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ORIGINALIA

SUMMARY

– Introduction: The administration by injection of hyaluronic acid (HA) for 3-5 weeks is effective in the treatment of patients with knee osteoarthritis (OA). Other products for intra-articular use have been recently introduced for the treatment of OA. Among these, a medical device, MD-Knee, produced by Guna S.p.A.; this study aims to estimate the cost-minimization of MD-Knee versus HA in the treatment of knee osteoarthritis.

– Methods and Results: We performed a cost-minimization analysis (CMA). The CMA was conducted from the perspective of the Italian National Health Service (NHS). Only direct medical costs (MD-Knee and HA) were considered. We performed a sensitivity analysis to test the robustness of the results. The mean 6-month cost per patient was € 75,00 with MD-Knee and € 185,00 with HA.

– Conclusion: From the Italian National Health Service's perspective, MD-Knee appears to be the cost-saving therapeutic option compared with HA in the treatment of patients with knee osteoarthritis.

KEY WORDS **COST, HYALURONIC ACID, ITALIAN NHS, MD-KNEE, SUPARTZ®**

A COST-MINIMISATION ANALYSIS OF MD-KNEE VERSUS HYALURONIC ACID IN THE TREATMENT OF PATIENTS WITH KNEE OSTEOARTHRITIS

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– ORIGINAL RESEARCH ARTICLE

INTRODUCTION

Osteoarthritis **(OA)** is a chronic degenerative disease of the joints that typically causes progressive damage to the articular cartilage and underlying bone (1).
It is one of the most common chronic diseases, with a prevalence of 11% and 24% in the adult population for the hip and knee OA, respectively (1).
It was estimated that approximately 303 million people worldwide were affected by OA in 2017 (2).
OA, which is more prevalent in the elderly population, is the most common cause of disability, including limitation of daily activities, and particularly pain (1). The pain is exacerbated by movement and decreases on resting, but as the disease advances, it can also occur when at rest.
The burden of disease associated with musculoskeletal diseases is continually increasing, becoming the second leading cause of disability in 2015 (years lived with disability, YLDs) (3).
Various studies have also investigated the existence of a possible relationship between OA of the knee and premature mortality.
These have identified an indicator of unfavourable results due to the limitations caused by musculoskeletal disease on the daily activities and physical functionality of the patients affected (4-8).
The FDA define the term "serious" as a disease or condition associated with morbidity that has substantial negative

impact on the day-to-day functioning of the individual (9).
OA shows all the characteristics of a serious condition. It restricts the essential daily activities of the person (walking, eating, communicating or taking care of themselves or other family members), causes premature ageing due to the loss of functionality within society, and increases the risk of mortality compared with the general population (9).
Since the life expectancy of the general population is continually increasing, the number of people with OA is also expected to grow.

– For the purpose of relieving pain and achieving an optimal clinical condition for the management of OA, International Guidelines recommend a therapeutic strategy that includes: **1)** non-pharmacological treatment (physiotherapy and rehabilitation), **2)** pharmacological treatment (non-steroidal anti-inflammatory drugs, analgesics, chondroprotective agents and intra-articular treatments), and **3)** surgical treatment (advanced stages of the disease) (10-15).

Much emphasis has been placed on non-pharmacological management over the past decade (1).
However, perhaps because the associated recommendations have not been sufficiently clear in terms of the timing, intensity, frequency, duration and implementation of procedures, various studies have shown that the non-pharmacological management of OA has not always led to optimal care results (16,17).
Although scientific evidence suggests low efficacy, paracetamol is widely recommended for the analgesic treatment of OA in the initial stages.
However, because this is associated with adverse events affecting the gastrointestinal system, cardiovascular system, liver and kidneys in the general population (especially in patients taking high dosages), its use must be carefully evaluated (18).

Among the pharmacological options, hyaluronic acid administered by infiltration plays a major role because it enables pain control and improves joint mobility, especially that of the knee (19). Double-blind controlled clinical studies have demonstrated its superior efficacy when compared with saline solution, arthrocentesis and NSAID treatments, along with an excellent tolerability profile (20,21). Hyaluronic acid has a well-known mechanism of action.
As well as safeguarding the viscoelastic properties of the synovial fluid, it plays an important part in maintaining the structural and functional characteristics of the articular cartilage (20,21).
Viscosupplementation is a procedure that involves the intra-articular infiltration of hyaluronic acid. Among the hyaluronic acid products currently available, **SUPARTZ®** is the most extensively analysed in clinical studies and the most widely used in practice (22).

– Since 2010, the treatment of painful and degenerative diseases of the musculoskeletal system has included an innovative therapeutic approach involving injectable medical devices (MD) based on porcine collagen.
Among those that are currently on the market is **MD-Knee** (Guna S.p.A.), a medical device available in vials of injectable solution based on porcine collagen. Porcine collagen is a good choice because of its biochemical similarity and the fact that porcine tissues have a very high average collagen content (19).
The reason for introducing collagen locally is structural, since the mechanical support provided by collagen constitutes an effective natural support scaffold (bio-scaffold).
This is because collagen replaces, strengthens and protects the cartilage, tendons, ligaments and joint capsules (23-26).

OBJECTIVE

The purpose of this economic assessment is to compare the benefits and costs of treatment associated with MD-Knee and SUPARTZ® in the treatment of knee OA in a hospital setting.

MATERIALS AND METHODS

Premise

The first phase of this economic assessment was based on a literature review carried out by consulting the PubMed database, to determine whether there were any clinical studies that had directly compared the two pharmacological treatment options (head-to-head).
There was only one study that satisfied this requirement (22). Its main features are summarised in the section on "clinical data".

Clinical data

The clinical study (randomised, double blind, prospective and multicentre), conducted in Italy by Martin-Martin *et* Al. assessed the non-inferiority of MD-Knee versus hyaluronic acid (SUPARTZ®) in the treatment of patients with knee OA.

– Enrolment onto the study began in March 2013 and ended in September 2013. Only patients with symptomatic OA of the knee were considered (please refer to the publication for specific inclusion and exclusion criteria). A total of 64 patients were enrolled, 32 of whom were treated with MD-Knee and 32 with SUPARTZ®. The study involved a total of 3 consultations per patient, one at the time of enrolment and a further two at 3 months and 6 months after enrolment.
The dosage regimen adopted for the two options was as follows: for MD-Knee, intra-articular injection of 4 ml collagen (two 2 ml-vials) once a week for 5 consecutive weeks; for SUPARTZ®, intra-articular injection of 2.5 ml hyaluronic acid once a week for 5 consecutive weeks.
The primary endpoint of the study was the Lequesne index of severity for osteoarthritis of the knee (ISK), while the Visual Analogue Scale (VAS) and the SF-36 questionnaire were the secondary endpoints (27). The ISK assessed the

severity of the knee OA, while the VAS and the SF-36 questionnaire assessed, respectively, variations in the pain and physical-mental state of the patients treated.
The main demographic features of the two treatment groups proved well balanced on enrolment and are described in TAB. 1.
At the time of the 3 and 6 month follow-ups, the ISK and VAS values highlighted a significant improvement in both groups compared with those measured during enrolment, with no statistically significant differences observed.
Furthermore, there was no statistically significant difference in the scores on the SF-36 questionnaire.
The results show that both pharmacological options are equally effective in relieving the symptoms of knee OA as measured 6 months after the start of treatment.

Parameters	MD-Knee (n. = 32)	SUPARTZ® (n. = 32)
Age (years ± SD)	69.41 ± 8.42	69.97 ± 9.5
Females, n. (%)	25 (86.2%)	20 (64.5%)
BMI (Kg/m^2)	27.2 ± 3.78	27.3 ± 3.56
Kellgren and Lawrence grade II, n. (%)	15 (51%)	17 (55%)
Kellgren and Lawrence grade III, n. (%)	14 (44%)	14 (44%)
ISK± SD	12.45 ± 2.63	12.6 ± 3.48
SF-36 ± SD	91.41 ± 20.01	93.07 ± 17.3
VAS ± SD	7.67 ± 1.41	7.42 ± 1.35

TAB. 1

Main demographic characteristics at enrolment (22).

Assessment technique

Given that the clinical study (22) showed no differences in efficacy, it was considered appropriate to compare MD-Knee and SUPARTZ® through a **cost-minimisation analysis (CMA)**, thus placing the emphasis on the drug costs only.

Timeframe

In accordance with the observation period of the reference clinical study (22), an analysis time period of 6 months, or 26 weeks, was adopted.

Analysis perspective

Since the two drugs are not currently reimbursed by the Italian National Health System, and the respective administrations tend to be carried out in a hospital setting (outpatient department or day hospital), the analysis perspective adopted here is that of the hospital, on the assumption that the same facility will be responsible for the purchase.

Consumption of resources and unit costs

The consumption of the two treatment regimens was calculated by multiplying the dosages indicated in the clinical study (22) by the corresponding market prices (retail price). A retail price of **€ 75.00** for a pack of ten 2 ml-vials of **MD-Knee** and a retail price of **€ 185.00** for a pack of five 2.5 ml pieces of **SUPARTZ®** were taken into account.

In accordance with the objective of the study (to estimate the incremental costs between the two therapies) and with the economic assessment technique adopted (CMA), no cost associated with administration was considered, insofar as it was assumed to be the same in both cases (weekly administration for 5 consecutive weeks).

Since no significant differences in terms of tolerability had been identified in the reference clinical study (22), no costs for the management of adverse events relating to the treatment administered were taken into account.

Sensitivity analysis

As stated in the Guidelines drawn up by the AIES group (Associazione Italiana di Economia Sanitaria) [Italian Association of Health Economics] (28), the sensitivity analysis should involve detailed analysis of the uncertainty of the result of the base case (or reference case, CDR).

In this assessment, the uncertainty analysis was carried out exclusively with reference to the purchase prices of the two pharmacological options. In this regard, to estimate the uncertainty relating to this variable, a threshold analysis was conducted in order to estimate the reductions in purchase price for which the two options would be cost-neutral.

RESULTS

Cost minimisation analysis

TAB. 2 shows the CMA results illustrating the average treatment costs for the two therapeutic alternatives.
– It is clear that, in view of the lower cost per single administration (**€ 15.00** vs **€ 37.00**), the patient treated with MD-Knee is associated with a lower average cost of treatment (**€ 75.00** vs **€ 185.00**), resulting in a saving of **€ 110.00** over the entire treatment cycle.

Sensitivity analysis

The threshold analysis conducted to estimate the uncertainty associated with the retail price shows how, if the price of MD-Knee is kept constant (base case), then only if there were a signifi-

TAB. 2

Results of the cost minimisation analysis.

Parameters	A	B
	MD-Knee	SUPARTZ®
Dose per administration	4 ml	2.5 ml
Cost per administration	€ 15.00	€ 37.00
Total No. administrations	5	5
Average cost of treatment	€ 75.00	€ 185.00
Difference (A-B)	**-€ 110.00**	

cant reduction in the price of SUPARTZ® **(-59.5%)** would the two therapeutic alternatives be cost-neutral, i.e. they would add up to the same average cost per patient treated (FIG. 1).

DISCUSSION

OA is a clinical condition that features in a large section of the population, especially the elderly. The constant and continuous ageing of the population due to the increase in life expectancy suggests that, in the near future, the number of patients affected by this disease will rise, and of these, approximately one quarter will suffer from knee osteoarthritis.

– As highlighted in other studies published in the literature, the adoption of a non-pharmacological strategy does not always prove an effective measure in countering OA (16,17).
For this reason, the identification of a pharmacological option that provides a satisfactory clinical response and, at the same time, delays or prevents surgical intervention, is becoming fundamental to addressing the problems associated with OA.
Among the pharmacological treatments, the administration of hyaluronic acid has proved to be more effective than using nonsteroidal anti-inflammatory drugs or analgesia (20,21).
The subsequent arrival on the market of injectable medical devices based on porcine collagen constituted an equally effective option in the management of knee OA, as also shown by the direct comparison study conducted in Italy by Martin-Martin *et al.* (22).

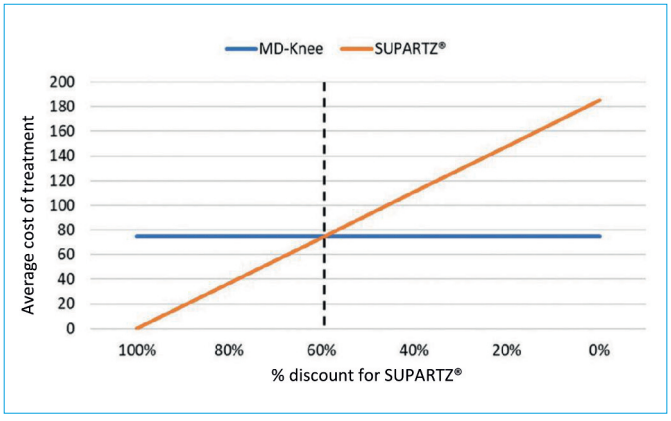
For the same effectiveness (22), the cost of treatment might be a subsequent driver of therapeutic choice, especially if considered within a broader discussion on the sustainability of healthcare spending.

In the light of the above, the intention here was to conduct a cost minimisation analysis aimed at comparing the cost associated with MD-Knee, an injectable Medical Device based on porcine collagen, with SUPARTZ®, a solution based on hyaluronic acid, over a **six-month period**.
Since neither of the drugs is reimbursed by the SSN, the hospital environment was adopted as the analytical setting, assuming that the same facility would be responsible for purchasing the drugs.
The result of the minimisation analysis showed a reduction in the average treatment cost for MD-Knee **(€ 75.00)** of **€ 110.00**, compared with SUPARTZ® **(€ 185.00)**.
Since the respective retail prices were considered, in order to take into account any discounts granted to hospitals in the event of bulk purchases of the drug, a threshold analysis was carried out to verify the price reduction for SUPARTZ® at which, if the MD-Knee were kept constant, the two alternatives would be cost-neutral.
As things stand, a reduction in the price of SUPARTZ® of almost **60%** would be required to make the average treatment cost the same for both alternatives.
It has not been done here, but it would be interesting to conduct a brief investigation to determine the average prices actually charged to hospitals for the purchase of the two drugs.
The result in favour of MD-Knee, expressed in terms of the lower average cost of treatment, could also be extended to include an analysis carried out from the point of view of the patient, thereby assuming that the patients themselves would be responsible for the drug purchase rather than the hospital.
In this case, we would be dealing with a lower impact on the social cost of knee OA.

This analysis must be read in light the of some observations.
To begin with, the comparison was carried out over a time period of just six months, as opposed to the probably longer follow-up period required for the management of knee OA.
The economic comparison actually reflects the observation timeframe adopted by the reference clinical study (22), and it was therefore considered more correct not to extrapolate the results of this to a longer time period.

FIG. 1

Threshold analysis.



A second observation concerns the fact that, in the economic assessment between the hyaluronic acid products available, only SUPARTZ® was considered.

There were two reasons for this choice: the first is that SUPARTZ® is widely used in clinical practice, with proven efficacy in previous studies, and the second is that, in the literature, there are no direct comparisons of MD-knee in relation to other types of hyaluronic acid (e.g., cross-linked, high molecular weight), which means that we cannot draw definitive conclusions on the efficacy of the MD-Knee medical device in relation to the latter.

CONCLUSIONS

Based on the results found here, it is believed that, in terms of managing knee osteoarthritis, MD-Knee constitutes a more efficient option than a medium molecular weight hyaluronic acid product such as SUPARTZ® for hospitals (or patients) since, with the same toxicity and efficacy, it leads to a lower average cost of treatment over a 6-month time period.

Disclosures

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Conflict of interest: None of the authors has financial interest related to this study to disclose.

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