Differences Regarding Branded HA in Italy, Part 2: Data from Clinical Studies on Knee, Hip, Shoulder, Ankle, Temporomandibular Joint, Vertebral Facets, and Carpometacarpal Joint

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ABSTRACT

OBJECTIVES: The aim of the current study is to collect scientific data on all branded hyaluronic acid (HA) products in Italy that are in use for intra-articular (IA) injection in osteoarthritis (OA) compared with that reported in the leaflet.

METHODS: An extensive literature research was performed for all articles reporting data on the IA use of HA in OA. Selected studies were taken into consideration only if they are related to products based on HAs that are currently marketed in Italy with the specific joint indication for IA use in patients affected by OA.

RESULTS: Sixty-two HA products are marketed in Italy: 30 products are indicated for the knee but only 8 were proved with some efficacy; 9 products were effective for the hip but only 6 had hip indication; 7 products proved to be effective for the shoulder but only 3 had the indication; 5 products proved effective for the ankle but only one had the indication; 6 products were effective for the temporomandibular joint but only 2 had the indication; only 2 proved effective for vertebral facet joints but only 1 had the indication; and 5 products proved effective for the carpometacarpal joint but only 2 had the indication.

CONCLUSIONS: There are only a few products with some evidences, while the majority of products remain without proof. Clinicians and regulators should request postmarketing studies from pharmaceuticals to corroborate with that reported in the leaflet and to gather more data, allowing the clinicians to choose the adequate product for the patient.

KEYWORDS: osteoarthritis, hyaluronic acid, hylan G-F20, knee, hip, ankle, TMJ, carpometacarpal, shoulder, vertebral facets

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Introduction

Osteoarthritis (OA) represents a leading cause of disability around the world, and its incidence is growing with the progressive aging of population.[1]

For the treatment of OA, clinicians may rely on different therapeutic aids, which vary depending on the phenotype of OA and its stage of advancement.[2]

Between the various therapeutic aids, the viscosupplementation is a viable alternative, with proven efficacy and safety profiles.[3] Guidelines on the treatment of OA are inconsistent with the viscosupplementation and have evolved over time.[4–6] As of now, the role of viscosupplementation in the treatment of OA is not entirely clear, and the correct indication for its use, such as the more suitable phenotypes or stages of OA , especially for joints other than the knee, is still unclear, and both the timing of treatment and the volume of the doses employed are still controversial.[2,3]

The technical expert panel (TEP) of ANTIAGE (non-profit Italian association for the intra-articular [IA] therapy by ultrasound guidance of the hip) has undertaken a research on several fronts to highlight the current evidence of the products based on hyaluronic acid (HA) for IA injection currently marketed in Italy, and specifically, the data that are available in the scientific literature.

In a previous study, the TEP of ANTIAGE reviewed the current scientific evidence of both *in vitro* effects and animal model data on branded HA products[7]; finally, a comparison was made between these results and the contents of leaflets of each branded product.

In the present study, the TEP of ANTIAGE wanted to collect the available data in the scientific literature on each branded HA formulation for OA management both in the knee (the most studied joint) and in the other joints. An extensive literature research was conducted in order to gather such data.

Materials and Methods

An extensive literature research was performed for all articles reporting data on the IA use of HA in OA. The research was restricted only to articles in English that were published in PubMed before July 6, 2014, the day of the literature research. In order to recruit studies for further analysis, the following MeSH terms were employed, separately or in combination: OA, HA/hyaluronate/hylan, IA, viscosupplementation, knee/hip/shoulder/ankle/tempuromandibular/carpometacarpal/vertebral facets (VFs). The studies that were recruited for further analysis were analyzed and consequently selected by two different reviewers. Therefore, selected studies were taken into consideration only if related to products based on HAs that are currently marketed in Italy for IA use in patients affected by OA.

We have summarized the data after careful selection of the studies currently available in the scientific literature on the IA use of branded HA products in the knee and the other joints.

Results

Knee. At the beginning, we identified 312 papers reporting on the use of HA for IA injection in the knee joint. The subsequent use of filters and analysis of titles and abstracts produced 26 randomized clinical trials (RCTs), with 10 more coming from the references from those papers, making a total of 36 papers (see Tables 1 and 2).[8–43]

Of the 36 studies included in this analysis, 13 studies report on the use of Hyalgan/Hyalectin/Hyalart, 21 studies report on Synvisc/Synvisc-One, 4 studies report on Supartz, 4 studies report on Orthovisc, and 1 study reports on Sinovial, Hyalubrix, Go-On, Adant, and Ostenil. Compiling the experience of respective studies, Synvisc/Synvisc-One was tested on a total of 3015 patients, Hyalgan/Hyalectin/Hyalart was tested on a total of 1821 patients, Supartz was tested on a total of 764 patients, Orthovisc was tested on a total of 271 patients, Sinovial was tested on a total of 381 patients, Hyalubrix was tested on a total of 109 patients, Go-On was tested on a total of 172 patients, Adant was tested on a total of 109 patients, and Ostenil was tested on a total of 220 patients.

Comparisons of HA. Included RCTs compare every HA with different comparators, such as saline solution, steroids, other HAs, physical therapy, and various other compounds such as PRP, clodronate, or peripheral blood stem cells (PBSCs). Of the 12 studies reporting on Hyalgan/Hyalectin/Hyalart, 8 studies report on the comparison of Hyalgan/Hyalectin/Hyalart versus saline solution, 2 studies report on the comparison of Hyalgan/Hyalectin/Hyalart versus other HAs (Synvisc and Go-On), and 2 studies report on the comparison of Hyalgan/Hyalectin/Hyalart versus other compounds (clodronate and PBSC), while another study reports on the effect compared with contralateral untreated knee. Of the 21 studies reporting on the comparison of Synvisc with other treatments, 5 studies report on the comparison versus saline solution, 2 studies on the comparison versus steroids, 8 studies on the comparison versus other HAs (unspecified Low Molecular Weight [LMW] HA, Orthovisc, Ostenil, Sinovial, Hyalgan, Supartz), 1 study on the comparison versus physical therapy, and 5 studies on the comparison versus other compounds or alternative therapies (arthrocentesis, Non Steroideal Anti Inflammatory Drugs [NSAID], no treatment). Supartz was compared in four studies: three studies versus saline solution and one study versus Synvisc. Four studies explored Orthovisc versus other therapeutic options: one study versus steroids, three studies versus other HAs (Synvisc, Ostenil), and one study versus physical therapy. The study on Sinovial compared this HA versus Synvisc, Go-On was compared with Hyalgan, Adant was tested against saline solution, Hyalubrix was compared with Platelet Rich Plasma (PRP), and the study on Ostenil reports on the comparison versus Synvisc and Orthovisc.

Dosing regimens. Dosing regimens varied slightly across the studies. Of the studies reporting on the comparison of Hyalgan/Hyalectin/Hyalart versus other therapeutic options, four studies used a dosing regimen of one per week for three weeks and in one study, the HA was administered by four weekly injections, while in two studies, HA was administered by five weekly injections. Supartz was used at a dosing regimen of one injection per week for five weeks. Synvisc was used at a dosing regimen of three weekly injections in all studies. Three weekly injections were administered in the comparative studies on Orthovisc, Sinovial, Hyalubrix, Go-On, and Ostenil. All dosing regimens, with the exclusion of the study on Synvisc-One, used a volume of 2 mL for each injection.

Outcomes. With respect to the study outcomes, all studies included in this analysis focused on the symptomatic efficacy of HA treatment as a primary outcome, while only four of them considered the structural effects of this approach. In the first study,[10] a radiological milder disease at baseline was predicting a minor joint space narrowing progression after 52 weeks from the beginning of the study in the group of patients treated with Hyalgan. In the second RCT,[43] the addiction of Synvisc to PBSC was able to improve the histological and magnetic resonance imaging (MRI) quality of articular cartilage repair in patients with chondral lesions. Another interesting study, a single-blind RCT, focused on the structural effects of Synvisc using MRI as a reference, showed cartilage preservation

Table 1. Studies reporting on efficacy and safety profiles of branded hyaluronic in knee OA in Italy.

AUTHOR, YEAR	BRANDED HA	N. OF PAT.	FOLLOW-UP (WEEKS)	COMPARATOR	WEEKLY INJECTIONS	PRIMARY OUTCOMES	SAEs
Grecomoro, 1987	Hyalgan®	34	8	Saline	3	Pain (VAS)	No
Dixon, 1988	Hyalgan®	63	48	Saline	up to 11 (*)	Pain (VAS)	No
Dougados, 1993	Hyalectin®	110	52	Saline	3	Disease activity	NR
Dahlberg, 1994	Supartz®	52	52	Saline	5		No
Henderson, 1994	Hyalgan®	91	20	Saline	5	Pain (VAS), paracetamol use	No
Adams, 1995	Synvisc®	102	26	NSAIDs+ AC; NSAIDs + Synvisc®	3	Pain, function	No
Lohmander, 1996	Supartz®	240	20	Saline	5	Pain (VAS)	No
Wu, 1997	Supartz®	90	24	Saline	5	Pain (VAS)	No
Wobig, 1998	Synvisc®	110	26	Saline	3	Pain (VAS), treatment success	No
Altman, 1999	Hyalgan®	495	26	saline and NSAIDs	5	Pain (VAS)	No
Wobig, 1999	Synvisc®	60	12	HA	3	Pain (VAS)	No
Huskisson, 1999	Hyalgan®	100	24	Saline	5	Pain (VAS), Lequesne Index	1
Miltner, 2002	Hyalart®	43	5	Controlateral knee	5	Isokinetic muscle force, pain (VAS), Lequesne Index	NR
Kahan, 2003	Synvisc®	253	36	Conventional treatment, NSAIDs	3	Lequesne, WOMAC, SF12, pain (walking), health related costs	No
Raynauld, 2002	Synvisc®	255	52	Appropriate care	3 (**)	Pain (WOMAC)	No
Karlsson, 2002	Synvisc® Supartz®	210	52	HA	3	Weight bearing pain, Lequesne Index, WOMAC	No
Jubb, 2003	Hyalgan®	408	52	Saline	3 (***)	JSW	NR
Leopold, 2003	Synvisc®	100	24	BM	3 (°)	WOMAC, pain (VAS), Knee Society clinical rating scale	No
Caborn, 2004	Synvisc®	218	26	TC	3 (°)	WOMAC A1, WOMAC, PGA, PhGA	No
Çubukçu, 2005	Synvisc®	30	8	Saline	3	Pain, WOMAC	No
Keratosun, 2005	Synvisc® Orthovisc®	92	52	HA	3	Hospital for Special Surgery Knee Score	No
Ozturk, 2006	Orthovisc®	40	52	Orthovisc® + TC on 1st and 4th injection	3 (°°)	Pain (VAS), WOMAC	No
Petrella, 2006	Hyalgan®	106	52	Saline	3	Pain (WOMAC)	No
Kotevoglu, 2006	Synvisc®	59	24	Orthovisc®, saline	3	WOMAC, PGA, PhGA	No
Atamaz, 2006	Synvisc®	80	52	Orthovisc®, physical therapy	3 (°°)	Pain (VAS, WOMAC), function (WOMAC)	No
Juni, 2007	Synvisc® Orthovisc®, Ostenil®	660	24	HA	3	Pain (WOMAC)	No
Raman, 2008	Synvisc® Hyalgan®	392	52	HA	3(Synvisc®) 5 (Hyalgan®)	Pain (VAS)	1
Diracoglu, 2009	Synvisc®	63	1	Saline	3	Pain (VAS), WOMAC, proprioception and isokinetic muscle force	No
Rossini, 2009	Hyalgan®	150	6	Clodronate	4	Pain (VAS), ROM, Lequesne Index, paracetamol use	No
Chevalier, 2010	SynviscOne®	253	26	Saline	1	Pain (WOMAC)	No
Pavelka, 2011	Sinovial® Synvisc®	381	52	HA	3	Pain (WOMAC)	No
Wang, 2011	Synvisc®	78	104	No treatment	3	Cartilage volume and defects	NR
Filardo, 2012	Hyalubrix®	109	52	PRP	3	IKDC, KOOS, Tegner score, EQ-VAS	No
Berenbaum, 2012	Go-On® Hyalgan®	437	26	HA	3	WOMAC, Pain (VAS), Lequesne Index	No
Saw, 2013	Hyalgan®	50	104	PBSC	5 (°°)	IKDC, MRI score	No

Notes: *Every other week. **Retreatment allowed after 4 weeks. ***Second addictional treatment after 4 months each. °1 injection for steroids. °°Retreatment after 6 months.
Abbreviations: SAEs, Serious Adverse Events; TC, Triamcinolone; BM, Betametasone; AC, Arthrocentsis; NR, Not Reported.

Table 2. Number of comparisons performed for branded hyaluronic acids in knee OA in Italy.

BRANDED HA	Vs STEROIDS	Vs OTHER HAS	Vs PHYSICAL THERAPY	Vs SALINE	Vs OTHER TREATMENTS	TOTAL
Hyalgan®	0	1	0	8	3	12
Supartz®	0	1	0	3	0	4
Synvisc®	2	8	1	5	5	21
Orthovisc®	1	3	1	0	0	5
Sinovial®	0	1	0	0	0	1
Hyalubrix®	0	0	0	0	1	1
Ostenil®	0	1	0	0	0	1

(both for cartilage volume and cartilage defects) in a group of patients treated with Hylan G-F 20 (four courses of three injections each, every six months) with respect to a control group receiving usual care for OA.[27] The fourth and more recent structural study, performed by Saw et al, reported on the adjunctive effect of PBSC administered with respect to Hyalgan alone in MRI and histological assays performed on the patients affected by knee OA.[25] Regarding safety of HA injection in knee, none of the papers reported an increased risk of adverse events after HA knee injection.

Hip. Twenty-three articles reported the effects of HA for hip OA (see Table 3).[44–66] Such studies included 8 RCTs, 13 cohort studies, and 2 retrospective studies. Cohort studies report the use of HA on a total of 3204 patients affected by hip OA, while RCTs report on a total of 881 patients. The two retrospective studies report on a total of 420 patients. Of the eight RCTs, three studies reported on the use of Synvisc, two studies reported on the use of Adant, two studies report on Hyalone, and one study reported on the use of Hyalgan, Ostenil, Synocrom, and Durolane.

RCTs. Of the three RCTs reporting on the use of Synvisc, the study by Tikiz et al.[52] was performed by comparing Synvisc versus Ostenil, both administered under fluoroscopic guidance at a dose of one vial every week for a total of three weeks. The second RCT reporting on the use of Synvisc, by van den Bekerom et al.[55], was performed with the comparison of Synvisc versus Adant and Synocrom, administered under fluoroscopic guidance by a single IA injection. In this RCT, van den Bekerom observed that 51% of patients undergoing IA injection did not receive a total hip replacement three years after injection, reporting for the first time how IA HA injection in hip OA may delay surgery. The third RCT investigating on Synvisc was performed by Spitzer et al.[59], and in this study, the injection of one vial of Synvisc every other week, for a total of two injections, was compared with corticosteroids, both compounds were administered under fluoroscopic guidance. A RCT investigating on the efficacy of Adant in hip OA was performed by Richette et al.[56] Adant and its comparator, saline solution, were administered under fluoroscopic guidance at a dose of one vial for a single injection. The only RCT on the use of Hyalgan in hip OA was performed by Qvistgaard et al.[54] and reported on the use of Hyalgan, administered under ultrasound guidance at a dose of one vial every week for a total of three injections, compared with saline solution and corticosteroids. The RCT by Migliore et al.[57] reported on the comparison of Hyalone and mepivacaine, both were administered under ultrasound guidance at a dose of one vial of Hyalone or 4 mL of mepivacaine every month for a total of two injections. Always regarding Hyalone, another RCT was performed by Battaglia et al, reporting the comparison on the use of this HA versus PRP in hip OA-affected patients.[65] Another RCT comparing the efficacy of a NASHA, Durolane, with corticosteroids, was performed by Atchia et al.[60] In this study, both Durolane and corticosteroids were administered at a single dose under ultrasound guidance. The only RCT reporting on the comparison of HA with PRP in hip OA is the one performed by Battaglia et al.[65], who compared Hyalubrix with PRP. Both Hyalubrix and PRP were administered with a single injection under ultrasound guidance.

Cohort studies. Of the 15 cohort studies, 7 studies reported on the use of Synvisc in hip OA, 2 studies reported on the use of Hyalgan, 2 studies reported on the use of Hyalone, and 1 study reported on the use of Durolane, Adant, and Synolis V-A. Dosing regimens for cohort studies varied from one injection every six months to cycles of one injection per week for a total of two to five injections. Of all the identified studies, only two studies were performed without image guidance for IA injection. All dosing regimens used a volume of 2 mL for each injection, except for the studies by Migliore et al, where a volume of 4 mL of Hyalone or Synolis V-A was used.

Retrospective studies. With respect to retrospective studies reporting on surgical delay for patients affected by hip OA undergoing IA HA injection, two studies published by Migliore et al focused on the effect of Hyalubrix (Hyalone) and Synvisc, both administered under US guidance with an injection of 4 mL of Hyalubrix and 2 mL of Synvisc, with a dosing regimen of one injection every six months.[63,64] In both studies, a delay in the need for total hip replacement was observed for patients undergoing IA HA injections.

Length of follow-up varied across the examined studies from 6 to 260 weeks. RCTs were characterized by a shorter

Table 3. Studies reporting on efficacy and safety profiles of branded hyaluronic acids in hip OA in Italy.

AUTHOR, YEAR	BRANDED HA	PAT.N.	FOLLOWUP (WEEKS)	COMPARATOR	INJECTION COURSE	IMAGE GUIDANCE	PRIMARY ENDPOINT	SAEs
Brigantini, 1994	Hyalgan®	44		None	3–5 weekly injections	None	Pain, Global assessment, NSAID	
Brocq, 2002	Synvisc®	22	24	None	1 or 2 injections	FL	Lequesne index	None
Conrozier, 2003	Synvisc®	57	12	None	1 or 2 injections	FL	Pain, Womac, Global assessment	None
Vad, 2003	Synvisc®	22	52	None	3 weekly injections	FL	Pain, AAOS, LLCS	None
Migliore, 2003	Hyalgan®	28	NR	None	1 to 3 weekly injections	US	Pain, Lequesne index, NSAID	None
Caglar-Yagci	Synvisc®	14	12	None	3 weekly injections	US	Pain, Lequesne index, 15 WT	None
Berg, 2004	Durolane®	31	12	None	1 injection	None	Womac, Global assessment	None
Migliore, 2005	Synvisc®	26	24	None	1 or 2 injections	US	Pain, Lequesne, NSAID	None
Tikiz, 2005	Synvisc vs Ostenil	43	24	HA	3 weekly injections	FL	Pain, Womac, Lequesne index	None
Migliore, 2006	Synvisc	36	36	None	1 or 2 injections	US	Pain, Womac, NSAID	None
Qvistgaard, 2005	Hyalgan®	101	12	Saline and CS	3 weekly injections	US	Pain on walking	None
van der Bekerom, 2008	Adant®, Synocrom®, Synvisc®	120	6	HA	1 injection	FL	Pain, Harris Hip Score	None
Richette, 2009	Adant®	85	12	Saline	1 injection	FL	Pain	None
Migliore, 2009	Hyalone®	42	24	mepivacaine	2 injections, every 6 monhts	US	Lequesne index	None
Eyigor, 2010	Adant®	21	24	None	3 weekly injections	FL	Pain, Lequesne index, NSAID	None
Spitzer, 2010	Synvisc®	313	26	CS	2 weekly injections	FL	Womac	None
Atchia, 2011	Durolane®	77	8	CS	1 injection	US	Womac	None
Migliore, 2011	Various HA	2343	104	None	1 injection every 6 months	US	NSAID	None
Migliore, 2011	Hyalone®	120	52	None	2 to 4 injections, every 6 momths	US	Pain, Lequesne index, NSAID	None
Migliore, 2012	Synvisc®	244	260	None	1 injection every 6 months	US	Rate of THR	None
Migliore, 2012	Hyalone®	176	96	None	1 injection every 6 months	US	Rate of THR	None
Battaglia, 2013	Hyalone®	100	52	PRP	1 injection	US	Harris Hips core, Pain VAS	None
Migliore, 2014	Synolis-VA®	20	52	None	1 injection every 6 months	US	Pain, Lequesne index, HAQ, NSAID	None

Abbreviations: FL, Fluoroscopy; US, ultrasound; CS, corticosteroids; THR, total hip replacement; SAEs, Serious Adverse Events.

length of follow-up, ranging from 6 to 52 weeks, while cohort studies ranged from 12 to 260 weeks.

None of the examined studies reported severe adverse events related to the use of HA in hip joint, and none of the studies focused on the structural effects exerted by HA in hip joint.

Shoulder. Twenty studies were identified on the use of HA in the shoulder (see Table 4).[67–86] Of these 20 studies, 13 were RCTs and 7 were cohort studies. RCTs reported on the use of HA on a total of 1786 patients, while cohort studies reported on the use of HA in 322 patients. The different pathologies for which the IA HA injections were performed were glenohumeral OA, adhesive capsulitis, partial or total rotator cuff tears, subacromial impingement, scapulohumeral OA, frozen shoulder, supraspinatus tendinosis, and shoulder pain. Follow-up times varied from 3 weeks to 33 months. Of the 13 RCTs on the use of IA HA, 7 studies reported on a direct comparison of HA against steroids, 5 studies reported on a comparison versus saline solution, and 3 studies reported on a confrontation versus physical therapy, while only 1 study compared Hyalgan versus Hylan G-F20. Dosing regimens varied across the examined studies with the number of injections varying from only one injection to five weekly injections. All dosing regimens used a volume of 2 mL for each injection.

Table 4. Studies reporting on efficacy and safety profiles of branded hyaluronic acids in shoulder pathologies in Italy.

AUTHOR, YEAR	BRANDED HA	PAT.N.	FOLLOWUP (WEEKS)	PATHOLOGIES TREATED	COMPARATOR	INJECTION COURSE	IMAGE GUIDANCE	PRIMARY OUTCOMES	SAEs
Leardini, 1988	Hyalgan®	29	2	Shoulder OA and periarthritis	None	3 weekly injections	NR	Joint mobility, pain on VAS, analgesic consumption	None
Rovetta, 1998	Hyalart® + TC	30	24	AC	TC	2 injections every 2 weeks and then 1 injection per month	NR	Pain VAS	NR
Shibata, 2001	Supartz®	78	4	RC tear	DM	5 weekly injections	NR	UCLA score	None
Tamai, 2004	Supartz® + LC	11	6	Frozen shoulder	None	5 weekly injections	NR	JOA + Dynamic MR	None
Calis, 2006	Orthovisc®	90	12	AC	TC and PT	1 inejction	NR	Pain VAS	NR
Valiveti, 2006	Hyalgan® Synvisc®	11	52	Shoulder OA or RC tear or MS	HA	3 weekly injections	NR	Physician VAS and Patient VAS	None
Silverstein, 2007	Synvisc®	30	24	Shoulder OA	None	3 weekly injections	NR	Pain VAS, UCLA SCORE, simple shoulder test	None
Meloni, 2008	Hyalgan®	50	12	Supraspinatus tendinosis	Saline	1 injection	NR	Pain VAS	NR
Blaine, 2008	Hyalgan®	660	24	Shoulder OA, AC, RC tear	Saline	5 weekly injections	NR	Pain VAS	None
Noel, 2009	Synvisc®	39	24	Shoulder OA with healthy RC	None	4 injections, 1 every month	NR	Pain VAS	None
Chou,2010	Supartz®	52	12	Partial RC tear	Saline	5 weekly injections	FL	Pain VAS and Constant Murley	None
Brander, 2010	Synvisc®	36	24	Shoulder OA and healthy RC	none	2 injections every 2 weeks	FL	WORC, Pain VAS	None
Tagliafico, 2011	Synvisc®	93	24	RC tear	none	3 weekly injections	US	Pain VAS and Constant	None
Ozgen, 2012	Synvisc® + PT	24	16	Supraspinatus tendinitis	PT	1 injection	NR	Pain VAS, ROM	None
Merolla, 2011	Synvisc®	84	24	Symptomatic shoulder OA	TC	3 weekly injections	NR	Pain VAS, Constant Murley, SPADI	None
Kim, 2012	Hyruan plus®	105	12	SI	TC and PT	3 weekly injections	US	American shoulder and elbow surgeon assessment	None
Penning, 2012	Ostenil® + LC	159	26	SI	TC + LC, saline + LC	3 weekly injections	NR	Pain VAS, Constant Murley, ROM	None
Kwon, 2013	Supartz®	300	52	Shoulder OA	saline	3 weekly injections	NR	Pain VAS, OMERACT-OARSI, ASES, PGA	None
Lim, 2014	Hyruan plus®	68	12	AC	MP + LC	1 injection	NR	Pain VAS, ASES score, Constant score, ROM	None
Penning, 2014	Ostenil® + LC	159	3	SI	TC +LC, saline + LC	3 weekly injections	NR	Pain VAS, drug intake	None

Abbreviations: FL, Fluoroscopy; US, Ultrasound; NR, not reported; SAEs, Serious Adverse Events; MS, Milwaukee shoulder; AC, Adhesive Capsulitis; SI, Subacromyal Impingement; TC, Triamcinolone; DM, Desametasone; PT, Physical Therapy; MP, Metylprednisolone; LC, Lidocaine.

Of the included studies, all studies, reported a positive symptomatic effect. None of the studies focused on the structural effects exerted by HA and, again, none of the studies reported serious adverse events after the IA use of all HAs tested.

Ankle. Ten articles reported the effects of viscosupplementation on ankle OA, of which five were RCTs and five were cohort studies (see Table 5).[87–96] RCTs reported the use of HA on a total of 157 patients, while cohort studies reported on a total of 292 patients. Among the five RCTs, two studies

reported on the use of Hyalgan, one study reported on the use of Adant, one study reported on the use of Synvisc, and one study reported on the use of Supartz. Of the 10 examined studies, only 3 studies performed IA injections by the use of an image guidance, such as fluoroscopy, while no other image guidance, such as ultrasound, was used. The Hyalgan RCTs were performed against saline solution with a weekly one vial injection for a total of five injections. The study by Salk et al.[87] used no image guidance, while the study by Cohen et al.[89] used fluoroscopic guidance for the IA injection. The study by Karatosun et al.[90] compared the use of a single vial of Adant administered weekly without image guidance for a total of three weeks against exercise therapy. DeGroot et al.[95] compared a single injection of Supartz with the injection of saline solution; all injections were performed under fluoroscopic guidance. Carpenter and Motley[91] compared Synvisc, administered without image guidance, associated with ankle arthroscopy to arthroscopy without joint injection, with a dosing regimen of one vial of Synvisc every week for a total of three weeks. Five cohort studies have been reported: three studies on the use of Synvisc, one study on the use of Supartz, and one study on the use of Euflexxa. More in detail in the study by Luciani et al.[92], Synvisc was administered by three weekly injections one vial for each injection, without image guidance. In the study by Witteveen et al.[93], Synvisc was administered with a single injection of one vial, eventually repeated after three months, without image guidance, while in the study by Hernandez et al.[96], Synvisc was administered under fluoroscopic guidance one vial every week for a total of three weeks. Of the remaining two cohort studies, in the study by Sun et al.[88], one vial of Supartz was administered without image guidance by one vial with five weekly injections, while in the study by Mei-Dan et al.[94], Euflexxa was administered at a dose of one vial by three weekly injections. Volume of HA injected for each injection was 2 mL in all the examined studies. Length of follow-up ranged from 12 to 52 weeks in both RCTs and cohort studies. None of the studies focused on the eventual structural effects exerted by HA nor reported severe adverse effects due to the IA injection.

Temporomandibular joint. Twenty-four articles reporting the effects of six HA-based products commercialized in Italy were found (see Table 6).[97–120] Such studies included 6 RCTs and 18 cohort studies. The RCTs reported the use of HA on a total of 271 patients, while cohort studies reported the use of HA on a total of 579 patients. All included studies reported blind injections without image guidance.

Of the seven studies reporting on the use of Artz®, six studies were performed by Sato et al.[97–102]; five case–control studies and one retrospective cohort study were conducted by administering five weekly injections. The seventh trial on the use of Artz, by Hirota,[103] was a prospective randomized study performed with two IA injections at two weeks interval. Other seven studies tested Hyalgan® in temporomandibular joint (TMJ) disorders: four RCTs, two observational clinical trials, and one case series.[104–110] Its efficacy was compared with Sinovial in one study and with Synvisc and corticosteroid in another study[109,110]; in all seven studies, patients received five weekly injections. As of Orthovisc®, two RCTs plus one controlled clinical trial reported on its efficacy in TMJ disorders; two injections at two weeks interval in the study by Alpaslan et al.[111], only one injection in the study by Alpaslan and Alpaslan,[112] and injected twice, once a week, in the study by Hepguler et al.[113] One randomized prospective study tested the three injections of Ostenil® at weekly interval,[114] while

Table 5. Studies reporting efficacy and safety profiles of branded hyaluronic acids in ankle OA in Italy.

AUTHOR, YEAR	PRODUCT	PAT.N.	FOLLOWUP (WEEKS)	COMPARATOR	INJECTION COURSES	IMAGE GUIDANCE	PRIMARY ENDPOINT	SAEs
Salk, 2006	Hyalgan®	17	24	Saline	5 weekly	None	AOS	None
Sun, 2006	Supartz®	75	24	None	5 weekly	None	AOS, AOFAS, ROM, Patients satisfaction, Rescue medication	None
Cohen, 2008	Hyalgan®	28	12	Saline	5 weekly	FL	AOS	None
Karatosun, 2008	Adant®	30	52	Exercise Therapy	3 weekly	None	AOFAS score, VAS pain	None
Carpenter, 2008	Synvisc® + Ankle Arthroscopy	26	NR	Ankle Arthroscopy	3 weekly	None	PAIN SCORE 10-point scale	None
Luciani, 2008	Synvisc®	21	72	None	3 weekly	None	AOS	None
Witteveen, 2008	Synvisc®	55	12	None	1 or 2, 3 months distance	None	Pain VAS Score	None
Mei-Dan, 2008	Euflexxa®	15	26	None	3 weekly	None	AOFAS	None
DeGroot, 2012	Supartz®	56	12	Saline	1	FL	AOFAS	None
Lucas y Hernandez, 2013	Synvisc®	18	52	None	3 every 2 weeks	FL	AOFAS	None

Abbreviations: FL, Fluoroscopy; SAEs, Serious Adverse Events.

Table 6. Studies reporting on efficacy and safety profiles of branded hyaluronic acid in tempuromandibular joint pathologies in Italy.

AUTHOR, YEAR	PRODUCT	PAT.N.	FOLLOWUP (WEEKS)	COMPARATOR	INJECTION COURSES	IMAGE GUIDANCE	PRIMARY OUTCOME	SAEs
Sato, 1997	Supartz®	26	NR	None	1	NR	MMO, tenderness of the TMJ and the masticatory muscles	NR
Hirota, 1998	Supartz®	15	NR	None	2 every 2 weeks	NR	Clinical assessment, MMO, Analysis of the synovial fluid	NR
Sato, 1999	Supartz®	21	52	None	1	NR	MRI, Clinical signs and symptoms	NR
Sato, 2001	Supartz®	60	104	None	1	NR	MMO, Protrusion	NR
Sato, 2002	Supartz®	20	76	None	NR	NR	EMG + Clinical Assessment	NR
Sato , 2003	Supartz®	20	76	None	NR	NR	Mandibular kinesiography, masticatory efficiency test	NR
Sato, 2006	Supartz®	55	More than 104	None	NR	NR	Transcranial X-Ray, panoramic jaw tomograms, Clinical findings	NR
Guarda-Nardini, 2002	Hyalgan®	10	24	None	5 weekly	NR	MMO, pain, masticatory efficiency	NR
Guarda-Nardini, 2005	Hyalgan®	20	24	None	5 weekly	NR	MMO, pain VAS, mastication efficiency, function, subjective evaluation	NR
Guarda-Nardini, 2007	Hyalgan®	25	52	None	5 weekly	NR	Pain, masticatory efficiency, MMO	NR
Guarda-Nardini, 2010	Hyalgan®	31	12	None	5 weekly	NR	Pain, functional limitation, ROM	NR
Guarda-Nardini, 2012	Hyalgan®	80	24	None	5 weekly	NR	Pain, Subjective chewing efficiency, Five-point Likert-type scale for Treatment tolerability and effectiveness, MMO	NR
Guarda-Nardini, 2012	Hyalgan®	40	12	Sinovial®	NR	NR	Pain VAS, Chewing efficiency VAS, Likert-type scale, MMO	NR
Manfredini, 2012	Hyalgan®/ Synvisc®/CS	72	12	AC VS AC plus CS VS AC plus LMW HA VS AC plus HMW HA	5 weekly	NR	Pain VAS, Chewing efficiency, Likert-type scale, MMO	NR
Alpaslan, 2000	Orthovisc®	25	2	None	2, every 2 weeks	NR	Facial diagram and VAS	NR
Alpaslan, 2001	Orthovisc®	41	104	None	2, every 2 weeks	NR	Pain, jaw function, clicking sounds , MMO	NR
Hepguler, 2002	Orthovisc®	38	24	Saline	2, every week	NR	Pain and sound intensity, Helkimo's index, joint vibration	NR
Basterzi, 2009	Ostenil®	33	52	None	3 weekly	NR	Pain, joint sounds, MMO	NR
Oliveras-Moreno, 2008	Ostenil mini®	41	12	Methocarbamol + paracetamol	1	NR	Pain, 100-point questionnaire	NR
Morey-Mas, 2010	Ostenil mini®	40	12	None	1	NR	Pain and TMJ function, MMO, clicking and sounds	NR
McCain JP, 1989	Synvisc®	55	NR	None	1	NR	Subjective evaluation, complications, surgeon's evaluation	NR
Yeung, 2006	Synvisc®	2	NR	None	1	MRI	MMO, lateral excursion, Pain, joint clicking	NR
Bjørnland, 2007	Synvisc®	40	24	Celestone	2, every 2 weeks	NR	Pain, joint sounds, mandibular function	NR
Møystad, 2008	Synvisc®	40	24	Corticosteroid	2, every 2 weeks	NR	Numeric CT score	NR

Abbreviations: MMO, Maximal Mouth Opening; LMW, Low molecular weight; HMW, High molecular weight; CS, corticosteroids; SAEs, Serious Adverse Events; AC, arthrocentesis; HA, hyaluronic acid; VS, versus.

Table 7. Studies reporting on efficacy and safety profiles of branded hyaluronic acids in vertebral facets joints osteoarthritis in Italy.

AUTHOR, YEAR	BRANDED HA	N. OF PATIENTS	FOLLOWUP (WEEKS)	COMPARATOR	INJECTION COURSES	IMAGE GUIDANCE	PRIMARY OUTCOMES	SAEs
Fuchs, 2005	Ostenil mini	60	24	TC	NR	CT	Pain, RMQ, ODQ, LBOS, SF-36	NR
DePalma, 2011	Synvisc	15	52	none	2, 10 days apart	FL	Pain VAS, ODI, SF-36, FTF distance, analgesic usage, patient satisfaction	none

Abbreviations: RMQ, Roland Morris Questionnaire; ODQ, Oswestry Disability Questionnaire; LBOS, Low Back Outcome Score; SF36, Short Form 36 questionnaire; ODI, Oswestry Disability index; FTF, finger to floor; FL, fluoroscopy; CT, Computerized Tomography; SAEs, Serious Adverse Events; TC, Triamcinolone.

two RCTs examined the single injection of Ostenil Mini® in TMJ.[115,116] Synvisc® TMJ injection was evaluated in four studies, three RCTs, and one prospective observational study with a single injection in one study,[117] and two injections two weeks apart in the other three studies.[118–120] Length of follow-up was varying, ranging from 12 to 24 weeks for RCTs and 2 to over 104 weeks for cohort studies.

None of the studies focused on the structural effects exerted by HA, and none of the studies reported serious adverse events caused by IA injection of HA.

Vertebral facets. Eleven studies reporting on the use of HA products in facet joints (FJs) were identified, of which only two studies reported on HA products commercialized in Italy: Ostenil mini® and Synvisc®,[121,122] whose efficacy profiles were examined by a RCT and a cohort study Table 7. Both studies used image guidance for the IA injection, with one study using fluoroscopy and the other using computerized tomography.

Fuchs et al.[121] demonstrated that Ostenil® mini injection of FJ in patients with chronic nonradicular pain in the lumbar spine was able to markedly reduce pain and improve both function and quality of life, with greater benefits in the long term compared with a course of IA glucocorticoids injections, on a total of 60 patients. The other study by DePalma et al, testing Synvisc® efficacy in 2011 on a total of 15 patients,[122] revealed that viscosupplementation for lumbar FJ arthropathy with Synvisc was associated with modest efficacy that predominately lasted up to six months. Length of follow-up varied from 24 (cohort study) to 52 weeks (RCT). None of the studies reported on the eventual structural effects exerted by HA nor reported serious adverse events after HA IA injection.

Carpometacarpal joint. A total of 10 papers, including 6 RCTs and 4 cohort studies, were identified (see Table 8).[123–132] RCTs reported on the IA use of Ostenil mini, Orthovisc, Sinovial mini, Synvisc, and Ostenil on a total of 283 patients,

Table 8. Studies reporting on the efficacy and safety profiles of braded hyaluronic acids in carpo-metacarpal joint osteoarthritis in Italy.

AUTHOR, YEAR	BRANDED HA	PAT.N.	FOLLOWUP (WEEKS)	COMPARATOR	INJECTION COURSES	PRIMARY OUTCOMES	IMAGE GUIDANCE	SAEs
Fuchs, 2006	Ostenil mini®	56	26	TC	3 weekly	Pain, swelling, grip power, range of motion	NR	NR
Stahl, 2005	Orthovisc®	52	24	MP	1	Pain, grip, pinch strength	NR	NR
Roux, 2007	Sinovial mini®	42	12	1 vs 2 vs 3 injections	1, 2, or 3 weekly	Pain, Dreiser functional index	NR	NR
Heyworth, 2008	Synvisc®	60	26	Steroids, saline	3 weekly	Pain, strength measures, DASH scores, ROM	NR	NR
Figen Ayhan, 2009	Synvisc®	33	24	Saline	1	Pain, pinch strenght, Dreiser Scores	NR	NR
Bahadir, 2009	Ostenil®	40	52	TC	1	Pain, pinch strength, grip strength, Duruoz hand index	NR	NR
Mandl, 2009	Synvisc®	32	26	None	3 weekly	Pain, DASH score, key strength, opposition pinch strength	NR	NR
Klauser, 2012	Hyalgan®	33	4	None	4 weekly	Pain, ultrasound thickening, PDUS-score	NR	NR
Ingegnoli, 2011	Hyalubrix®	16	24	None	3 weekly	Pain, Dreiser index, PDUS score	Ultrasound	NR
Frizziero, 2014	Hyalgan®	58	24	None	3 weekly	Pain, NSAID intake, ab-/adduction, pinch strength	NR	None

Abbreviations: ROM, Range of motion; SAEs, Serious Adverse Events; TC, Triamcinolone; MP, Metylprednisolone.

while cohort studies reported on the use of Synvisc, Hyalgan, and Hyalubrix on a total of 139 patients. The RCTs on Ostenil, Ostenil mini, and Orthovisc compared the results of HAs versus steroids, the RCTs on Synvisc reported on the comparison versus saline and/or steroids, and the RCT on Sinovial mini reported on the use of different injection courses. Injection courses ranged from one single injection to four weekly injections, with five studies administering HA by three weekly injections, three studies administering HA by a single injection, and one study administering HA by four weekly injections. Seven studies were characterized by a follow-up length of 24–26 weeks, one study had a follow-up length of 52 weeks, one study had a follow-up length of 12 weeks, and one study had a follow-up length of only 4 weeks. Image guidance was reported in only one study, by Ingegnoli et al.[131], that performed all injections under ultrasound guidance, while all other studies used no image guidance to perform IA injections. None of the studies focused on the eventual structural effects exerted by HA, and none of the studies reported severe adverse events related to the IA HA injection.

Discussion

Knee. RCTs on the use of HAs marketed in Italy involve only nine products. This is particularly interesting, as 30 of 62 HA products marketed in Italy report to be indicated for IA use in knee OA, while only Hyalgan, Supartz, Synvisc, Orthovisc, Sinovial, Hyalubrix, Go-On, Adant, and Ostenil proved their efficacy by a RCT. The use of HA in knee OA is worldwide diffused. This lack of data emphasizes the necessity of performing more studies in order to establish not only efficacy and safety profiles of HA with respect to placebo or other compounds suitable for IA injection but also to show specific differences between various brands of HAs marketed in Italy. HAs may differ in several aspects, such as molecular weight, concentration, molecular structure, and combination with other substances, thus making the panorama of possible therapeutic agents for IA use heterogeneous. Such heterogeneity, that could be relevant in order to better treat subgroups of patients, needs to be defined in terms of efficacy, safety, indication, and dosing regimen, but this objective is still far from being achieved. Assessing eventual differences could grant the possibility of treating with a more suited therapy different phenotypes of patients who may respond better to certain HAs. In our opinion, this lack of data is in part due to the fact that HAs are registered, in the majority of cases, as medical devices, thus needing low level of evidence studies to obtain registration and approval for marketing.

Another important issue to be considered is dosing regimens. All RCTs on Synvisc used a dosing regimen of three weekly injections of Synvisc, except for the study by Chevalier et al.[20], where a single injection of 6 mL of Synvisc (Synvisc-One) proved to be as effective and safe as other dosing regimens. Also, despite the different molecular weights and compositions, all RCTs on Hyalubriux, Orthovisc, Sinovial, Go-On, Adant, and Ostenil used a dosing regimen of three weekly injections, while all RCTs on Supartz used a dosing regimen of five weekly injections. Only for Hyalgan, dosing regimens varied between three and five weekly injections. There is a lack of data about any specific indication or about efficacy and safety profiles for different adoptable regimens. In addition, the question about the appropriateness of the dosing regimen recommended in the package insert remains unclear for the brands without studies. For all products that have no studies published so far, it remains unclear how an appropriate dosage can be suggested in the leaflet.

Considering image guidance, none of the reported studies used any kind of image guidance or assistance to perform IA injections. Image guidance may represent the proof of the correct placement of the compounds introduced in IA space, thus granting the link between the observed effect and the substance injected. In our opinion, especially in RCTs, image guidance may play a relevant role and should be used at least in certain cases.

In all the RCTs examined, safety profiles were excellent, with no severe adverse events observed at the adopted dosing regimens. Concerns on the safety of HA were raised in the international guidelines on the management of knee OA, but data reported in RCTs gathered in this study seem to contradict these concerns.

Only four studies reporting the structural effects exerted by HA were performed in knee OA. Three studies demonstrated protective effects of Hyalgan and Synvisc on cartilage degradation, while another study focused on the possible role of PBSC, but such data are still scarce and do not allow conclusive statements.

Hip. Of the total 23 studies identified, 8 RCTs and 15 cohort studies have investigated VS in hip OA. Interestingly, it was reported that 21 of 23 studies were performed under image guidance (ultrasound or fluoroscopic), thus making clear that the majority of authors preferred to administer IA drugs in hip joint using image guidance. Of the 62 HAs marketed in Italy for IA use, only 9 products have studies that reported to be efficacious and safe in patients affected by hip OA in scientific studies (Adant, Durolane, Hyalgan, Hyalone, Jointex, Ostenil, Synocrom, Synolis V-A, and Synvisc). Oddly, of such nine products, only six (Durolane, Hyalubrix/Hyalone, Ostenil, Synocrom, Synolis V-A, and Synvisc) report on their instructions for use to be indicated for hip IA injection. On the contrary, there are several products, such as Coxarthrum, Fermathron, Kartilage, and Viscoplus, all marketed in Italy, that are reported as specifically indicated for hip joint in their leaflet, although having no evidences in scientific literature on their use in hip OA.

Shoulder. Only 7 of the 62 HA products marketed in Italy for IA use have evidences in scientific literature on their use in the shoulder (Hyalgan, Hyruan plus, Orthovisc, Ostenil, SportVis, Supartz, and Synvisc), and of these 7 products, only 3 products (Synvisc, Orthovisc in the Orthovisc mini

formulation, and Ostenil) report on their leaflet to be indicated for IA use in the shoulder. On the contrary, there are several products that report to be indicated for shoulder IA injections, but have no evidence on their use (Fermathron S, Go-On, Kartilage and Kartilage cross, Synocrom, and Viscoplus). Of the 24 included studies, 3 studies were performed before the year 2000, 8 studies were performed between 2000 and 2009, and 13 studies were performed in the last five years, showing an increase in the interest for this kind of therapy over time. Furthermore, it was reported that the majority of studies involved less than 100 patients, with only 6 studies involving over 100 patients and 1study involving over 500 patients, although the study by Blaine et al included the patients affected by shoulder pain caused by different pathologies. Also, HA was used for different pathologies causing shoulder pain (shoulder OA, adhesive capsulitis, rotator cuff tears, frozen shoulder, tendinosis and tendinitis of supraspinatus, and shoulder impingement), thus making results heterogeneous and unlikely to understand the correct clinical indication. Follow-up time was short for a large number of studies, with only three studies having a follow-up time of over six months. Dosing regimens still represent areas open for discussion, as many branded HAs have no data on this and no international validation was reached for the doses and the number of injections to be performed, although all studies injected 2 mL of various HAs for each injection. Interestingly, of the seven products having scientific evidences about their use in shoulder pathologies, only three products (Orthovisc, Ostenil, and Synvisc) report that the HA is indicated for shoulder in their leaflet. On the contrary, there are several products marketed in Italy for IA use, such as Fermathron, Go-On, Kartilage, Synocrom, Synolis V-A, and Viscoplus, that report on their leaflet to be indicated for shoulder but have no evidence in scientific literature.

Ankle. Only 10 studies on the use of various HAs may be found in scientific literature on ankle viscosupplementation. Of the 62 HAs merchandised in Italy for IA use, only 5 HAs have evidences on their use in ankle OA, and only 3 products (Adant, Hyalgan, and Supartz) were tested by RCT, while Synvisc and Euflexxa have data from cohort studies. Interestingly, of the five abovementioned HAs, only Synvisc is indicated for IA use in ankle joint in its leaflet. On the contrary, Durolane SJ, Fermathron, Kartilage, Orthovisc mini, Ostenil, Synocrom, and Synolis V-A report on their leaflet to be indicated for IA use in ankle joint, although no scientific evidence is present in literature to confirm this indication. The potential for treating ankle OA of the joint by viscosupplementation has been reported by all the studies mentioned; however, no dosing studies have been published till date, and dosing and administration regimens in ankle joint remain an area open for discussion, as there is no international validation of a therapeutic protocol for this joint as well. All studies examined in the present work report on the use of a volume of a single vial of HA with 2 mL of compound injected, but such data remain inconclusive. Moreover, the use of image guidance was reported for only three studies, and interestingly, no studies performed IA injection under ultrasound guidance.

Temporomandibular joint. Data about the use of HA in TMJ pathologies cover only a small portion of HAs marketed in Italy. HAs having scientific evidence about their use in TMJ are Supartz, Hyalgan, Orthovisc, Ostenil, Ostenil mini, and Synvisc. Interestingly, of these six HAs, only Ostenil mini and Orthovisc report in their leaflet to be indicated for TMJ, while other HAs do not report such indication. On the contrary, there are HAs that are indicated in their leaflet for IA use in TMJ (Go-On mini, Intragel mini, Jointex mini, Rhizarthrum, Sinovial mini, Synocrom, Yaral mini, and Viscoplus), although having no scientific evidences on their use in this joint. Dosing regimens that were used ranged from one to five weekly injections, stressing the fact that also for this joint a standardization of IA therapy in terms of dosage and dosing regimens is still far to be reached. Moreover, establishing the exact volume of compounds to inject is of particular relevance in small joints such as this, where bigger volumes may stress joint capsule or even damage it.

Vertebral facets. Evidences on the use of HA in Vertebtal Facets joints (VFn) and their pathologies are extremely limited. Only 2 of the 62 products marketed in Italy as HA for IA use have been tested and reported in scientific literature. Ostenil mini seemed to prove better than steroids in pain relief and function, while Synvisc, studied without comparator, exerted modest effects that seemed to last for six months. Of these two HAs, only Ostenil mini is indicated for use in VFs, while this indication is not reported in the leaflet for Synvisc. On the contrary, Viscoplus and Go-On mini are indicated for use in *spine* in their leaflet, but no scientific evidence can up to now support this indication. Both studies used image guidance for the IA injection, being it computerized tomography or fluoroscopy, thus stressing the relevance of image guidance in performing such a difficult IA injection. Interestingly, none of the three HAs, reporting in their leaflet to be indicated in spine joint pathologies, report about the need of an image guidance for performing this kind of IA injection. Moreover, even the diagnosis of FJ OA is difficult and often underestimated in its prevalence and in its relevance in generating complicated clinical features. Further research in this field is required not only to assess clear dosing regimens, as for other joints, but the efficacy and safety profiles of HA also seem to remain unclear, in order to define the role of VS in the patients affected by VFs' OA.

Carpometacarpal joint. Six RCTs and four cohort studies were identified. RCTs reported on the comparison of five HAs (Sinovial mini, Ostenil mini, Ostenil, Synvisc, and Orthovisc) with saline solution or steroids, while cohort studies reported the use of Synvisc, Hyalgan, and Hyalubrix. Of such HAs, only Ostenil mini and Sinovial mini report on their leaflet to be indicated for use in CMC joint, while some of the HAs marketed in Italy report such indication without having any evidence in scientific literature to support it (Rhizarthrum, Durolane SJ, Go-On mini, Intragel mini, Jointex mini, Orthovisc mini, various forms of Synocrom, and

Yaral mini). Only one study reported that IA injections were performed under ultrasound guidance, while other studies did not report any image guidance or assistance; similar to what was reported for other joints, image guidance may play a fundamental role in the assessment of efficacy and safety profiles, especially in RCTs, as it guarantees the certainty of having the compound properly positioned within the joint, giving the possibility of a correct interpretation of the data. Dosing regimens varied from one to four weekly injections of 2 mL of HA, independent of the length of follow-up, and this still represents a need for further discussion and analysis, as a standardization of therapeutic processes especially for the volume to be introduced, based on the use of IA HA, is missing for this joint as well.

Conclusion

After reviewing the data regarding the use of branded HAs marketed in Italy for IA use, it is clear that there are only a few products with some evidences and the majority of products remain without evidences on their use. Since most of the HAs for IA use are classified as medical devices, regulatory rules are less rigid, thus needing low level of evidence studies. Clinicians and regulators should request postmarketing studies from pharmaceuticals producing HAs for IA use not only to corroborate with that reported in the leaflet but also to add evidence to the eventual differences in indications, efficacy, and safety profiles of each product and to adequately support their use in clinical practice.

It is easy to assume that this lack of data in the scientific literature with respect to that reported in the package insert for the HA products can be observed in other countries, making it even more urgent for the production of further data.

Author Contributions

Conceived and designed the experiments: AM, CF. Analyzed the data: EB, ODL, ADS, AMahmoud, MB, ST. Wrote the first draft of the manuscript: EB, ODL, ADS, AMahmoud. Contributed to the writing of the manuscript: MB, ST. Agree with manuscript results and conclusions: AM, EB, ADS, ODL, AMahmoud, MB, ST, CF. Jointly developed the structure and arguments for the paper: AM, EB. Made critical revisions and approved final version: AM, EB, ODL, ADS, AMahmoud, MB, CF, ST. All authors reviewed and approved of the final manuscript.

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