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Cost effectiveness of intra-articular hyaluronic acid and disease modifying drugs in knee osteoarthritis

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Running title: Cost-effectiveness in knee osteoarthritis

Abstract (239 words)

Background: The place of disease modifying osteoarthritis drugs and intra-articular hyaluronic acid in the therapeutic arsenal of knee osteoarthritis remains uncertain. Indeed, these treatments have demonstrated symptomatic efficacy but no efficacy for disease modification.

Objective: This report reviews the cost effectiveness of intra-articular hyaluronic acid (IAHA) and disease modifying osteoarthritis drugs (DMOADs) used in the treatment of knee osteoarthritis.

Methods: A systematic literature search of MEDLINE, Scopus, EMBASE and Cochrane databases for articles was performed independently by 2 rheumatologists who used the same predefined eligible criteria. Papers without abstracts and in languages other than English or French were excluded. Extracted costs were annualized and converted to 2015 euros (€) by using the Consumer Price Index of the relevant countries and the 2013 Purchasing Power Parities between these countries and the European Union average.

Results: A total of 95 abstracts were selected, and 13 articles were considered for the review. Nine articles were on IAHA and 4 articles on DMOADs. Only one article directly compared different IAHA compound. Articles showed substantial heterogeneity in methodological approaches. The incremental cost-effectiveness ratios (ICER) ranged from 4,000 to 57,550€ and from 240 to 53,225€ per QALY gained for DMOADs and IAHA respectively.

Conclusions:

This review highlights substantial heterogeneity between studies, ranging from cost saving (or dominating) position to very high ICERs, far above the acceptability threshold of 50,000 €/QALY. Additional research is needed to display reliable and robust ICER estimates for knee OA therapies.

Keywords: Osteoarthritis, Cost-effectiveness, Hip, Knee, Systematic review

Word count: 2222

Key points

- The position of disease modifying osteoarthritis drugs (DMOADs) and intra-articular hyaluronic acid (IAHA) in the therapeutic arsenal of knee osteoarthritis remains debated.
- This review highlights substantial heterogeneity: a multiplication factor of 14-fold (DMOADs) and 175-fold (IAHA) between the lowest and highest ICER estimate.
- Additional research is needed to display reliable and robust ICERs for these knee osteoarthritis therapies.

Introduction

Osteoarthritis is the most frequent or prevalent chronic joint disease and a major contributor to functional disability and loss of autonomy in older adults [1]. OA has become a research priority in the European Community (Horizon 2020 Framework Programme) [3]. Hip and knee OA causes the greatest burden to the population in terms of pain, stiffness and disability, thereby leading to the need for prosthetic joint replacement for the most severe cases [4]. The burden to society is expected to be high because of the prevalence of symptomatic knee OA (prevalence of 10% to 20%) [5–11].

According to the OA Research Society International, disease management of knee OA included non-pharmacological treatment (weight management, exercise, strength training) and pharmacological treatment (NSAIDs, acetaminophen, duloxetine and intra-articular corticosteroids) [12]. These treatments mainly aim at alleviating symptoms improve functional capacity and potentially postpone the time for prosthesis surgery. Other therapies exist to treat the symptoms of knee OA patients such as disease modifying osteoarthritis drugs (DMOADs) and intra-articular hyaluronic acid (IAHA). However, their position in the therapeutic arsenal remains debated [12–14]. Indeed, these treatments have demonstrated some symptomatic efficacy but no real efficacy for disease modification [12].

For the therapies with significant health benefit but additional cost to the health system, cost-effectiveness evaluation are needed to provide valuable information to clinicians and decision makers about whether the provision of the treatment is an efficient and fair way to allocate resources – unavoidably limited – for the overall improvement of population health. We aimed to review the cost-effectiveness analyses of DMOADs and IAHA for knee OA

Methods

Research question and literature search

We performed a systematic search of articles in, MEDLINE via PubMed, Scopus, EMBASE and Cochrane databases across the period from 1966 to May 2018. We used the Participants, Interventions, Comparisons and Outcomes (PICO) strategy for the research question as follows: population, knee OA; intervention, IAHA or DMOADs; control, others treatments and no treatment OA; and outcome, incremental cost per QALY gained [15]. The algorithm used to search article titles, abstracts and key words were ("Osteoarthritis"[Mesh]) AND

"Cost-Benefit Analysis"[Mesh]) for MEDLINE, (Cost-Effectiveness AND Osteoarthritis) for Scopus, (Cost-Effectiveness AND Knee Osteoarthritis) for EMBASE and (Cost AND Osteoarthritis) for the Cochrane database.

Article selection

The titles and abstracts of all articles identified were independently screened by 2 rheumatologists (JHS and IL) who used predefined criteria to identify relevant articles; disagreements were resolved by consensus. Abstracts were excluded if 1) data focused on NSAIDs, analgesics, non-pharmacological treatment or surgical procedures, 2) no cost-effectiveness data were reported, 3) no primary data were reported (e.g., literature review), 5) abstracts from conferences, symposia or scientific meetings were not considered (Figure 1). The full texts of the remaining articles were then retrieved. We excluded articles that had insufficient, imprecise or incomplete data (e.g., indirect costs only, lack of direct cost breakdown) and uncontrolled before-after studies. We used the Cochrane Collaboration tool for the assessment of risk of bias [16] to evaluate the quality of the RCT studies included in this systematic review according to the level of bias risk (supplemental data).

Data extraction

Data extracted were the following: study parameters, i.e., type of model, sample size, country of the study and sponsor (academic or pharma industry); treatment characteristics, i.e., International Nonproprietary Names (INN), commercial name to differentiate compounds with the same INN (IAHA), dosage, duration; clinical outcomes, i.e., pain based on visual analogue scale (VAS), function based on Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [17] or SF-12 Health Survey [18] and health gain based on Health Utilities Index 3 (HUI 3) [19,20] or EQ-5D Instruments [21] and expressed in quality-adjusted life years (QALY).

Treatment costs were extracted from articles that described assessing them from a payer or societal perspective. In addition, Incremental cost-effectiveness ratios (ICER) were included when available. This ratio relates the difference in costs between a medicine and the comparator to the difference in outcomes. There were valued as the cost per QALY gained. Extracted or elicited costs were converted to an annual cost and to 2017 euros (€) by using the Consumer Price Index of the relevant countries and the 2017 Purchasing Power Parities (Organization for Economic Cooperation and Development, www.oecd.org) between these countries [22].

Results

Literature search

We obtained 95 article titles with abstracts through the meta-search, and 20 abstracts were selected. The assessment of full texts resulted in 13 articles selected for the review (Figure 1): four concerned DMOADs and nine IAHA [23–35]. Two articles were excluded because of their design : that was observational multicentre non controlled before-after studies [36,37]. One non randomized case control study was included since the two study groups were comparable as baseline in turn of (age, sex, WOMAC, quality of life, Radiological stage) [35].

Selected studies

The 13 articles were heterogeneous (Table 1). Study design were model simulation of knee OA (n=4) [26,28,30,31], randomized clinical trial (n=8) [23–25,27,29,32–34] or case control study (n=1) [35]. Sample sizes varied from 37 to 1,000. Control group were usual care (n=8) [23,26,27,30–34] or imposed care (n=5) [24,25,28,29,35]. Different perspectives have been used to evaluate costs: perspective was societal (n=6) [23,27–29,31,33] or payer (n=7) [24–26,30,32,34,35]. Studies were conducted in Europe (n=5) [23,25,33–35], North America (n=4), South America (n=1) [31] [26,27,30,32], Asia (n=2) [28,29] and multi-continental study (n=1) [24]. Periods of publication were 1995-2000 (n=2), 2000-2005 (n=2), 2005-2010 (n=3), and after 2010 (n=6). Treatment characteristics were not specified in one study [26]. Because of substantial heterogeneity, no pooling was possible and only descriptive results could be presented. The quality of RCT studies was evaluated according to the level of bias risk (supplemental data).

Patient characteristics

All articles described symptomatic OA patients. Most studies included OA patients based on ACR criteria [38,39], with radiographic criteria. Twelve articles included only knee OA patients and 1 article included knee and hip OA patients. The median patient follow-up in trial based studies was 9 months (interquartile range [IQR] 6–12). The mean age was reported in all studies: mean 64 ± 5 years (median 63, IQR 62–66).

Cost-effectiveness estimates for DMOADs (Table 2)

The variation in cost between the treatment group and the control group varies between 10 € and 2,300 €. The variation in incremental effectiveness between the treatment group and the control group varies between 0.01 and 0.025 QALY. ICERs varies between 4,000 to 57,550€ per QALY gained [25,26]. In RCT studies, ICERs

was 4,000€ per QALY gained [25]. In simulation model studies, ICERs was 57550€ per QALY gained [26]. Two studies had a negative ICER [23,25], in both cases it was dominant (less expensive and more effective).

Cost-effectiveness estimates for IAHA (Table 2)

The variation in cost between the treatment group and the control group varies between 0€ and 955€. The variation in incremental effectiveness between the treatment group and the control group varies between 0.0031 and 0.115 QALY. ICERs varies between 240 to 53,225€ per QALY gained. Among academic studies, ICERs yielded a broader range of ICERs, from 10,195 to 53,225€ [27–29,33], compared to industry-sponsored studies, with values from 240 to 39,375€ per QALY gained [30–32,34,35]. The ICER estimates also varied with the model time frame. For studies with 6 months follow-up, ICERs ranged from 240 to 53,225€ per QALY gained. For studies with 12 months follow-up, ICERs ranged between 10,195 to 39,375€ per QALY gained. Only one lifetime modeling beyond the trials were performed, allowing the integration of the possible long term benefits of the treatments [31]. In RCT studies, ICERs varies between 4,390 to 13,450€ per QALY gained [27,29,32–34]. In simulation model study, ICERs varies between 305 to 53,225€ per QALY gained [28,30,31]. For the studies using “usual care” (NSAID, physiotherapy and paracetamol) as control treatment, ICER ranged from 4,390 to 39,375€ per QALY gained [27,30–34]. For studies with payers perspective, ICERs ranged between 240 to 39,375€ per QALY gained [30,32,34,35]. For studies with societal perspective, ICERs ranged between 305 to 53,225€ per QALY gained [27–29,31,33]. One study had a negative ICER with a dominance (less expensive and more effective) [29].

Discussion

We performed a systematic review of the literature of cost-effectiveness analysis of DMOADs and IAHA in knee OA. Depending on the type of study (trial-based or model-based), the control group and the duration of follow-up, OA articles reported different ICER estimates, with a multiplication factor of 14-fold (DMOADs) and 222-fold (IAHA) between the lowest and highest ICER estimate.

Several sources of heterogeneity could be mentioned and taken into account when interpreting the results of this review. The sample size of the trial: The economic appraisal should be factored into sample size calculations. However, it is common for the sample size of the trial, to be based on primary clinical outcomes alone. As a consequence, the economic comparisons can be underpowered [40,41]. There was also an issue with time horizon. The median patient follow-up was short. Indeed, clinical trials rarely extend beyond a few years and are

often conducted over much shorter periods [40,41]. Yet, OA is a chronic disease, a lifetime horizon is most often appropriate and some long term benefits of the treatments, e.g. reduction in joint prosthesis need, were not estimated [42]. A third source of heterogeneity was the nature of the control group – placebo versus usual care – may maximize the incremental cost-effectiveness due to the higher effect size of the intervention compared to the placebo (PMID : 20228282)[43]. Fourthly, the perspective may differ between the studies. In cost-benefit analysis, societal perspective should be the preferred method over the health care or payer perspective. A cost-benefit analysis accounting for all the societal benefits and costs enable more reliable and transparent decisions taken by policy-makers, especially in chronic diseases in which patients, family members and caregivers are often largely impacted [44]. Conversely NICE recommends the use of the payer perspective, i.e., the perspective of the National Health Service and personal and social services', focusing on direct costs and avoiding potential biases against non at-work people in the indirect cost elicitation [45].

Finally, the impact of the study sponsor should be mentioned. The primary objectives of research and development clearly differ between industry and academics [46]. The two types of research should not be opposed, but should take the form of a constructive collaboration, increasing the chances of reaching each individual goal [47]. In our review, all ICER estimates of industry-sponsored studies fell within the “acceptable” ICER range (0 to 50,000 €/QALY), although those from academic studies did not always.

No DMOADs cost-effectiveness studies were identified in the published literature. A model to assess cost-effectiveness was constructed using cohort simulation for glucosamine [48], resulting in a dominant position for this agent. This estimate was particularly dependent on the magnitude of the quality of life gain and clearly lacks of robustness (48). The cost effectiveness of IAHA has been studied in a limited number of review articles which suggest that IAHA may be cost effective compared with usual care [49–51]. The only 3 reviews included two, 1 and 10 articles respectively. The present study brings additional and more comprehensive information, including six recent articles not included in previous metaanalysis and providing more robust conclusions [29–33,35].

OA definition is also a quite challenging field for such research. There is a lack of consensus for OA definition. Variable definitions of knee OA can be used – clinical, radiological or both [52,53]. Actually, from a public health perspective, a diagnosis based on both clinical and radiological features is recommended [52]. In addition, some authors recently suggested separating OA by phenotypes, reflecting different risk factors, comorbidities and potentially pathogenic pathways [54,55]. Comorbidities such as obesity are closely related with knee OA [56]. These data were not systematically collected in clinical trials, and usually not collected or analyzed in

administrative databases which could be an alternative source of data for economic modelling. In the present work, we could not assess this new “view” of OA because the reviewed articles did not provide enough details on medical history or comorbidities. However, integrating these phenotypic specificities in future epidemiological and economic analyses will be interesting; such phenotypes could have substantial impact on Quality Adjusted Life Year, thereby resulting in major differences in cost estimates.

Finally, there is a lack consensus for economic modelization up to recent years [42,57]. Recently, a reference case for economic assessment in osteoarthritis was proposed[42], but never implemented since then. In addition, there is a need for cost-effectiveness threshold to state whether the health benefits are worth the financial investment because the additional resources required are not available to fund other effective treatments. This cost-effectiveness threshold will vary from country to country. [26] : in the UK values of £20,000–30,000/QALY (approximately 50,000 €/QALY) are typically used, although it is 80,000 €/QALY in The Netherlands [58]. However, there is a lack of understanding about what thresholds mean and their implications [59][60–62].

Conclusion

In conclusion, the results of this systematic literature review indicate there is substantial uncertainty for DMOADs and IAHA ICER estimates due to heterogeneity of studies. ICER of industry-sponsored studies are clearly favorable than those of academic studies. For this reason, it appears difficult to conclude that these treatments are cost-effective in the management of osteoarthritis of the knee with the commonly accepted thresholds. Additional research is needed to display reliable and robust ICER estimates for knee OA therapies.

Data Availability Statement: Authors can confirm that all relevant data are included in the article and/or its supplementary information files

Competing interests: Author disclosures of honoraria for advice or public speaking, grants received and/or advisory board participation are as follows:

JHS: Jean Hugues Salmon has received consultancy fees from Abbvie, BMS, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, UCB

ACR:None

ICL: Isabelle Charlot-Lambrecht has received consultancy fees from Amgen, MSD

JPE: Jean Paul Eschard has received consultancy fees from Abbvie, BMS, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, Sanofi, UCB

DJ: None

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Conflict of interest:

Bruno Fautrel has received research grants from AbbVie, Lilly, MSD and Pfizer, and consultancy fees from AbbVie, Biogen, BMS, Celgene, Janssen, Lilly, Medac, MSD, NORDIC Pharma, Novartis, Pfizer, Roche, Sanofi-Aventis, SOBI, UCB. Jean Paul Eschard has received consultancy fees from Abbvie, BMS, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, Sanofi, UCB. Jean Hugues Salmon has received consultancy fees from Abbvie, BMS, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, UCB. Isabelle Charlot-Lambrecht has received consultancy fees from Amgen, MSD

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Figure 1: Flowchart of the study

Table 1: Methodological characteristics of the cost-effectiveness studies in knee OA

Author	Country	Sponsor	OA diagnosis	Radiographic OA	Type of study	Time horizon	n	OA outcome	OA outcome	Treatment	Control group	Perspective	Year and currency
For disease modifying osteoarthritis drugs													
Fagnani, 1998 [23]	France	Pharma industry	Knee and hip	NR	Trial-based	9 months	207	Lequesne, VAS AIMS2, NHP	QALY (Lequesne's index)	Diacerein	Usual care: Physical therapy, NSAIDs, acetaminophen, IACS, DMOADs	Societal	FF 1995
Bruyere, 2009 [24]	International	Pharma industry	ACR knee	Yes	Trial-based	24 months	622	HUI 3, VAS WOMAC	QALY (HUI 3)	Chondroitine sulphate	Imposed care : Placebo	Payer	€ 2 008
Scholtissen, 2010 [25]	Spain Portugal	Academic	ACR knee	NR	Trial-based	6 months	266	HUI 3 WOMAC	QALY (HUI 3)	Glucosamine	Imposed care : Acetaminophen or Placebo	Payer	€ 2 009
Losina, 2013 [26]	US	Academic	Knee	Yes	Model-based	10 years	NR	QALE	QALY	All DMOADs	Usual care: Physical therapy, NSAIDs and acetaminophen	Payer	\$US 2013
For intra-articular hyaluronic acid													
Torrance, 2002 [27]	Canada	Academic	Knee	Yes	Trial-based	12 months	255	HUI 3 WOMAC	QALY (HUI 3)	Hylan G-F 20	Usual care: Physical therapy, NSAIDs and acetaminophen	Societal	\$CA 1999
Kahan, 2003 [34]	France	Pharma Industry	ACR knee	Yes	Trial-based	9 months	506	Lequesne, WOMAC, SF-12	QALY (Lequesne's index)	Hylan G-F 20	Usual care: Physical therapy, NSAIDs, IACS and acetaminophen	Payer	€ 1998
Yen, 2004 [28]	Taiwan	Academic	Knee	Yes	Model-based	6 months	300	VAS	QALY (VAS)	SH	Imposed care : Celecoxib 100 mg X 2 or Naproxen 250 mg X 3	Societal	\$US 2002
Chou, 2009 [29]	Taiwan	Academic	ACR knee	Yes	Trial-based	6 months	37	VAS, HSS WOMAC	QALY (VAS)	Hylane G-F 20	Imposed care : Sodium hyaluronate	Societal	\$NT 2006
Hatoum, 2014 [30]	US	Pharma Industry	ACR knee	Yes	Model-based	12 months	214	HUI 3, VAS WOMAC	QALY (HUI 3)	SH	Usual care: Physical therapy, NSAIDs, IACS and acetaminophen	Payer	\$US 2012
Castro, 2015 [31]	Colombia	Pharma industry	Knee	Yes	Model-based	20 years	1000	WOMAC	QALY (WOMAC)	Hylan G-F 20	Usual care: Physical therapy, NSAIDs, IACS and acetaminophen	Societal	\$US 2015
Rosen, 2016 [32]	US	Pharma industry	ACR knee	Yes	Trial-based	6 months	30 1038 346	HUI 3, VAS WOMAC	QALY (HUI 3)	Hylan G-F 20 or SH or NASHA	Usual care: Physical therapy, NSAIDs and acetaminophen	Payer	\$US 2015
Hermans, 2017 [33]	Netherlands	Academic	Knee	Yes	Trial-based	12 months	156	EuroQol-5D	QALY (EuroQol-5D)	Hylan G-F 20	Usual care: Physical therapy, NSAIDs and acetaminophen	Societal	€ 2010
Thomas, 2017 [35]	France	Pharma Industry	Knee	Yes	Case control	6 months	401	EuroQol-5D WOMAC	QALY (EuroQol-5D)	SH	Imposed care : NSAIDs	Payer	€ 2014

ACR : American College of Rheumatology ; AIMS2 : Arthritis Impact Measurement Scales ; DMOADs : disease modifying osteoarthritis drugs ; HSS : Hospital for Special Surgery ; HUI : Health Utilities Index ; IACS : intra-articular corticosteroids ; NASHA : Non animal stabilized hyaluronic acid ; NHP : Nottingham Health Profil ; NSAIDs : nonsteroidal anti-inflammatory drugs ; NR : non reported ; QALE : quality-adjusted life expectancy ; QALY : quality-adjusted life years ; SF-12 : The 12-Item Short Form Health Survey ; SH : Sodium Hyaluronate ; VAS : visual analogue scale ; WOMAC : Western Ontario and McMaster Universities Osteoarthritis Index

Table 2: Results of the cost-effectiveness studies (in € 2017 / QALY)

Author	Treatment	Dosage	Control group	Time horizon	Cost in the Intervention arm (€ 2017)	Cost in the Control arm (€ 2017)	Δ cost	Effectiveness in the Intervention arm (QALY)	Effectiveness in the Control arm (QALY)	Δ incremental effectiveness	ICER
For disease modifying osteoarthritis drugs											
Fagnani, 1998 [23]	Diacerein	100 mg/d	Usual care: Physical therapy, NSAIDs, acetaminophen, IACS, DMOADs	9 months	490	470	20	NA	NA	NA	NA*
Bruyere, 2009 [24]	Chondroitine sulphate	800 mg/d	Imposed care : Placebo	24 months	405	655	-250	0,097	0,072	0,025	Dominant
Scholtissen 2010 [25]	Glucosamine	1500 mg/d	Imposed care : Acetaminophen or Placebo	6 months	45	55 5	-10 40	NR	NR	0,01 0,01	Dominant 4,000
Losina, 2013 [26]	All DMOADs	NA	Usual care: Physical therapy, NSAIDs and acetaminophen	10 years	NR	NR	2300	NR	NR	0.04	57,550
For intra-articular hyaluronic acid											
Torrance, 2002 [27]	Synvisc®	3 injections	Usual care: Physical therapy, NSAIDs and acetaminophen	12 months	2,845	1,890	955	NR	NR	0,071	13,450
Kahan, 2003 [34]	Synvisc®	3 injections	Usual care: Physical therapy, NSAIDs, IACS and acetaminophen	9 months	1,070	1,070	0	NA	NA	NA	NA*
Yen, 2004 [28]	Artz®	5 injections	Imposed care : Celecoxib 100 mg X 2 or Naproxen 250 mg X 3	6 months	880	715 650	165 230	0,0031	0	0,0031 0,008	53,225 28,750
Chou, 2009 [29]	Synvisc®	3 injections	Imposed care : Artz® (5 injections)	6 months	235	310	-75	0,060	0,041	0,019	Dominant
Hatoum, 2014 [30]	Euflexxa®	6 injections	Usual care: Physical therapy, NSAIDs, IACS and acetaminophen	12 months	1470	525	945	0,164	0,14	0,024	39,375
Castro, 2015 [31]	Synvisc®	1 or 2 injections /y	Usual care: Physical therapy, NSAIDs, IACS and acetaminophen	20 years	26,875	26,545	330	15.43	14.34	1.09	305
Rosen, 2016 [32]	Euflexxa®	3 injections	Usual care: Physical therapy, NSAIDs and acetaminophen	6 months	820	315	505	0,145	0,03	0,115	4,390
	Artz®	3 injections			740	315	425	0,095	0,03	0,065	6,540
	Synvisc®	3 injections			1,050	315	735	0,124	0,03	0,094	7,820
	Durolane®	1 injection			660	315	345	0,085	0,03	0,055	6,275
	Hyalgan®	3 injections			645	315	330	0,073	0,03	0,043	7,675
Hermans, 2017 [33]	Synvisc®	3 injections	Usual care: Physical therapy, NSAIDs and acetaminophen	12 months	8655	8125	530	0,779	0,727	0,052	10195
Thomas, 2017 [35]	Arthrum®	3 injections	NSAIDs	6 months	230	220	10	NR	NR	0,042	240

IACS : intra-articular corticosteroids ; ICER : Incremental Cost-Effectiveness Ratio ; NA : not available ; NR : non reported ; NSAIDs : nonsteroidal anti- inflammatory drugs

* ICER was estimated 20€ per point gain on Lequesne's index

