Hylan G-F 20 has better pain relief and cost-effectiveness than sodium hyaluronate in treating early osteoarthritic knees in Taiwan
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

CRD summary
This study evaluated the effectiveness and cost-effectiveness of different molecular weight hyaluronic acid formulations (Artz and Synvisc), as a viscosupplement for osteoarthritis of the knee. The authors concluded that Synvisc provided better pain relief, and was less costly than Artz, but further research was required. The utility outcome methods and the study results were not adequately reported, and the effectiveness and cost analysis was limited, so it is not clear how valid or certain the results are.

Type of economic evaluation
Cost-utility analysis

Study objective
This study evaluated the effectiveness and cost-effectiveness of different molecular weight hyaluronic acid formulations, as a viscosupplement for osteoarthritis of the knee.

Interventions
Sodium hyaluronate (Artz) with a molecular weight of 600 to 1,200 thousand Daltons (kDa) was compared with chemically cross-linked Hylan G-F 20 (Synvisc) with a molecular weight of 6,000 kDa. Artz was administered as five, weekly intra-articular injections, while Synvisc was administered as three, weekly intra-articular injections.

Location/setting
Taiwan/out-patient care.

Methods
Analytical approach:
The economic evaluation was conducted alongside a clinical study. The time horizon was 26 weeks. The perspectives were not explicitly stated.

Effectiveness data:
The primary clinical outcome was quality of life, measured on a 100mm Visual Analogue Scale (VAS). Higher scores on the VAS corresponded to worse states of health. Other outcomes included the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index, Lequesne's index, and the Hospital for Special Surgery (HSS) knee score. The effectiveness data were from an observational study, in which each knee was injected with a different drug. The patient chose which knee was given which drug; most patients chose Artz for their more painful knee. Study power was calculated based on the ability to detect a 30mm difference on the VAS, for global quality of life, at 80% power, with a significance of p=0.05. This estimated a sample of 32 patients; 41 patients were recruited, for each group, to allow 20% drop out.

Monetary benefit and utility valuations:
VAS measures were transformed to utility scores by subtracting the VAS score from 100, and dividing by 100.

Measure of benefit:
Quality-adjusted life-years (QALYs) were the summary measure of benefit. These were calculated for 37 individual participants, at each follow-up point, using area under the curve calculations.
Cost data:
The costs of the injections were calculated using Taiwan National Health Insurance Program payments. Patient co-payments for the injections were also reported. The costs were reported in Taiwan dollars (TWD).

Analysis of uncertainty:
Tests for statistically significant differences were conducted, using two-way repeated analysis of variance, Wilcoxon rank sum tests, student’s t-tests, and the Mann-Whitney U test. The Mann-Whitney U tests were used to analyse the QALY and incremental cost-effectiveness ratio (ICER) differences between Artz and Synvisc. Confidence intervals were reported for the ICERs.

Results
The cost to the national health service was TWD 1,415 for one Artz injection, and TWD 1,915 for one Synvisc injection, resulting in total injection costs of TWD 7,075 for Artz (five injections) and TWD 5,745 for Synvisc (three injections).

Total utility gained was 0.04101 for Artz, and 0.05977 for Synvisc. The average cost-effectiveness ratio (individual treatment cost divided by the individual treatment effect) was TWD 297,355 per QALY for Artz, and TWD 241,456 per QALY for Synvisc.

The cost to the patient, for an out-patient visit, was TWD 460, producing a cost of TWD 2,300 for Artz injections and TWD 1,380 for Synvisc injections. The average cost-effectiveness ratio was TWD 96,667 per QALY for Artz, and TWD 58,000 per QALY for Synvisc.

Analysing the costs to the health service and the patient, the average cost-effectiveness ratio was TWD 394,021 per QALY for Artz, and TWD 299,456 per QALY for Synvisc.

The average cost-effectiveness ratios were statistically significantly different, for Artz compared with Synvisc, analysing national health service costs (p=0.002) and analysing patient costs (p=0.001). The differences in QALYs were also statistically significantly different (p=0.018).

Patients receiving Synvisc had consistently better clinical outcomes on the VAS, WOMAC Osteoarthritis Index, and Lequesne’s index, but these differences were not statistically significant when time was included as a covariate for effectiveness.

Authors' conclusions
The authors concluded that Synvisc provided better pain relief, and was less costly than Artz, but acknowledged that further research was required to define patients’ responsiveness to treatments.

CRD commentary
Interventions:
The interventions were sufficiently described and appear to have been appropriate. The authors indicated that a placebo effect was observed for injections in osteoarthritis, but no placebo group was included. They indicated that placebo effects were unlikely to affect the outcomes at four to six months.

Effectiveness/benefits:
The methods for gathering health outcomes and benefits were reported sufficiently. The study design was non-randomised with patients choosing which knee was given which treatment. As the authors noted, this could introduce bias as the condition that received Artz was more serious than the condition that received Synvisc. They acknowledged that no statistically significant differences in initial clinical scores were observed, but the status of Artz patients appeared to be worse; no adjustments were made to account for this imbalance. The study may have been underpowered, as it was designed to detect a larger change in the VAS than was found. The calculation of the utilities was done using a 100mm VAS, with worse scores being higher on the scale, which is opposite to how global quality of life is usually measured. It is not clear what the results represent as a general utility is the quality of an individual rather than one knee, and different drugs were given to different knees. This was not well described. The utilities from the VAS may not be comparable with those obtained using other measures.
Costs:
The perspectives were those of the national health service, the patient, and these two combined. As the authors acknowledged, the costs of physician time, administration, and patient travel were not included. The authors thought that their inclusion could improve the cost-effectiveness of Synvisc as there were two fewer injections. The comparison with starting values, assumes that patients who did not receive injections incurred no health care costs; this is unlikely to be true. Not all the relevant costs were considered.

Analysis and results:
The results were adequately reported, but not all appropriate comparisons were made. A full incremental analysis was not conducted, as both interventions were compared with initial values, not with each other. The interventions should have been compared with each other by calculating the difference in cost between the two and the difference in QALYs gained between the two, to calculate the incremental cost-effectiveness ratio, if possible. The authors calculated 95% confidence intervals for their average cost-effectiveness ratios, but these appear to have been erroneous as none of the confidence intervals contained their respective mean estimate.

Concluding remarks:
The utility outcome methods and the study results were not adequately reported, and the effectiveness and cost analysis was limited, so it is not clear how valid or certain the results are.

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