PRP for the treatment of Osteoarthritis

Economic evaluation in PRP treatment. Research style and methods

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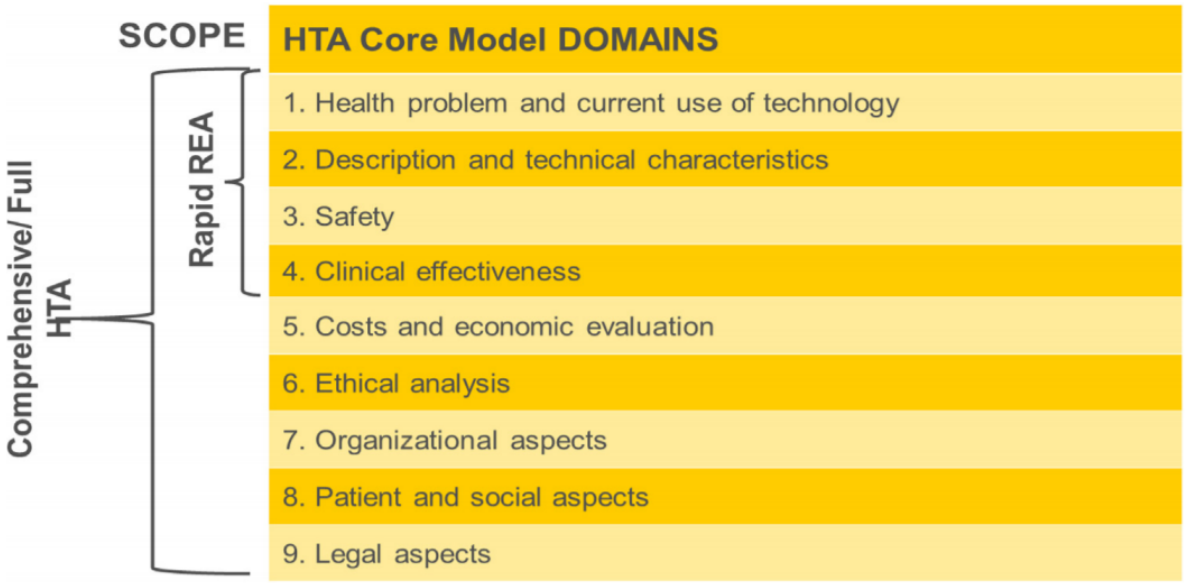
Economic evaluations and resource scarcity

The healthcare sector as the whole human activities is affected by scarcity of resources. In contrast with limited resources (e.g. the time of surgeon, specialized equipment, or the number of beds, budgets) there are unlimited wants and expectations (i.e. unlimited needs of patients). This leads to the necessity to choose among different ways to use the scarce resources. The choice of producing specific goods or services has to face the opportunity cost of the decisions, that is the benefits that are forgone by using those resources to produce different services or goods.

According to this statement, using resources on one healthcare activity inevitably means sacrificing an activity somewhere else. Economic evaluation facilitates comparisons between health care programs, treatment services and interventions in terms of both costs and consequences of those interventions. Drummond, Stoddart and Torrance (1987) defined economic evaluation as "the comparative analysis of alternative courses of action in terms of both their costs and consequences". Usually a new technology has a better effectiveness but higher cost with respect to the standard of care. This is a typical problem attaining the best resources allocation. The goal of health economic evaluation, through the use of modelling, is to maximize the benefits from health care spending.

Economic evaluation is an important part of the health technology assessment (HTA) that is a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of a new health technology (Kristensen et al., 2017). The HTA core model is a framework with nine domains (such as effectiveness, safety, organizational, economic, patient, and social aspects) that comprise all aspects potentially relevant for HTA and thus value assessment (Fig. 1).

Fig. 1 – The domains of the HTA Core Model. HTA, health technology assessment; REA, relative effectiveness assessment.



Economic evaluation is important, together with other domains, because (due to resource scarcity) a decision explicit or not is always made. Even if we do not care for economic evaluations we make choices that have economic impact. Therefore, economic evaluation can help to maximize health results with the budget at our disposal taking into account opportunity cost. Thus, the aim of this article is to assess the cost-effectiveness of the IA PRP therapy with respect to Hyaluronic Acid for patients with mild to severe knee pain due to Osteoarthritis (OA) and who failed to respond to conventional therapy.

OA Burden of disease and economic impact

Osteoarthritis (OA) is one of the main causes of musculoskeletal disorders (second only to back and neck pain), accounting for 17 million years lived with disability (YLDs) in 2010 (Vos T et al.,2016). As shown in Global Health Observatory data repository they are the 8th in the whole

world and the 4th in western countries for disability adjusted life years (DALYs) (WHO 2017). OA results to be the 11th out of 291 pathologies for burden of disability (YLDs) and 38th per DALYs (Murray CJ et al., 2012; Cross M., et al., 2014). Considering Disability Adjusted Life Years (DALYs), over the period 1990-2010, OA burden of disease has grown at a faster pace than musculoskeletal diseases as a whole (64% vs 45%) and also with respect to all causes disease DALYs (64% vs -0,5%). Moreover, in western countries the number of total joint arthroplasty, which can be considered as the final stage of OA (knee and hip OA), is growing (Hiligsmann et al. 2013, Culliford et al., 2015). OA onset is associated to older age and obesity. The increasing of these two population characteristics will lead to significant rises in prevalence.

The burden of OA is correlated to a high economic impact in terms of both direct health-related costs and indirect costs. The heterogeneity of cost-of-illness studies do not allow to have a clear amount of cost related to OA In western countries, where the prevalence is higher, the total costs relating to treatment for OA are estimated at between 1% and 2.5% of Gross Domestic Product (GDP). A systematic review concludes that the social cost of osteoarthritis could be between 0.25% and 0.50% of a country's GDP (Puig-Junoy et al. 2015). A review of 32 cost-of-illness studies states that the weighted average annual costs per patient living with knee and hip OA is € 11100, € 9500 and € 4400 for total, direct and indirect costs, respectively (Salmon et al. 20016) . OA costs may vary considerably between countries and population. In Italy annual total costs per patient have been estimated in € 3000 (€ 1300 as direct health-related costs and € 1700 as indirect costs adjusted in 2013) (Leardini et al., 2004). In France, the study by Le Pen et al. estimated that healthcare costs (doctor visits, medicines, and hospitalizations) for patients with osteoarthritis account for around 1.7% of France's total healthcare expenditure in 2002. Bertin et al. (2014) provide a health economic update of the patient costs associated with hip or knee OA treated in the community and in medical, surgical and obstetric care (MSO) and post-acute care and rehabilitation (PAC) hospitals in France in 2010. The annual costs per community patient were € 715 and € 764 for hip and knee OA, respectively, including a cost to the healthcare system of € 425 and € 454, that is, an estimated € 3.5 billion (€ 2 billion to the healthcare system) for 4.6 million patients. Hospitalization engendered annual costs of € 9,797 per patient with hip OA and € 11,644 per patient with knee OA, that is, a total cost of € 1.955 billion for patients hospitalized for hip or knee OA in 2010. A Canadian study estimated direct health related costs in Canadian dollars (CAD) $2233 per patient per year (Tarride et al., 2013), while a Dutch study found indirect costs due to loss of productivity in € 722 (with median € 217) per patient per month (Hermans et al. 2012). In the United States, OA has been estimated contributing to more than for US$ 24 billion in health care expenditures(losina et al. 2015). Studies focused on the annual cost of medical care for persons with OA and report

costs ranging from US$ 989 to US$ 10,313 in the US (White et al., 2008, Xie et al, 2007). The main direct health-related cost driver is the total joint arthroplasty (Piscitelli et al., 2013). The steady increasing, year after year, of surgery incidence lead costs to grow (Chen et al 2012) for the foreseeable future.

Epidemiologic and economic trends can put under pressure the National Healthcare Systems. Thus, there is a great need for a treatment that can delay the progression of the disease and reduce the growth of these costs. The goal of therapies should be slowing down the progression of the pathology in order to delay (or to avoid) the surgery. At this stage of knee OA evolution, for patients in need of longer term care and not responding to conservative therapies, but not already needing a total knee replacement (TKR) other two IA therapies are used in OA management: Hyaluronic acid (HA) and platelet-rich-plasma (PRP).

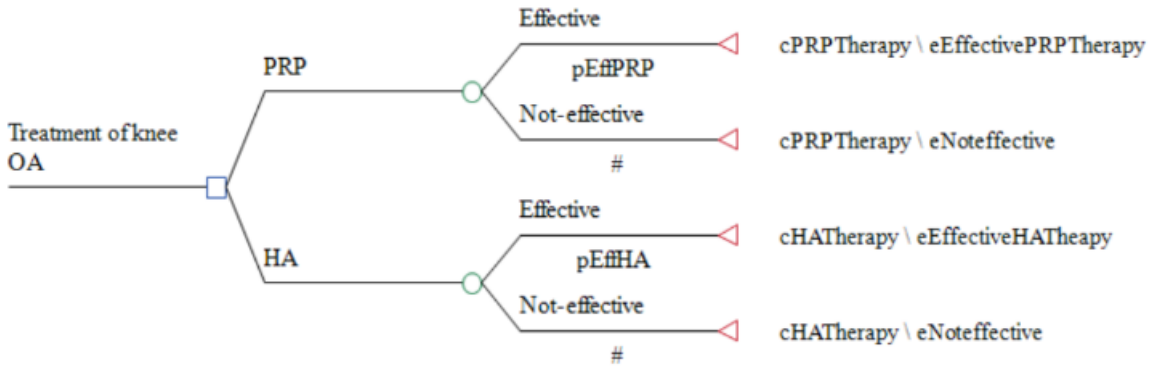
Clinical trials have indicated that PRP is at least as effective if not superior to the current treatment of choice, viscosupplementation. The results of several meta-analyses confirm the major effectiveness of PRP (Khoshbin et al., 2013, Laudy et al., 2015, Campbell et al., 2015, Moen et. Al 2016, Dai et al., 2017, Shen et al., 2017, Wu et al., 2020). For example, Moen et al. 2016 in a meta-analysis of 17 controlled clinical trials including 1660 patients PRP shoed moderate evidence that PRP is superior to hyaluronic acid and placebo for both pain and function. Dai et al. 2017 in a meta-analysis of 10 RCTs comparing HA vs PRP injections for knee OA found that at one-year follow up PRP was more effective for pain relief and functional improvement.A recent study on consensus statement from French-speaking experts reports, among the 25 recommendations selected, the following: ‘Intra-articular injections of PRP are an effective symptomatic treatment for early to moderate knee osteoarthritis’. This recommendation was considered appropriate with a relative agreement (Median = 8; rank = 6–9). Level of evidence 1A (Eymard et al.,2020). On the other hand, the method to produce PRP needs a medical device and a longer time-consuming process (which in addition may require the presence of a physician depending on the regulation of the country in question), leading the therapy to be more costly than the comparator (HA). PRP seems to be in the classical situation introduced in the first section of this chapter, that is a technology more effective, but more costly. Therefore, we need an economic analysis to ensure PRP is a value for money therapy.

Cost effectiveness analysis

To investigate if PRP is a cost-effective solution for the treatment of knee osteoarthritis, (Landi et al., 2018; Russo et al., 2019; Russo et al., 2017) conducted an economic evaluation in terms of cost-utility of intra-articular PRP therapy with respect to hyaluronic acid in four different countries, France, Italy, Germany and USA since the costs of osteoarthritis may vary depending on the country and population.

A decision tree model that evaluates the choice between PRP and HA for OA knee disease has been developed, including costs, probabilities and clinical benefits of both therapies (figure 2). The decision tree is one of the model techniques most used to perform economic evaluations.

Fig. 2 Cost-effectiveness model of PRP vs HA



Only direct costs of the therapies were included, indirect cost such as loss of days of work, loss of productivity or expenses due to travel to the doctors for the visits were not included. The time horizon considered in the model is one year because there are no robust clinic evidences on a longer period. The evaluation of the effectiveness was performed using published and publicly available data in articles and meta-analysis (Khoshbin et al., 2013, Laudy et al., 2015, Campbell et al., 2015, Moen et. Al 2016, Dai et al., 2017, Shen et al., 2017, Wu et al., 2020).. All studies reported effectiveness through illness specific scales such as IKDC, WOMAC, and VAS. In this work WOMAC scores were transformed in QALYs using the conversion procedure of Wailoo (2014)

which it allows to compare the incremental effectiveness ratio (ICER) with the willingness to pay threshold (WTP) of each countries and determines the cost-effectiveness. The incremental cost-effectiveness ratio (ICER) is a statistic used to summarize the cost-effectiveness of a health care intervention. It is defined by the difference in cost between two possible interventions, divided by the difference in their effect. It represents the average incremental cost associated with 1 additional unit of the measure of effect. Each country can have a different WTP. For Italy, France and Germany we use a WTP of €30,000. For Us $50,000.

Incremental Cost-Effectiveness Ratio (ICER)

$$\text{ICER} = \frac{(C_1 - C_0)}{(E_1 - E_0)}$$

Deterministic and probabilistic sensibility analyses are reported in order to evaluate the robustness of the results and account for the different sources of uncertainty. In the analysis were used conservative parameter for effectiveness. In detail, the incremental effectiveness of PRP is 0.042 QALYs and the effectiveness has been modelled with uniform distributions to model the potential uncertainty around the differential effectiveness of the two therapies.

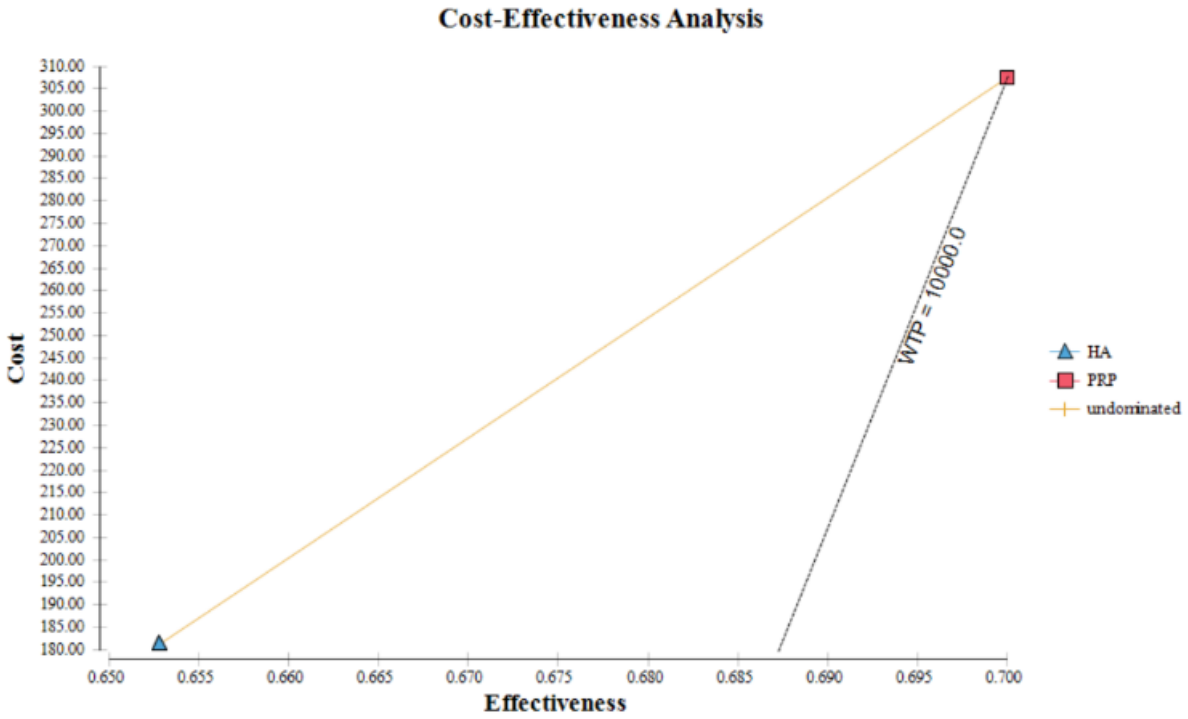
Results shows none of the therapies dominates the other, but PRP results the cost-effective therapy in each country. PRP therapy is confirmed more costly in each country, but it is value for money thanks to a major effectiveness. In each country the base case scenario reports an ICER lower than the thresholds of 30,000€/QALY (see table 1). For Germany, Italy and France even using a lower threshold of 10,000€/QALY PRP is cost-effective. In table 1 are showed the synthetic results for the three country. Hereafter we report some figures and tables from the German case, but the other countries have similar results.

Table 1 Cost-effectiveness results synthesis for each countries

Summary	ICER (€/qaly)			PSA - Probabilistic sensitivity analyses	
Country	Base case scenario	Min	Max	% CE cases WTP € 10,000	% CE cases WTP €30,000
Italy	2,127	1,300	3,439	77	85
France	2,675	1,659	4,847	76	84
Germany	4,237	2,500	7,575	72	80

CE cases= the percentage of cases cost effective in montecalo simulation

Fig. 3: Cost-effectiveness plane (ICER) PRP vs HA



The probabilistic sensitivity analysis was performed through a Monte Carlo simulation considering 10,000 scenarios (or cases). All the parameters and variables of the model vary according to the assigned distribution. Establishing a WTP of €30,000 per QALY, the PRP is cost-effective in the 80% of the scenarios for Germany, 84% France, 85% Italy. See figure 4.

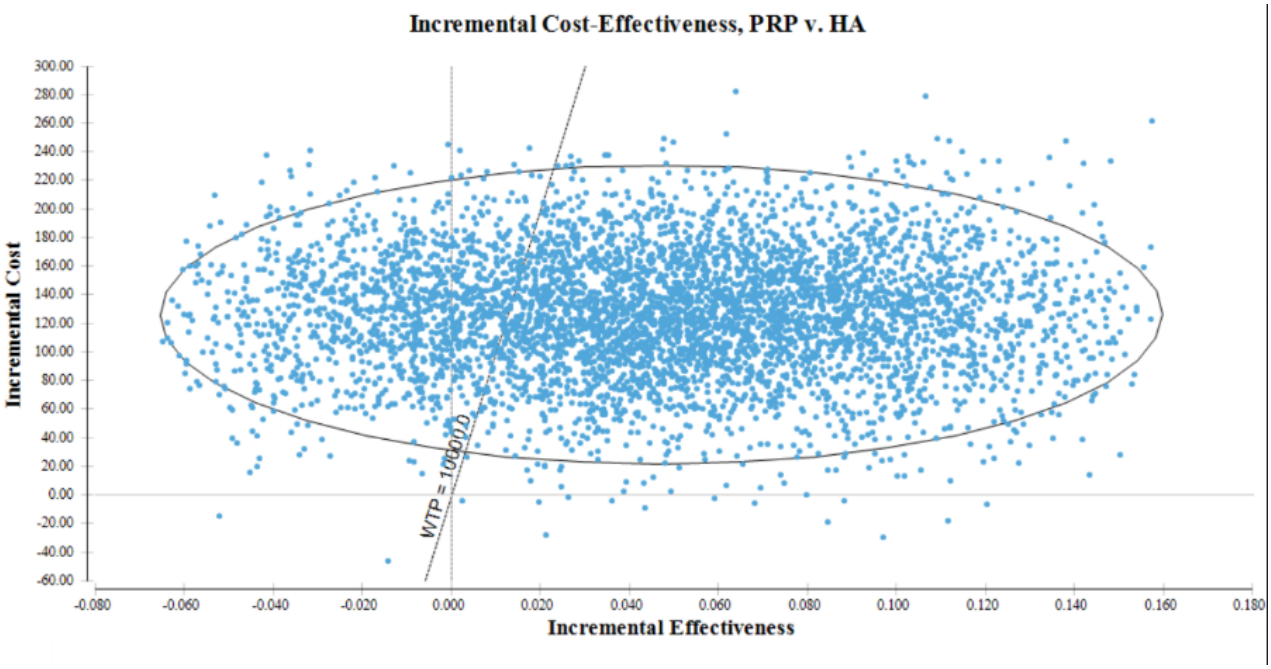


Fig. 4 Cost-effectiveness acceptability curve of PRP vs HA under various WTP thresholds.

In the United States, most insurance providers do not cover the cost of PRP injections. Despite this and the fact that they have not yet received FDA approval, PRP is attractive option for patients who do not respond to other treatments and are unable to or do not wish to undergo surgery. The adoption of PRP is increasing throughout the United States (Piuzzi et al. 2018). Analysis of a region in South Florida revealed that PRP treatment was offered by about a third of orthopedic offices and that the cost of PRP injections varied considerably between practices, ranging from $350 to $1,700 (Alcerro and Lavernia, 2019). The authors made the above analysis also for US. The results are (at the moment of this publication) under peer review. We report here the main preliminary results. In the base case scenario, PRP strategy has an ICER (incremental cost effectiveness ratio) of US$24,375 per QALY that is below the acceptable threshold for cost-effectiveness in the medical literature of US $50,000 per quality adjusted life year for US. The PSA shows PRP has 75% probability to be cost-effective respect to Hyaluronic Acid. A threshold analysis show how PRP is the cost-effective strategy within the price for single injection of US$ 1,100. At this cost, we would have an ICER of US$ 50,000. Therefore, if the price is higher PRP is not cost-effective anymore. Despite some peculiarities the results as for European country show PRP as a cost-effective therapy.

Another studies sought to determine the breakeven point at which PRP would be cost-effective for the payor based on the relative utility gained per dollar spent relative to the cost data for hyaluronic acid and saline injection at 6 months and 12 months (Bendich et al., 2020). The authors found that PRP to be cost-effective than HA at 6 months, PRP injections should not cost more than $3,703.03. At 12 months to be more effective than saline, PRP should not cost more than $1,192.08. This study found that PRP was more

cost-effective relative to other injectables for knee osteoarthritis as well as compared to the acceptable threshold for cost-effectiveness in the medical literature of $50,000 per quality adjusted life years.

These initial studies demonstrate that PRP is a cost-effective therapy for osteoarthritis based on analysis of data from a one-year period. However, osteoarthritis is a chronic disease that develops over decades, thus clinical trials of longer duration are needed for a better economic evaluation.

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