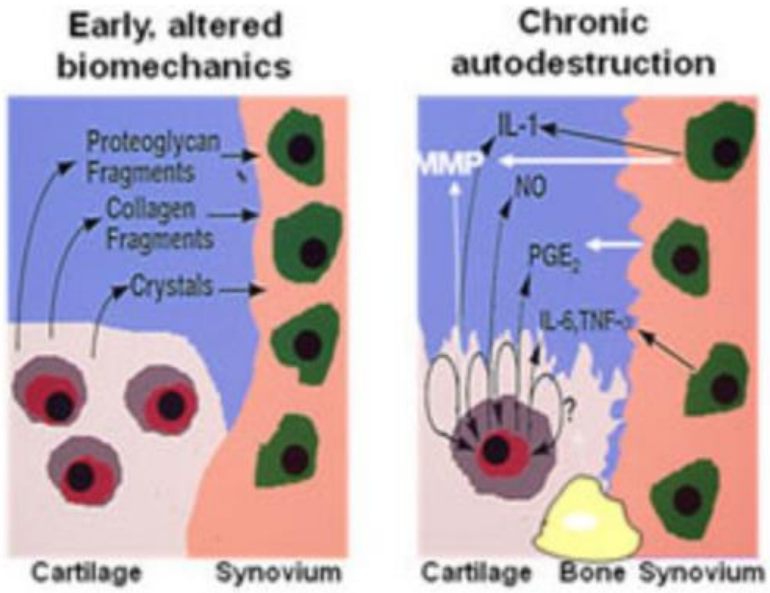


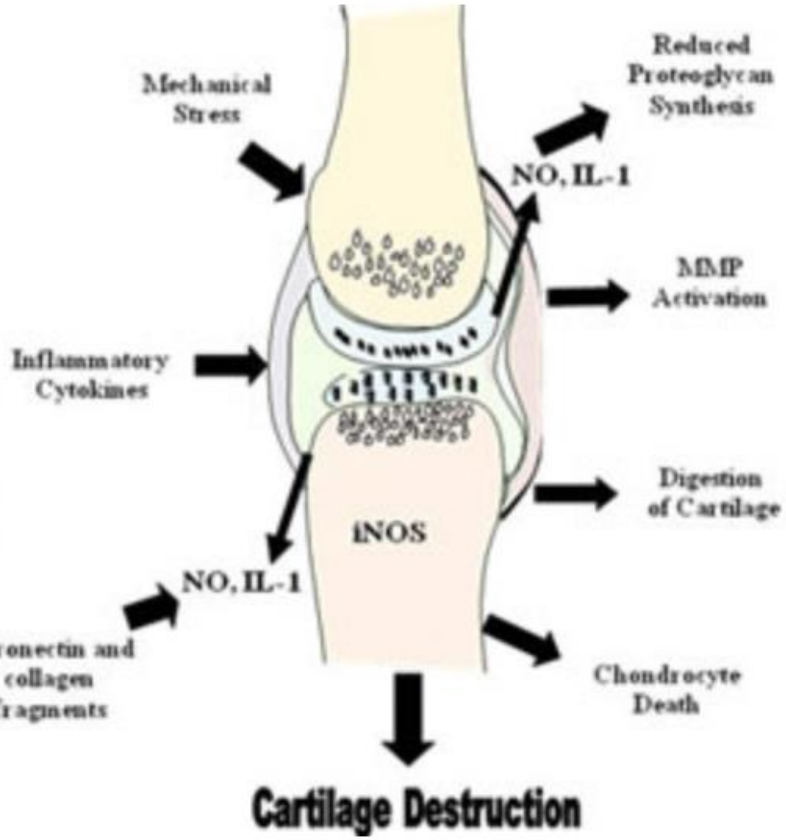
Knee osteoarthritis

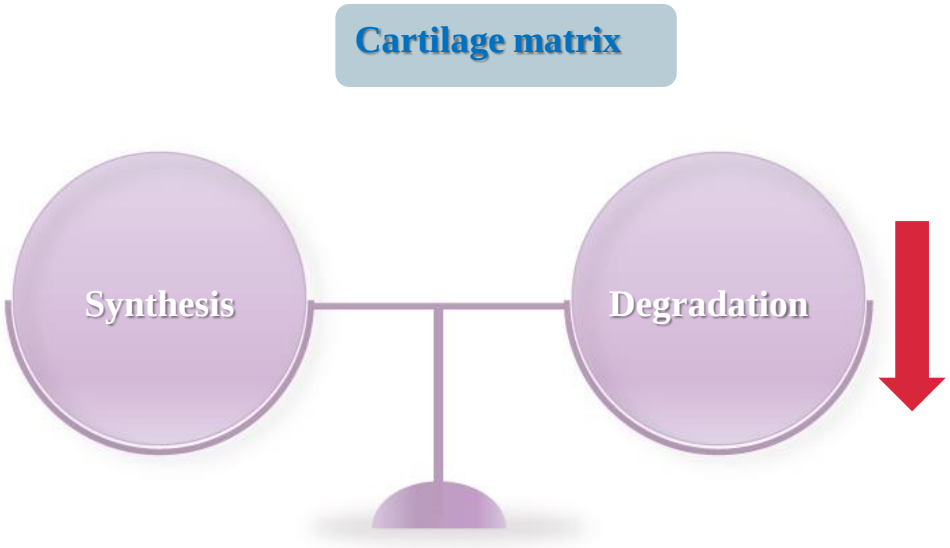


Loss of articular cartilage

Knee osteoarthritis







Loss of articular cartilage

Knee osteoarthritis

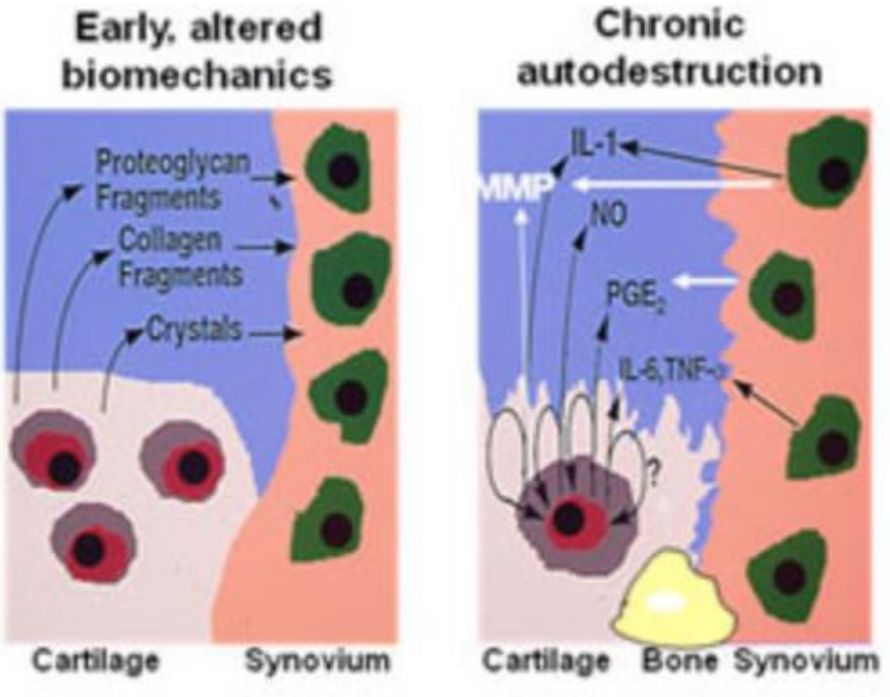
Extracellular matrix of articular cartilage

Water

+

Collagenous framework

: GAG, PG, HA

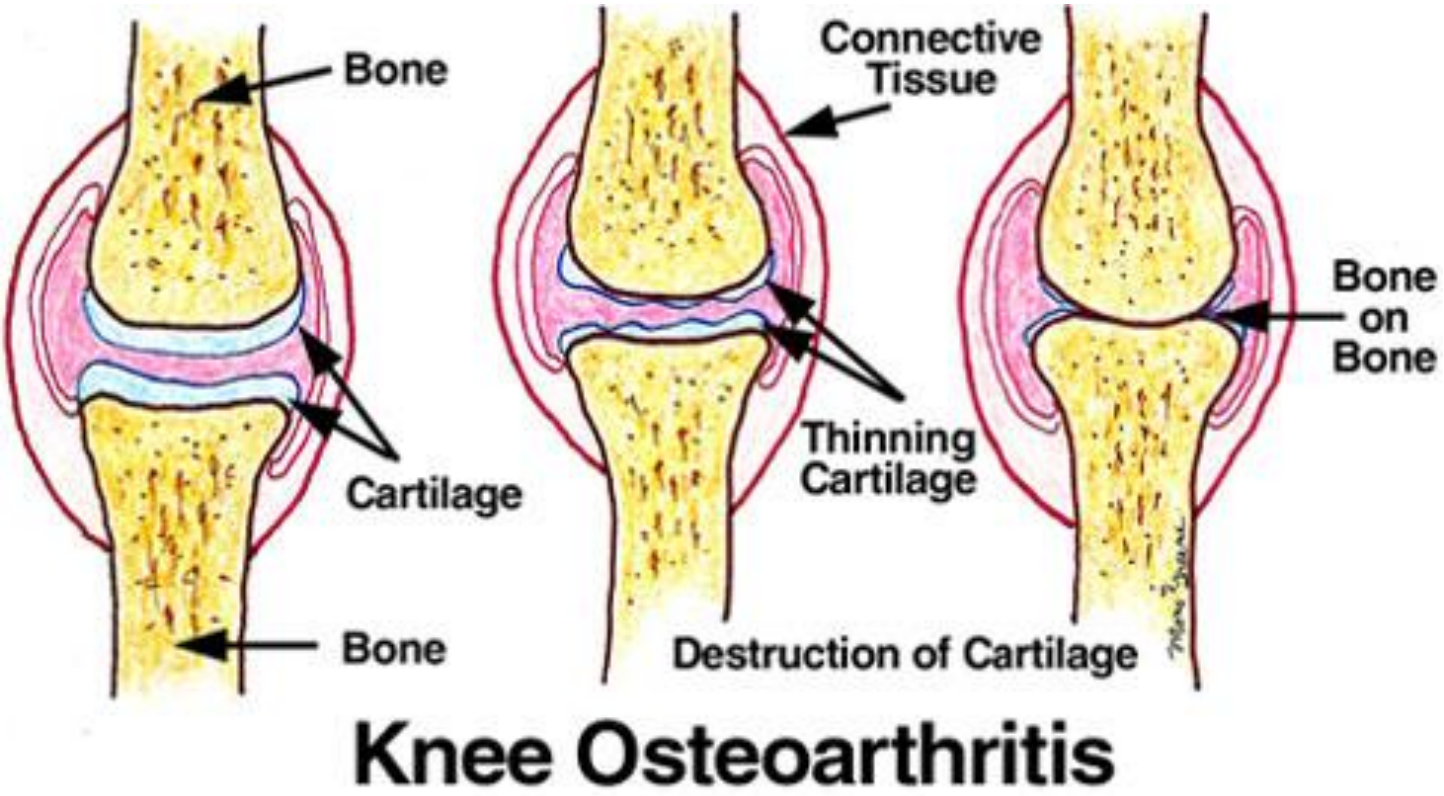


Aggrecan binds HA and provides compressibility and elasticity to cartilage

First pathological changes in knee OA is degradation of aggrecan by aggrecanases

→ Cartilage erosion

Knee osteoarthritis



Joint fluid

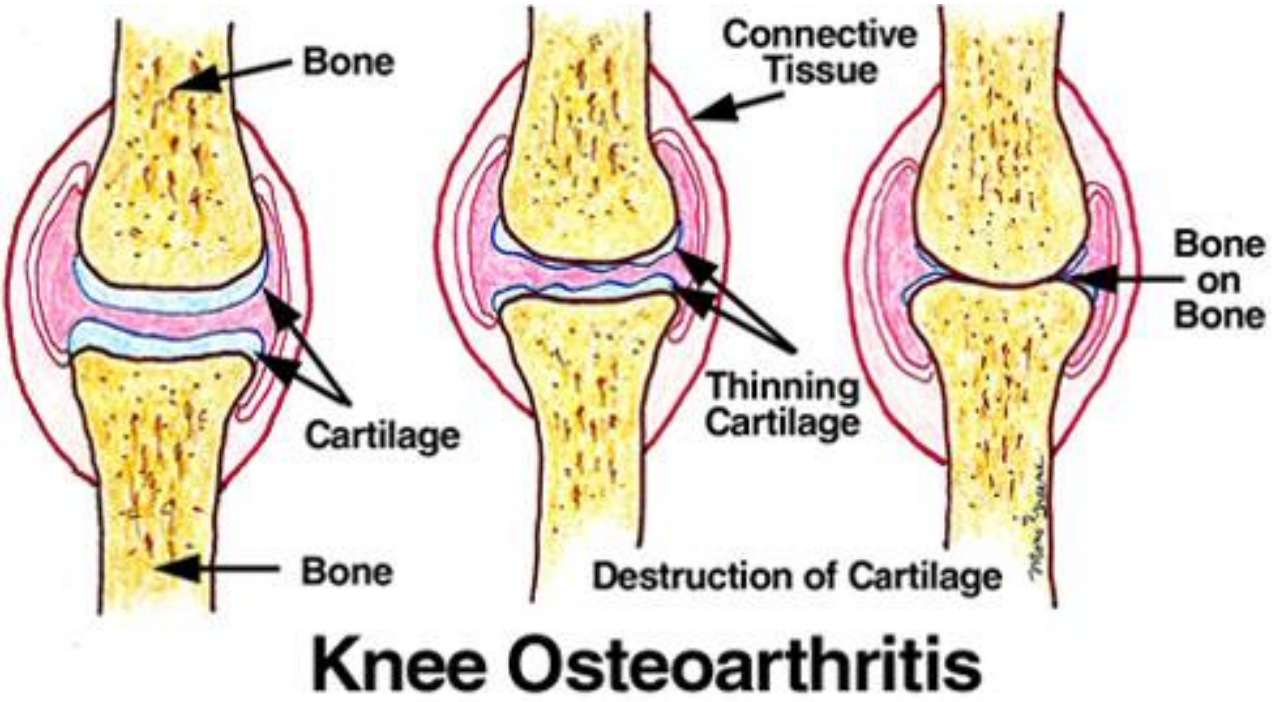
Lubricant and shock absorber
Protecting articular cartilage and joint structures
Supplies oxygen and nutrients
Removes carbon dioxide and metabolic wastes

HA molecules

Filter by restricting entrance of large plasma proteins
Facilitating passage of nutrition
Anti-inflammatory effects, inhibits phagocytosis and leukocyte adherence, reduces inflammatory mediators, and reduces release of arachidonic acid from synovial fibroblasts

Molecular weight & Concentration

Knee osteoarthritis



↑ Joint fluid

↓ Concentration of HA molecules

Disrupts stability of cartilage matrix
Reduces homeostatic and chondroprotective effects
Reduces viscoelasticity

Increasing susceptibility of joint to damage by biomechanical forces

Low MW HA

Accelerates progression of OA joint damage

Exogenous HA administration

- In 1934, first GAG from vitreous humor of bovine eye and named it “hyaluronic acid” by Karl Meyer and John Palmer
- “Hyaluronan” was introduced in 1986 to conform to polysaccharide nomenclature
- 1st therapeutic injections of HA in animal Track horses for Traumatic arthritis
- In humans, since 1970s for treating joint pain and other health conditions

Exogenous HA administration

Oral bioavailability 5%

Intra-articular injection

- Direct augmentation of synovial fluid elasticity and viscosity (?)
- Injected HA is short (< 48 hours) for most viscosupplements

High molecular HA injection

- Clinical benefits of pain and mobility are long lasting
- (clinical studies show effects lasting up to a year after a single injection)
- HA concentration 6 months postinjection with significantly increased viscoelasticity

Exogenous HA administration

Table 1 Biological effects of HA

Effects on extracellular matrix	Effects on immune cells	Effects on inflammatory mediators

• Enhanced HA synthesis
• Enhanced synthesis of PG and chondroitin sulfate
• Suppressed PG release from extracellular matrix
• Prevents PG breakdown from cartilage
• Reduced markers of cartilage breakdown (chondroitin 4- and 6-sulfates)
	• Inhibits proliferation and activation
	• Reduced motility of lymphocytes and macrophages
	• Inhibits phagocytosis
	• Suppresses aggregation of neutrophils
	• Inhibits adhesion and neutrophil-associated cartilage destruction
		• Reduced levels of
		  ○ Prostaglandins
		  ○ Leukotrienes
		• Increased production of cAMP
		• Reduced expression/activity of
		  ○ IL-1, IL-6
		  ○ Stromelysin
		  ○ TNF-α
		  ○ TIMP-1 (inhibits MMP)
		  ○ Plasminogen activator
		• Reduced arachidonic acid release
		• Antioxidant effects
		• Reduced production of NO

Note: Data from Moreland,[1] Abate and Salini,[6] and Kusayama et al.[9]

Abbreviations: HA, hyaluronic acid; PG, proteoglycans; cAMP, cyclic adenosine monophosphate; IL-1, interleukin-1; IL-6, interleukin-6; TNF-α, tumor necrosis factor α; TIMP-1, tissue inhibitor of metalloproteinases-1; MMP, metalloproteinase; NO, nitric oxide.

Exogenous HA administration

HA injection

Structural and mechanical roles

Signaling molecule

Interacts with receptors on surfaces of a range of different cells

Promotion of endogenous HA production

Suppresses cartilage damage by reducing activity of fibronectin fragments & reduces production and activity of various inflammatory mediators

Antioxidant effects in menisci and synovium

High MW HA

Decreased ongoing nerve activity and movement-evoked nociception

Clinical effectiveness of viscosupplementation

Intra-articular HA

At least as effective or more effective than oral NSAIDs, COX-2 inhibitors, paracetamol or IA corticosteroids **improving pain and function**

Greater effect on **stiffness**

However, expert consensus is that because viscosupplements **differ widely** in terms of origin, MW, molecular structure, method of cross-linking, rheological behavior, and formulation, it may not necessarily be appropriate to extrapolate clinical results from one to another

Bannuru RR. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteo- arthritis – meta-analysis. *Osteoarthritis Cartilage*. 2011;19(6):611–619.
Bannuru RR. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Ann Intern Med*. 2015;162(1):46–54.

Contents

Hyaluronic acid

1990년대 주 1회 * 5주 히알루론산 관절염 치료제

히알루론산 L사, 하이히알플러스 H사

2005년 주 1회 * 3주 투여 치료제

히루안플러스 L사, 하이히알 H사

하이알포르테 S사, 히야론퍼스트 D사

2014년 주 1회 투여 치료제 출시

시노비안 L사

출처 : 메디소비자뉴스

Sodium hyalunonate 25mg/2.5ml

성분 및 함량	Sod. hyaluronate 25mg/2.5ml Syringe

No Image

코드	IHYAL	상품명	Hya(하이알)		
분류	전문	의약품번호	399	제약회사	신풍

약효분류	Other Metabolic Agents
약리	관절연골 표면의 피복, 보호, 연골의 변형·변화의 억제, 병적 관절액 및 윤활기능의 개선.
효능	변형성 슬관절증, 견관절 주위염.
용법	1주 1회 1관을 5주 동안 슬관절강내 또는 견관절내(견관절강, 견봉하활액포 또는 상완 이두근 장두건 건초)에 투여.
부작용	동통, 부종, 안면발적, 종창, 구기, 구토, 발열, 쇽.
금기	혈관내 투여, 안과용 사용.
주의	① 이 약을 투여시 무균조작하 시행할 것. ② 증상의 개선이 없는 경우 5회 한도로 하여 투여를 중지할 것. ③ 냉장보관.
임부	안전성 미확립.
비고	

Sodium hyalunonate 20mg/2ml SR

성분 및 함량	Sod. hyaluronate 20mg/2ml SR

No Image

코드	IHYALB	상품명	Hyruan Plus(히루안플러스)		
분류	전문	의약품번호	399	제약회사	LG

약효분류	Other Metabolic Agents
약리	PGE2 억제를 통한 항염증작용, 진통작용, 연골보호효과, 내인성 hyaluronic acid 생성유도.
효능	슬관절의 골관절염, 견괄절 주위염 치료.
용법	1주 1회 1Syringe를 3주간 슬관절강 내 또는 견관절강내 투여.
부작용	흑, 부종, 안면발적, 동통, 종창, 구기, 구토, 발열.
금기	이 약에 과민증인 환자.
주의	① 간장애 또는 그 병력이 있는 환자, 투여관절부에 피부질환 또는 감염이 있는 환자. ② 증상이 없는 경우 3회 한도로 하여 투여를 중지한다. ③ 안과용, 혈관내로 투여하지 않는다. ④ 주사침은 22~23G정도를 사용한다.
임부	안전성 미확립.
비고	

Sodium hyalunonate (BDDE cross-linked) PFS

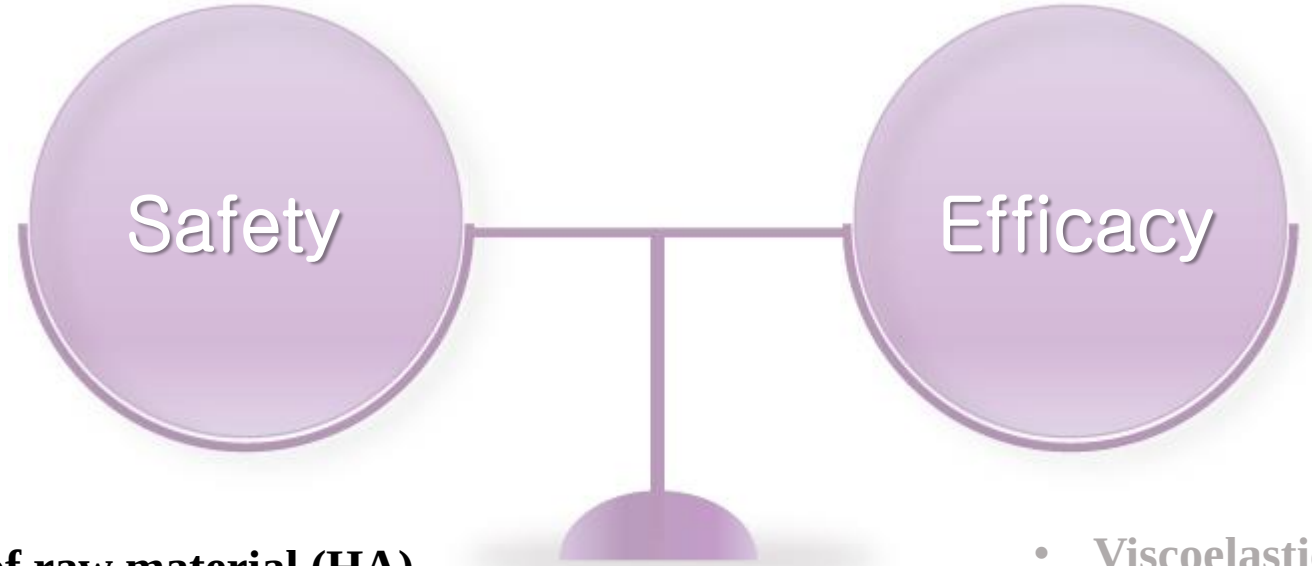
성분 및 함량	Sodium hyaluronate 60mg (BDDE cross-linked sodium hyaluronate gel 3g)/3ml PFS

크게보기

코드	IHYALC	상품명	Synovian(시노비안)		
분류	전문	의약품번호	399	제약회사	LG생명과학
색상		모양	원형	제형	정제

약효분류	Other Metabolic Agents
약리	관절강 내 투여된 히알루론산은 관절 내 활액을 보충하여 윤활 및 충격 완충작용을 하고 염증 관련 cytokine 생성과 chondrocyte apoptosis를 억제하여 연골의 염증과 파괴 및 통증을 억제하는 효과를 나타냄.
효능	슬관절의 골관절염.
용법	성인 : 1회 3ml, 슬관절강 내 투여, 증상에 따라 투여 간격(6개월 이상)을 고려하여 적절히 투여함.
부작용	통증, 홍반, 부종, 종창, 열감, 비인두염, 발열, 상기도 감염, 사지통증, 방광염, 소화불량, 감각이상, 근골격통, 족저근막염.
금기	이 약에 과민증 기왕력자, 투여 관절강에 감염이나 심한 염증이 있는 환자, 투여 부위 피부에 감염이나 피부질환이 있는 환자.
주의	① 타 약물 과민증 기왕력자, 간장애 환자. ② 혈관 내, 관절 외, 윤활조직에는 투여하지 말 것. ③ 살균소독제(벤잘코늄염화물 등 제4급 암모늄염, 클로르헥시딘)에 의해 침전을 일으킬 수 있음. ④ 재투여에 대한 안전성.유효성 미확립. ⑤ 차광 실온보관.
임부	안전성 미확립.
비고	BDDE : 1,4-Butanediol Diglycidyl Ether.

Ideal Viscosupplement



- **Purity of raw material (HA)**
- **Amount of cross-linking agent**

- **Viscoelasticity**
- **Duration**

Purity of Hyaluronic acid

Highly-purified HA의 필요성

- Low purity의 HA는 hypersensitivity 등의 부작용을 발생시킴
- Highly-purified HA를 사용해야 **adverse event를 감소**시킬 수 있음

	High protein included		Low protein included	
Adverse effect type	*Number of adverse events*	*Incidence[a] of adverse events (per 100 treated)*	*Number of adverse events*	*Indicidence[a] of adverse events (per 100 treated)*
Hypersensitivity	104	0.07	52	0.02
Injection site inflammation	68	0.05	49	0.02
Other	50	0.04	43	0.02
Total	222	0.15	144	0.06

[a]Assuming 144,000 patients treated in 1999 and 262,000 in 2000 (based on the number of syringes sold).

Friedman PM et al. Dermatol Surg. 2002 Jun;28(6):491-4.

Purity of Hyaluronic acid

- HA 원료 및 완제 생산

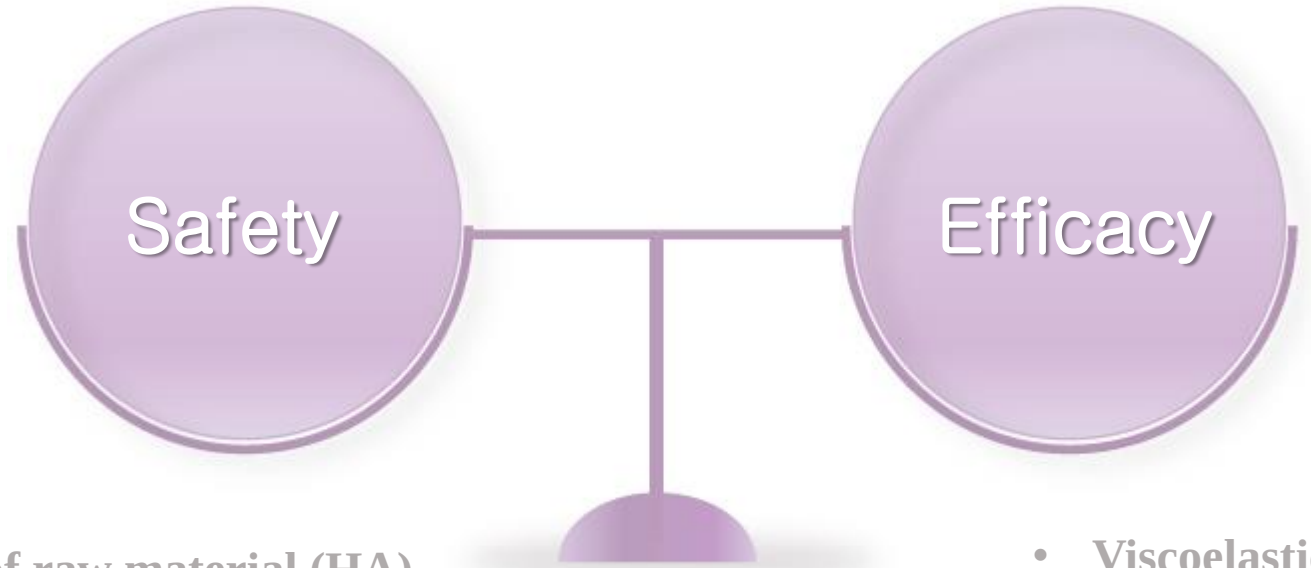
	원료 생산	완제 생산	허가 판매
LO화학	O	O	O
H사,S사	X	X	O

- HA품질 관리기준

	유럽약전기준	LO화학 HA 관리기준	LO화학 HA 분석결과
Sterility Test	N/A	Sterile	Sterile
Bacterial Endotoxins	≤ 0.5 EU/mg(parenteral)	≤ 0.05 EU/mg	0.01 EU/mg
Nucleic Acids	≤ 0.5	≤ 0.5	0.0
Protein	≤ 0.1% (Parenteral)	≤ 0.1%	0.0%

의약품통합정보시스템 (nedrug.mfds.go.kr), European Pharmacopoeia 9.0 3583-5
Data on file. LG Chem R&D center. Report for characterization of SYNOVIAN®. RCH-SA-002.

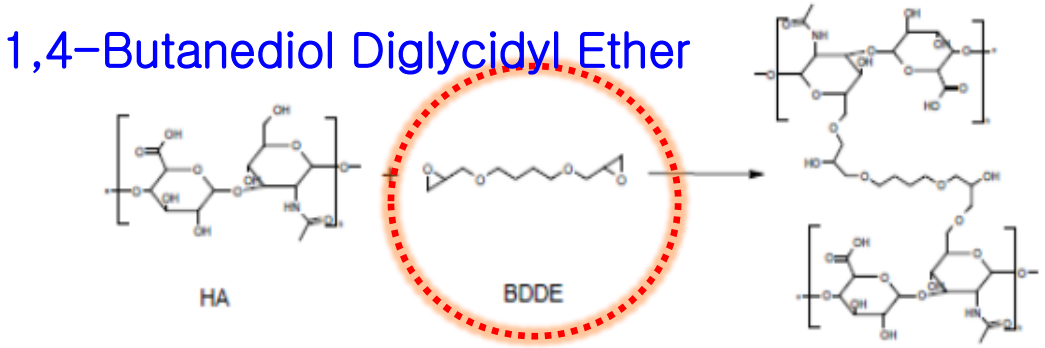
Ideal Viscosupplement



- Purity of raw material (HA)
- **Amount of cross-linking agent**

- Viscoelasticity
- Duration

Process of Cross-linking



Linear Hyaluronic acid

비가교 HA 관절주사제는 낮은 점탄성으로 지속시간 짧음

Crosslinked Hyaluronic acid

지속시간 증대를 위해 가교제 사용하여 겔형태로 제조

Cross-linking agent (BDDE)

BDDE (1,4-Butanediol Diglycidyl Ether)

- 약 15년 이상 HA 제제에 있어 가교결합제로 사용되어온 화학 성분
- 다양한 가교제중 안전성이 우수

Cross-linking agent	LD_{50} (Rat, PO)
BDDE	1,134 mg/kg
Glutaraldehyde	134 mg/kg
Formaldehyde	100 mg/kg
Divinylsulfone	32 mg/kg
Polyethylene oxide	22 mg/kg
DEO (Diepoxyoctane)	1.07 mL/kg

LD_{50} (lethal dose 50%): 실험동물에서 실험군의 50%를 사망에 이르게 하는 물질의 양

Chemical material safety data sheet (BDDE, Formaldehyde, Glutaraldehyde, Polyehylene oxide, Divinylsulfone)

Safety from Cross-linking Agent

가교제(BDDE)

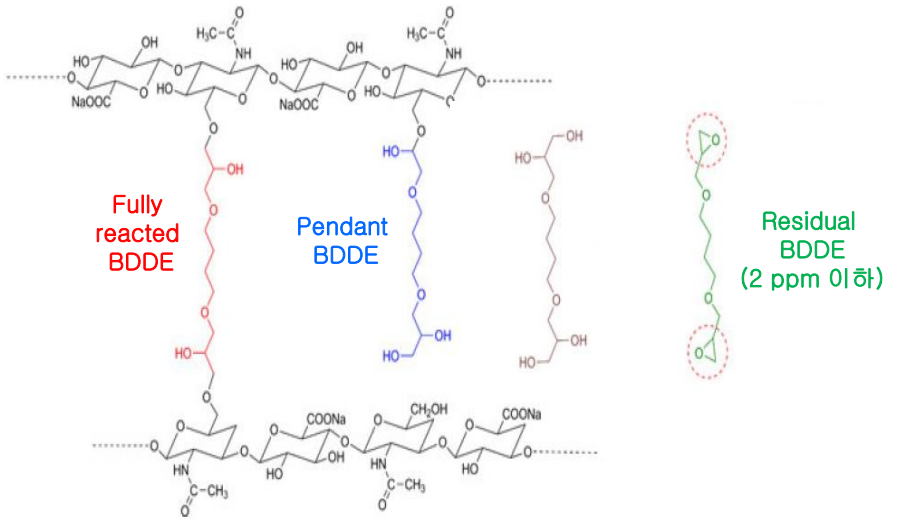
지속 시간 vs 안정성

많은 양의 가교제

Pendant type BDDE 및 BDDE 유래 by-product를 생성시켜 hypersensitivity 유발

안전한 가교제 사용 및 가교제의 투입량을 최소화하여 독성을 감소

- ✓ The cross-linking agents used are reactive agents that may be cytotoxic and, in certain cases, mutagenic. Owing to this, their residual presence in the final hydrogel must be highly monitored.
- ✓ The pendant type remains, making it a highly suspected cause of the filer-induced hypersensitivity reaction



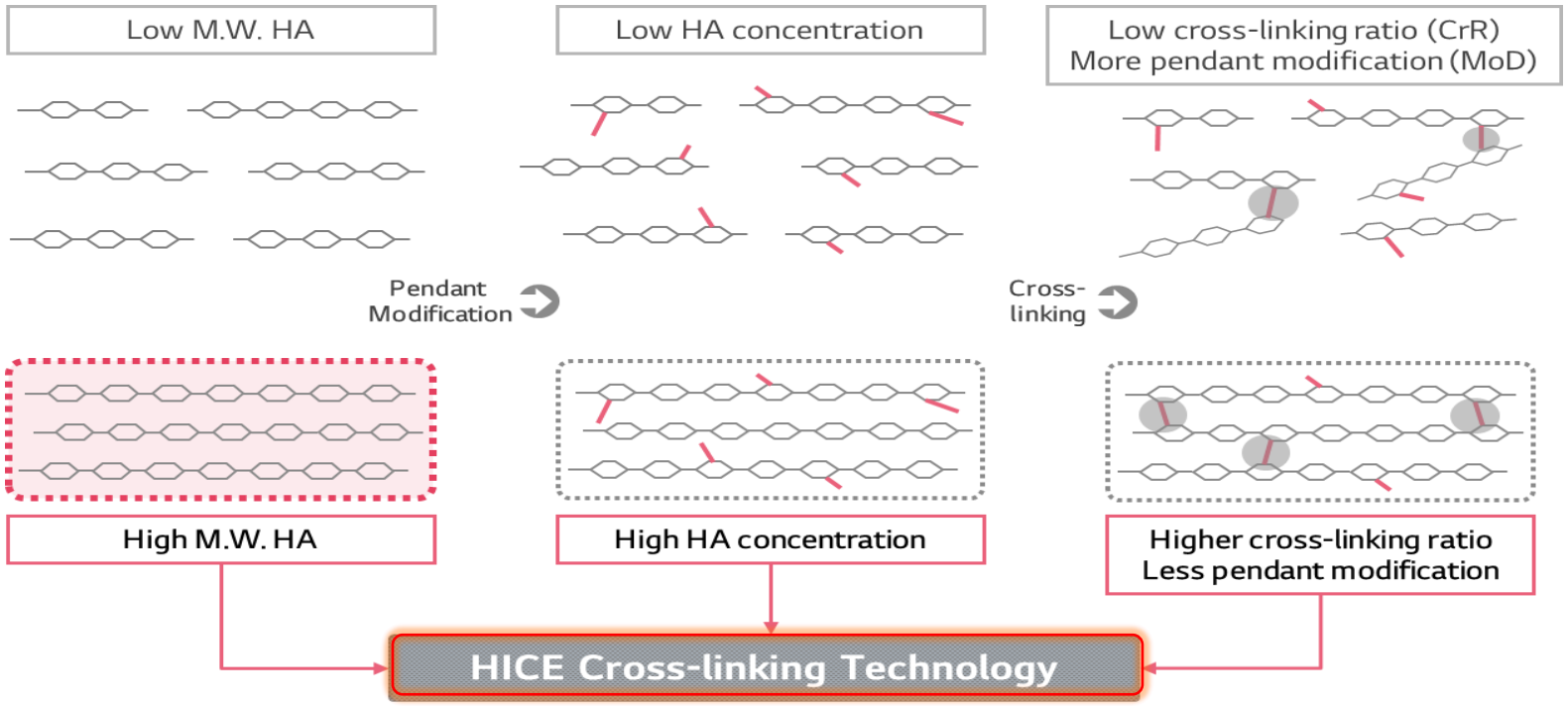
Filler complications, ISBN 978-981-13-6638-3. Fidalgo J et al. Med Devices (Auckl). 2018 Oct 15;11:367-376. De Boulle K et al. Dermatol Surg. 2013 Dec;39(12):1758-66.

Cross-linking Technology

HICE 가교기술

최소한의 BDDE 사용

높은 점탄성



HICE, high concentration equalized

Cross-linking Technology

HICE 가교기술

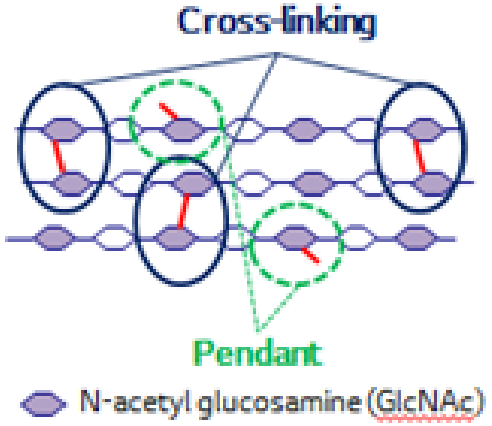
최소한의 BDDE 사용

높은 점탄성

높은 가교효율(CrR)

최소한의 BDDE 투입을 통한 낮은 변형율 (MoD)

(CrR, 약 24%; MoD, 약 1.8%)



Modification Degree (MOD)

$$= \frac{n_{(total\ BDDE)}}{n_{(total\ GlcNAc)}}$$

$$= \frac{5}{12} = 0.42$$

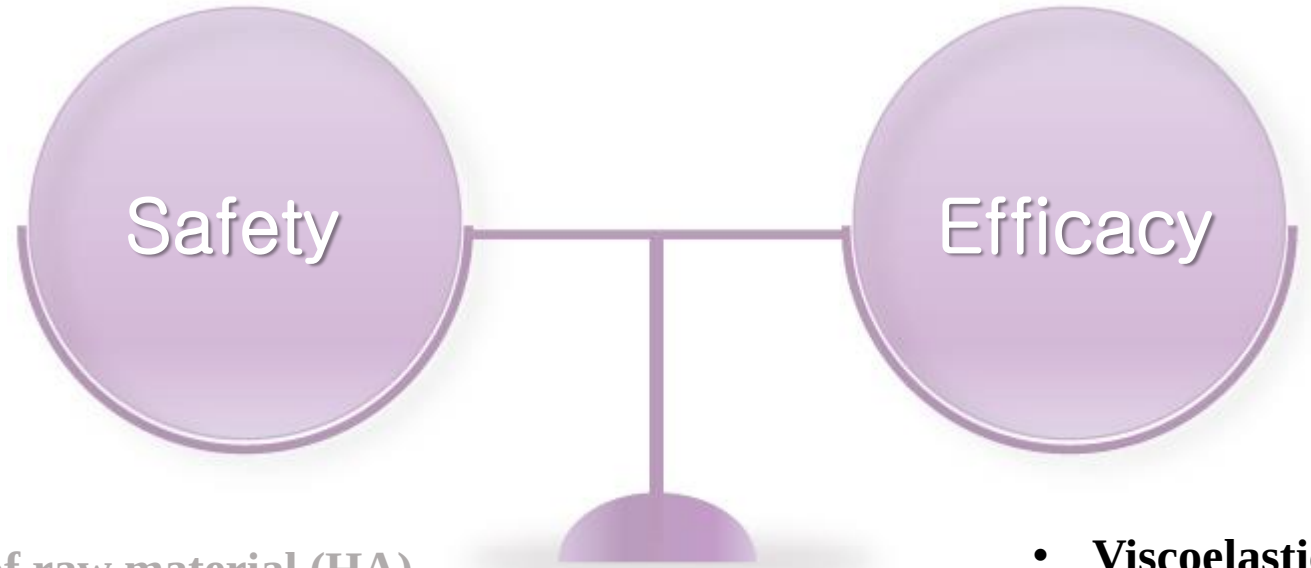
Cross-linking Ratio (CrR)

$$= \frac{n_{(cross-linked\ BDDE)}}{n_{(total\ BDDE)}}$$

$$= \frac{3}{5} = 0.6$$

HICE, high concentration equalized

Ideal Viscosupplement



- Purity of raw material (HA)
- Amount of cross-linking agent

- **Viscoelasticity**
- Duration

Viscoelasticity

HA viscosupplement의 점탄성 → 관절에서 충격흡수와 윤활제 역할

점탄성이 높을수록 지속기간 및 효능이 우수할 수 있으나

너무 높으면 면역 반응을 유발할 수 있음

정상인의 관절활액 이상

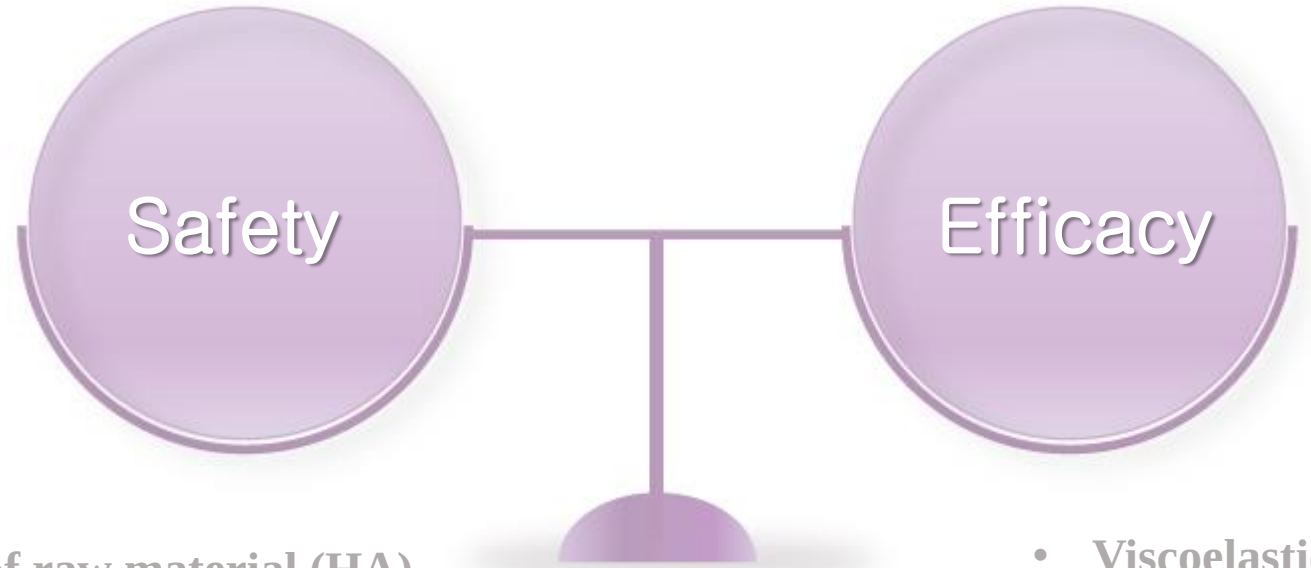
조직반응을 유발하지 않는 수준의 점탄성 범위

구분		G' (탄성) (Storage modulus, Pa, at 2.5 Hz)	G" (점성) (Loss modulus, Pa, at 2.5 Hz)
정상인의 연령별 관절 활액	18~27세	117 ± 13	45 ± 8
	27~35세	22.6 ± 0.7	7.2 ± 0.8
	52~78세	18.9 ± 3.3	10.1 ± 1.2
OA 환자의 활액		8.5 ± 5.4	4.8 ± 2.8
HA viscosupplement		**309**	**50**

Balazs, E.A. The physical properties of synovial fluid and the special role of hyaluronic acid: In Disorders in Knee. (A. Helfet ,ed.) T.B. Lippincott, Philadelphia p. 63-75

Data on file. LG Chem R&D center. Report for characterization of SYNOVIAN®. RCH-SA-002.

Ideal Viscosupplement



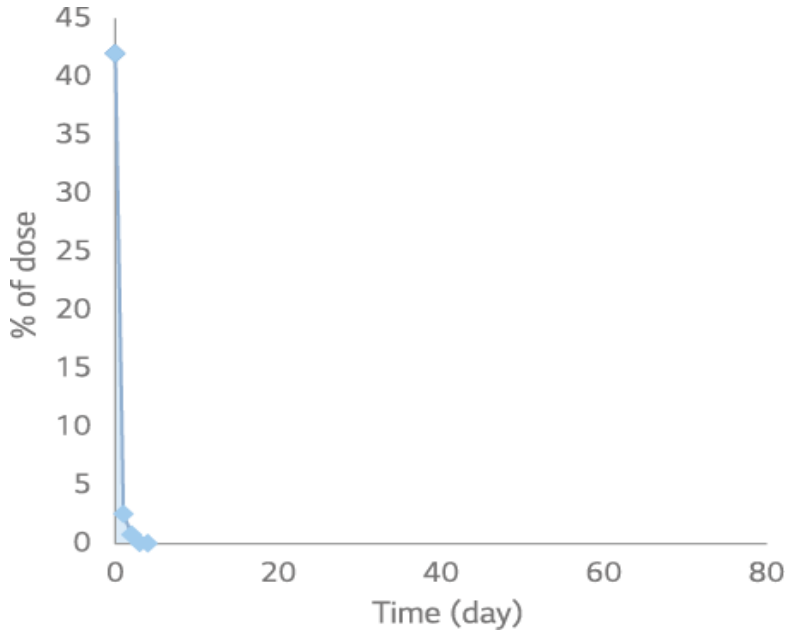
- Purity of raw material (HA)
- Amount of cross-linking agent

- Viscoelasticity
- **Duration**

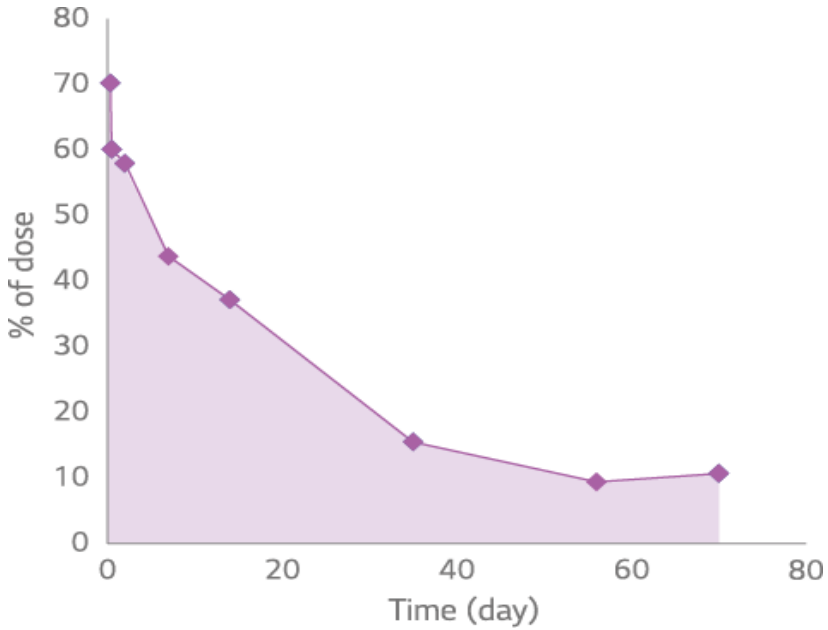
Efficacy 지속시간

HICE 가교기술 → 반감기가 증대 →
관절 내에서 지속적인 효과

Duration of Linear HA*



Duration of Cross-linked HA**



*3회 제형; **1회 제형

HICE, high concentration equalized

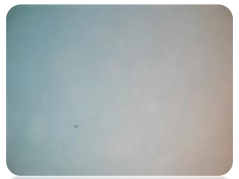
1. PHARMACOKINETIC, DISTRIBUTION AND EXCRETION STUDIES IN THE RABBIT AFTER INTRA-ARTICULAR DOSING, Huntingdon Life Sciences Ltd
2. Absorption, Distribution and Excretion in Rats Following Sing Intra-Articular Administration of 14C-COMPOUND, Sekisui Medical Co., Ltd.

Compliance 주입력

HA성상은 가교공정에 따라 monophasic과 biphasic으로 구분

Monophasic HA: 높은 입자간 응집력 → 주사시에 많은 힘 요구

Biphasic HA: 낮은 응집력 → monophasic HA 보다 적은 힘으로 편리하게 주사

	Monophasic HA	Biphasic HA
형태	 응집성이 높은 균질한 젤의 형	 입자 형태
특징	응집력 ↑, 탄성↓	탄성 ↑, 응집력 ↓
주입시 압력	높은 주입력 필요	상대적으로 낮은 주입력 필요

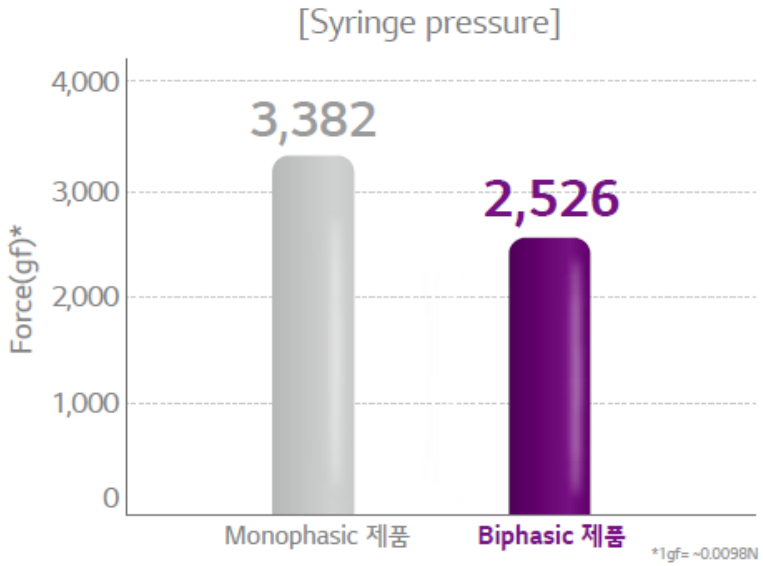


Figure 3. Measurement of syringeability. Greater injection power is needed for the monophasic HA than the biphasic HA.

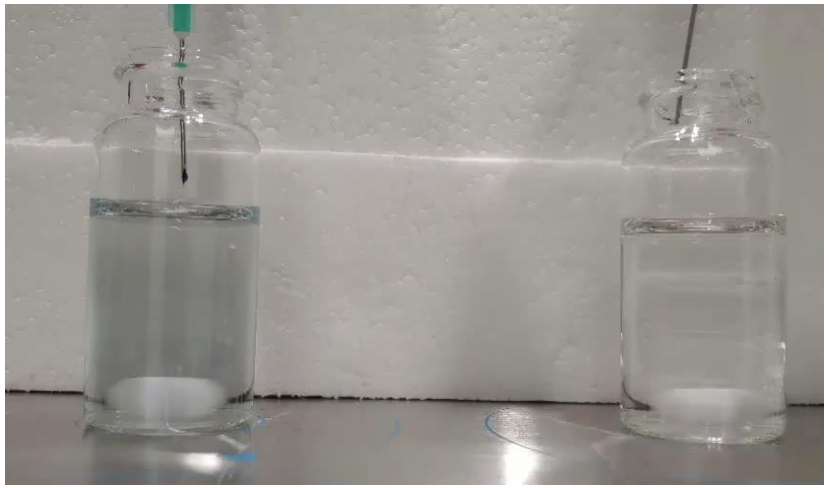
1. Flynn TC et al. Dermatol Surg. 2011 May;37(5):637-43. **2.** Park KY et al. J Eur Acad Dermatol Venereol. 2014 May;28(5):565-8.

Compliance 주입력

Biphasic HA 응집력이 낮아, 낮은 주입력으로 편리하게 주사

Biphasic HA

Monophasic HA



낮은 응집성 → 관절강내 주입시 골고루 분포.”

	A제품	시O비안®
HA 성상	Monophasic	**Biphasic**
특징	응집력이 높음 → 높은 주입력 필요	응집력이 낮음 → 상대적으로 낮은 주입력 필요
응집력 (gf)	88.1	**44.1**
평균 주입력 (N) (10초 주입시)	75	**28**
시린지 타입	유리	플라스틱

LG화학 자사 시험 결과, Data on file. LG Chem R&D center. Report for characterization of SYNOVIAN® . RCH-SA-003 , RCH-SA-004

Compliance 주입력 COC syringe

Glass syringe는 주사압이 가해질 때 깨짐 발생

Pharmaceutical Development and Technology

http://informahealthcare.com/phd
ISSN:1083-7450(print),1097-9867(electronic)

Pharm Dev Technol, 2015; 20(1): 1–11
 DOI: 10.3109/10837450.2014.982825

informa healthcare

REVIEW ARTICLE

Pre-filled syringes: a review of the history, manufacturin and challenges

Gregory Sacha[1], J. Aaron Rogers[2], and Reagan L. Miller[3]

[1]Department of Research and Development, Baxter Medical Products, Bloomington, IN, U Baxter Medical Products, Bloomington, IN, USA, and [3]Department of Research and Develo Lake, IL, USA

the glass syringe Luer cone left behind during manufacturing have led to aggregation and particle formation in protein solutions. These issues coupled with breakage concerns have lead to the development of plastic pre-fillable syringes. There are several types of plastic syringes available: cyclic olefin polymer (COP), cyclic olefin copolymer (COC), polypropylene (PP) and polycarbonate (PC) (Figures 7 a).

Figure 7.
Schott polymeric syringe.
(시노비안® syringe)

Sacha G et al. Pharm Dev Technol. 2015 Jan;20(1):1-11.

Compliance 주입력 COC syringe

Crosslinked HA

높은 응집력으로 인해 깨짐 위험

제품	구분	HA 성상	평균 주입력 (N)	주사기 타입
시O비안®	1회 제형 가교 HA	Biphasic	28	COC 플라스틱
히O안플러스®	3회 제형 고분자 HA	Biphasic	8	유리
A제품	1회 제형 가교 HA	Monophasic	75	유리

Needle: 21G thin wall, Injection velocity: 5mm/s

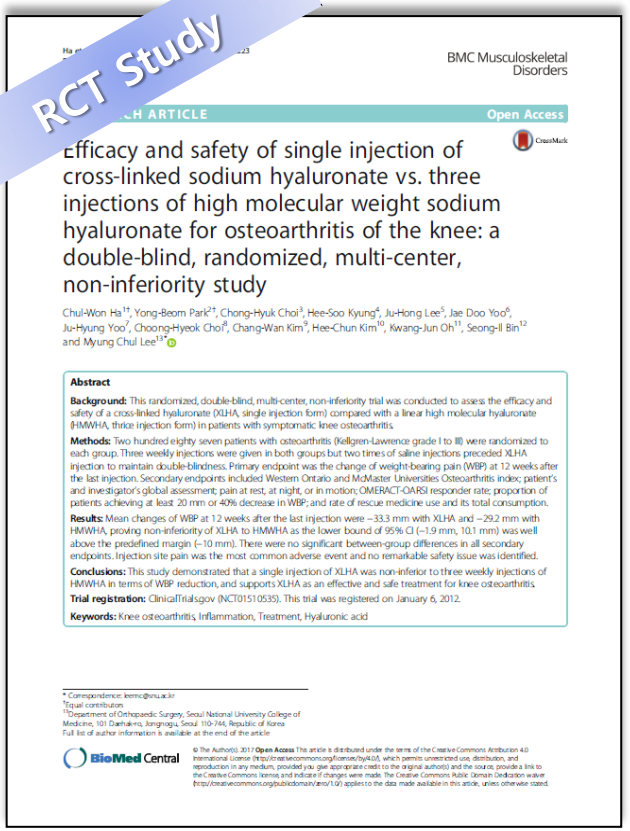
LG화학 자사 시험 결과, Data on file. LG Chem R&D center. Report for characterization of SYNOVIAN® . RCH-SA-003

Contents

Clinical data

효과 및 안전성

RCT Study



BMC Musculoskeletal Disorders

RESEARCH ARTICLE Open Access

Efficacy and safety of single injection of cross-linked sodium hyaluronate vs. three injections of high molecular weight sodium hyaluronate for osteoarthritis of the knee: a double-blind, randomized, multi-center, non-inferiority study

Chul-Won Ha[1†], Yong-Beom Park[2*†], Chong-Hyuk Choi[3], Hee-Soo Kyung[4], Ju-Hong Lee[5], Jae Doo Yoo[6], Ju-Hyung Yoo[7], Choong-Hyeok Choi[8], Chang-Wan Kim[9], Hee-Chun Kim[10], Kwang-Jun Oh[11], Seong-Il Bin[12] and Myung Chul Lee[13*]

Abstract

Background: This randomized, double-blind, multi-center, non-inferiority trial was conducted to assess the efficacy and safety of a cross-linked hyaluronate (XLHA, single injection form) compared with a linear high molecular hyaluronate (HMWHA, thrice injection form) in patients with symptomatic knee osteoarthritis.

Methods: Two hundred eighty seven patients with osteoarthritis (Kellgren-Lawrence grade I to III) were randomized to each group. Three weekly injections were given in both groups but two times of saline injections preceded XLHA injection to maintain double-blindness. Primary endpoint was the change of weight-bearing pain (WBP) at 12 weeks after the last injection. Secondary endpoints included Western Ontario and McMaster Universities Osteoarthritis index; patient's and investigator's global assessment; pain at rest, at night, or in motion; OMERACT-OARSI responder rate; proportion of patients achieving at least 20 mm or 40% decrease in WBP; and rate of rescue medicine use and its total consumption.

Results: Mean changes of WBP at 12 weeks after the last injection were −33.3 mm with XLHA and −29.2 mm with HMWHA, proving non-inferiority of XLHA to HMWHA as the lower bound of 95% CI (−1.9 mm, 10.1 mm) was well above the predefined margin (−10 mm). There were no significant between-group differences in all secondary endpoints. Injection site pain was the most common adverse event and no remarkable safety issue was identified.

Conclusions: This study demonstrated that a single injection of XLHA was non-inferior to three weekly injections of HMWHA in terms of WBP reduction, and supports XLHA as an effective and safe treatment for knee osteoarthritis.

Trial registration: ClinicalTrials.gov (NCT01510535). This trial was registered on January 6, 2012.

Keywords: Knee osteoarthritis, Inflammation, Treatment, Hyaluronic acid

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Full list of author information is available at the end of the article

Repeated Inj. study

Rheumatology

CrossMark

...cy and efficacy of bi-annual intra-articular LBSA0103 injections in patients with knee osteoarthritis

Jin Kyu Lee[1] · Chong-Hyuk Choi[2] · Kwang-Jun Oh[3] · Hee-Soo Kyung[4] · Ju-Hyung Yoo[5] · Chul-Won Ha[6] · Seong-Il Bin[7] · Seung-Baik Kang[8] · Myung Ku Kim[9] · Ju-Hong Lee[10] · Myung Chul Lee[11]

Received: 29 March 2017 / Accepted: 17 August 2017

Abstract The objective of this study is to assess the safety and efficacy of repeated intra-articular injection of high molecular weight hyaluronic acid (LBSA0103) at a 26-week interval, in patients with osteoarthritis of the knee. The study was an open-label, single arm, multicentre prospective trial conducted in patients with symptomatic knee osteoarthritis. The intervention consisted of two intra-articular injections of LBSA0103, with the second injection performed 26 weeks after the first injection. The primary outcome was the incidence of adverse drug reactions related to each injection. Assessment of efficacy of repeated injections in terms of maintenance of pain relief was a secondary objective of this study. Of the 185 patients screened, 174 patients received the first injection and 153 patients received both injections of LBSA0103. Nine adverse drug reactions occurred in seven patients (4.02%) after the first injection, while only one adverse drug reaction occurred (0.65%) after the second injection. As a secondary outcome measure, the improvements in the efficacy parameters including total WOMAC score and weight-bearing pain were all significant at both week 13 and 39 compared to the baseline value ($P < 0.001$), and improvements after the second injection were consistent with those after the initial injection of LBSA0103 (between week 26 and week 39, $P < 0.001$). Repeated intra-articular injection of LBSA0103 at a 26-week interval is safe without

Electronic supplementary material The online version of this article (doi:10.1007/s00296-017-3803-5) contains supplementary material, which is available to authorized users.

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Published online: 22 August 2017

Springer

1. Ha CW et al, BMC Musculoskelet Disord. 2017 May 26;18(1):223 **2.** Certification of suitability of monographs of the European Pharmacopoeia, EDQM

Clinical data

주사부위 이상반응	단회투여 임상		재투여 임상	
	시오비안® (139명)	A제품 (137명)	시오비안® (153명)	A제품 (87명)
통증	43.2%	56.2%	32.7%	36.8%
홍반, 발적	19.4%	21.9%	7.2%	9.2%
종창(Swelling), 부종	12.2%	23.4%	4.6%	11.5%
열감	23.7%	35.8%	20.3%	14.9%

(not the result of head to head)

각 제품 허가사항 내 '사용상의 주의사항'

Ongoing clinical evaluation

Post marketing surveillance (PMS)

연구제목	OOOO주의 시판 후 안전성 및 유효성 확인을 위한 사용성적조사
제품명	OOOO주 Prefilled syringe 3.0mL
연구방법	시판 후 사용성적조사
연구대상자	OOOO주를 투여하는 만 19세 이상의 성인
총 연구대상자수	목표 조사대상 3,000명
연구기간	2013년 10월 15일부터 2019년 10월 14
추적조사기간	각 조사 대상자별 투여 후 3 개월까지

Ongoing clinical evaluation

Observation study

연구제목	슬관절의 골관절염 환자에서 OOOO주를 투여하였을때의 injection portal 별로 주사부위 반응을 평가하기 위한 다기관, 전향적 관찰연구
제품명	OOOO주 Prefilled syringe 3.0mL
연구방법	다기관, 전향적 관찰연구
연구대상자	슬관절의 골관절염 (Osteoarthrities in the knee)으로 진단받은 환자 중 담당의사의 판단 하에 OOOO주를 투여 받을 환자
참여기관수	약 100개 기관 (예정)
총 연구대상자수	약 2,000명
연구기간	조사개시일 ~ 2019년 9월 (마지막 대상자 방문 완료)
추적조사기간	각 조사 대상자별 최대 2주 ± 3일

Observational Study

CURRENT MEDICAL RESEARCH AND OPINION
https://doi.org/10.1080/03007995.2021.1950132
Article ST-096181/1950132

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Safety of a single intra-articular injection of LBSA0103 hyaluronic acid in patients with osteoarthritis of the knee: a multicenter, single-arm, prospective, cohort study

Ki-Mo Jang[a], Yong-Geun Park[b], Won Kee Choi[c], Young Yool Chung[d], Kwang Kyoun Kim[e], Jang Woo Lee[f], Soong Joon Lee[g], Yunae Eom[h] and Jae-Hyuk Yang[i]

[a]Department of Orthopedic Surgery, Korea University Anam Hospital, Korea University College of Medicine, Seoul, Republic of Korea; [b]Department of Orthopedic Surgery, Jeju National University Hospital, Jeju National University School of Medicine, Jeju, Republic of Korea; [c]Department of Orthopedic Surgery, Daegu Catholic University Hospital, Daegu, Republic of Korea; [d]Department of Orthopedic Surgery, Kwangju Christian Hospital, Gwangju, Republic of Korea; [e]Department of Orthopedic Surgery, Konyang University Hospital, Konyang University College of Medicine, Daejeon, Republic of Korea; [f]Department of Physical Medicine and Rehabilitation, National Health Insurance Service Ilsan Hospital, Goyang, Republic of Korea; [g]Department of Orthopedic Surgery, Seoul National University Boramae Medical Center, Seoul, Republic of Korea; [h]Life Sciences R&D, LG Chem, Ltd, Seoul, Republic of Korea; [i]Department of Orthopedic Surgery, Hanyang University Guri Hospital, Guri, Republic of Korea

ABSTRACT

Objective: LBSA0103 is a recently developed high-molecular-weight, cross-linked, non-animal hyaluronic acid (HA). The safety of LBSA0103 has been investigated only in a limited number of patients, therefore this prospective study was designed. This study sought to assess the safety including injection-site reactions and adverse drug reactions after a single intra-articular injection of LBSA0103 in patients with osteoarthritis (OA) of the knee joint.

Methods: This study was a multicenter, single-arm, prospective cohort study. After screening, eligible patients with OA of the knee joint (Kellgren–Lawrence grades I–III) were enrolled, received a single intra-articular HA (LBSA0103) injection, and were followed up for two weeks. Any adverse events including injection-site reactions and adverse drug reactions were evaluated by the investigators.

Results: A total of 1949 subjects (2976 knee joints) was enrolled, all of whom received a single intra-articular injection of LBSA0103. Injection-site reactions occurred in 5.59% of enrolled subjects (109/1949), and the most frequently reported injection-site reaction was pain (4.87%), followed by swelling (1.03%). Most of the injection-site reactions were transient and resolved within 14 days without additional treatment. The incidence of adverse drug reactions other than injection-site reactions was 0.67% (13/1949). Most adverse events were of mild severity. No serious adverse events related to the study drug were reported.

Conclusions: A single intra-articular injection of LBSA0103 in patients with OA of the knee joint was safe, and no significant safety concerns were observed. As such, LBSA0103 could be safely applied as an intra-articular injection for the management of knee OA.

Trial Registration: The study was registered at ClinicalTrials.gov (identifier: NCT04369261).

ARTICLE HISTORY
Received 27 December 2020
Revised 23 April 2021
Accepted 16 June 2021

KEYWORDS
Safety; intra-articular injection; hyaluronic acid; osteoarthritis; knee

Introduction

Osteoarthritis (OA) is a degenerative joint disorder causing joint pain and functional impairment and is the most frequently diagnosed condition in patients with chronic musculoskeletal pain[1]. OA is a slowly progressive disorder with different degrees of disease severity and that requires long-term management with various treatment options during its course[2–5]. Although OA may occur in any synovial joint in the body, the knee joint is one of the most common manifestations of this disease[6–8]. As the knee joint takes on a substantial amount of the weight-bearing load, OA of the knee joint can lead to significant disability if left untreated[9–11].

Current treatments for knee OA focus on managing symptoms and associated impairments to enhance the quality of life and delay surgical treatment. The benefits of pharmacologic and non-pharmacologic interventions are well-documented, and non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used agents[12–14]. However, prolonged use of NSAIDs carries the risk of adverse cardiovascular and gastrointestinal side effects[15]. When lifestyle modifications, bracing, physical therapy, and NSAIDs fail to relieve OA symptoms, intra-articular hyaluronic acid (HA) injections are often considered as an alternative option[16,17]. In knee OA, synovial fluid viscosity and elasticity as well as

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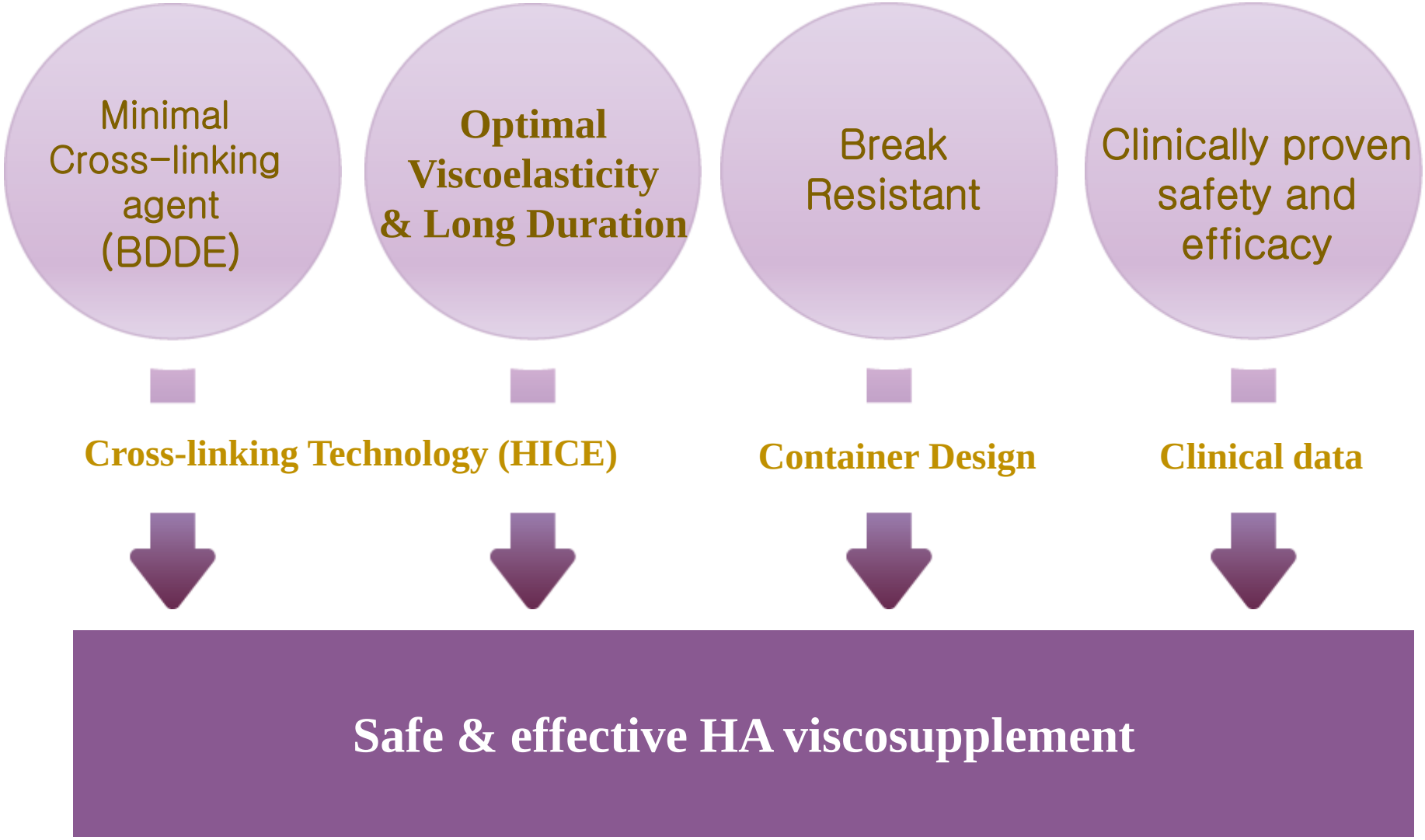
www.cmrojournal.com

Conclusion


Minimal Cross-linking agent (BDDE)
Optimal Viscoelasticity & Long Duration
Break Resistant
Clinically proven safety and efficacy
Cross-linking Technology (HICE)
Container Design
Clinical data
Safe & effective HA viscosupplement

경청해주셔서 감사합니다.