Collagenase clostridium histolyticum for the treatment of Dupuytren's contracture: systematic review and economic evaluation

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Scientific summary

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Scientific summary

Background

Dupuytren's disease is a benign, slowly progressive condition that affects the palmar and digital fascia in the hand. The disease is common, costly and associated with considerable functional impairment. It is characterised by thickening of the palmar skin and by the formation of nodules, which usually precede the development of fibrotic cords. As the disease progresses, the cords gradually contract [i.e. Dupuytren's contracture (DC)], leading to progressive flexion deformities in the fingers, particularly of the metacarpophalangeal (MCP) and/or proximal interphalangeal (PIP) joints.

There is currently no cure for Dupuytren's disease, and the goal of treatment is to restore hand function. Management of the disease is dependent on disease progression and degree of deformity, and most people do not seek or require treatment. Surgery remains the treatment of choice for severe contractures and some cases of moderate symptoms. Contracture may, however, recur in operated digits or in previously uninvolved areas of the hand, and complications are relatively common after surgery. Recently, the injection of collagenase clostridium histolyticum (Xiapex®, Pfizer Ltd) into the cord has been proposed as a non-operative, clinically viable alternative to surgery in some patients.

Objectives

To evaluate the clinical effectiveness and cost-effectiveness of collagenase as an alternative to surgery for treatment of adults presenting with DC with a palpable cord.

Methods

The assessment comprises (1) a systematic review of clinical studies; (2) a systematic review of cost-effectiveness studies; (3) a critique of the manufacturer economic evaluation; and (4) a de novo economic analysis.

Systematic review of clinical studies

The population under consideration was adults with DC with a palpable cord. The intervention was collagenase and the comparator was surgery, including fasciectomy, dermofasciectomy, open fasciotomy and percutaneous needle fasciotomy (PNF). Evidence was considered from randomised controlled trials (RCTs), non-randomised comparative studies and observational studies involving collagenase and/or surgical interventions.

Major electronic databases including MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Science Citation Index and the Cochrane Controlled Trials Register were searched from 1990 to February 2014. Reports of relevant evidence synthesis were sought from the Cochrane Database of Systematic Reviews and from the Database of Abstracts of Reviews of Effects. Evidence of relevant ongoing studies was sought from relevant databases. Conference proceedings of relevant clinical meetings were screened for the period 2011–13. All steps of the review process were performed independently by two reviewers. Meta-analyses were performed according to the availability of suitable data. Findings were summarised narratively when a quantitative synthesis proved unsuitable.

Review of the manufacturer's submission

The manufacturer's submission to the National Institute for Health and Care Excellence (NICE) consisted of a pragmatic literature review and cost-minimisation model. The literature review was summarised and the cost-minimisation analysis critically appraised.

Development of a de novo decision analysis

A de novo decision-analytic model, from the perspective of the NHS and Personal Social Services (PSS), was developed. Costs of treatment strategies were estimated for collagenase, PNF and limited fasciectomy (LF). A cost–utility Markov model was developed using TreeAge Pro (TreeAge Software, Inc., Williamstown, MA, USA), with results presented as cost per quality-adjusted life-year (QALY) gained. The alternative treatment pathways were embedded in the Markov model simulating the downstream impact of treatment. Thirteen events and states were used to model the care pathways: (1) initial treatment; (2) treatment success; (3) treatment failure; (4) recurrence; (5) second-line treatment; (6) treatment success following second-line treatment; (7) treatment failure following second-line treatment; (8) recurrence following second-line treatment; (9) third-line treatment; (10) treatment success following third-line treatment; (11) treatment failure following third-line treatment; (12) recurrence following third-line treatment; and (13) treatment complications. The model allowed the consequences of treatment strategies in terms of recurrence rates, health-related quality of life and costs to be captured over the adopted lifetime horizon. Costs were discounted at 3.5% per annum. Costs incorporated in the model included those associated with treatment, complications and further treatment following a possible recurrence. Health-state utilities associated with pre- and post-treatment were incorporated in the model. Incremental cost-effectiveness ratios (ICERs) were calculated, applying a ceiling ratio of £20,000 per QALY. Results for the base-case analysis were presented on the cost-effectiveness plane. Uncertainty was assessed by conducting deterministic and probabilistic sensitivity analyses, with results presented using cost-effectiveness acceptability curves (CEACs).

Subgroup analysis

Two subgroup analyses were conducted to assess (1) a population of patients with moderate disease and a mean of 1.47 affected joints; and (2) a population of patients with severe disease and 1.43 affected joints.

Results

Systematic review of clinical studies

The literature searches identified 720 potentially relevant citations and 502 conference proceedings. We selected and retrieved 187 reports for full-text assessment and subsequently excluded 153 reports. We included a total of five RCTs (493 participants) comparing collagenase with placebo, three RCTs (334 participants) comparing various surgical procedures, two non-randomised studies (105 participants) comparing collagenase with surgery, five non-randomised studies (3571 participants) comparing various surgical procedures and 15 collagenase case series (3154 participants). We further identified 18 ongoing trials.

Summary of benefits and risks

No head-to-head RCTs of collagenase versus surgery were identified. Of the five RCTs comparing collagenase with placebo, three provided outcome measures that could be assessed in meta-analyses. Primary MCP joints and PIP joints treated with collagenase were significantly more likely to achieve clinical success (i.e. reduction of contracture to 0–5° of normal 30 days after last injection) or clinical improvement (i.e. reduction in contracture of at least 50% 30 days after last injection) than those treated with placebo, with greater reduction for MCP joints than for PIP joints. Participants receiving collagenase showed significantly greater changes in contracture and range of motion from baseline than those who received placebo. Adverse events were generally mild to moderate and observed significantly more often in participants treated with collagenase (e.g. peripheral oedema, pain in extremity, injection site pain, injection site haemorrhage, pruritus). Four serious adverse events were reported among participants treated with collagenase (one case of complex regional pain syndrome, two cases of tendon rupture and one case

of flexion pulley rupture). Recurrence rates were derived mainly from observational studies. Recurrence rates for MCP joints varied from 0% at 1 year to 27% at 3 years, whereas those for PIP joints varied from 0% at 1 year to 56% at 3 years. The manufacturer provided 5-year observational data for the Collagenase Optimal Reduction of Dupuytren's – Long-term Evaluation of Success (CORDLESS) ongoing study that includes patients from previous collagenase cohorts. The rate of recurrence for successfully treated joints at 5 years was 46.7%. One small observational study (eight participants), with the longest published follow-up data (8 years), reported a recurrence rate of 67% (4/6) for MCP joints and 100% (2/2) for PIP joints.

The two non-randomised comparative studies assessing collagenase versus surgery (fasciectomy and PNF, respectively) were at high risk of bias and produced variable results.

The quality of RCTs and non-randomised comparative studies assessing different surgical techniques varied across studies, with inconsistencies in the type of surgical methods assessed, definition and measurement of efficacy and length of follow-up. In general, MCP joints showed greater clinical success than PIP joints, with slightly higher success rates for fasciectomy than fasciotomy. RCTs reported rates of recurrence that ranged from 13% for fasciectomy at 3 years to 85% for PNF at 5 years. Rates of recurrence in non-RCTs ranged from 0% to 50% for fasciectomy at around 3 years and from 15% to 50% for open fasciotomy at around 2 years. Serious adverse events across all studies on surgical interventions were low.

An indirect meta-analysis proved unfeasible owing to the lack of a common comparator.

Summary of cost-effectiveness

Systematic review of cost-effectiveness studies

Two cost–utility studies, conducted in the USA and Canada, were included and appraised against the *British Medical Journal* checklist for referees of economic analyses. These studies indicated that the cost of collagenase needed to be significantly reduced if it was to offer a cost-effective alternative to surgery.

Review of the manufacturer's submission

Three main concerns were identified: (1) the assumption of clinical equivalence between treatments was deemed untenable given that no direct comparative studies were identified and so a cost-minimisation approach was not likely to be appropriate; (2) PNF was not included as a comparator; and (3) some of the costing assumptions appeared implausible (e.g. assuming no further costs for treatment failures).

Decision analysis

The QALY differences between strategies were small, but it was found that LF produced an increase in QALYs in comparison with PNF and collagenase. LF was the procedure with the lowest recurrence rate and highest probability of treatment success. PNF was the least costly treatment strategy. Under base-case assumptions, collagenase was dominated (i.e. it was more costly and less effective than PNF and LF) and, as such, does not represent a cost-effective use of resources. LF was associated with additional costs over PNF of £1199 but generated an additional 0.11 QALYs gained. The ICER for LF was £10,871 per QALY gained in comparison with PNF. Applying a ceiling willingness-to-pay (WTP) threshold of £20,000 per QALY gained, LF was the preferable option from a cost-effectiveness perspective.

It is worth mentioning that the manufacturer limited their analysis to a subgroup of the population and assumed vial sharing. Their initial treatment costs of £1739 have been derived by costing treatment for a mean of 1.445 joints, using a mean of 1.6 injections per joint. These costs comprise administration costs of £969 (0.58/0.9 × £650 vial price × 1.6 injections × 1.445 joints) and outpatient visit costs of £756 [(1.6 × £225 (injection visit) + 1.6 × £102 (finger manipulation visit)] × 1.445 joints. A further £14 is added for the splint. Our model is based on no vial sharing, the treatment of three joints and 1.6 injections per joint, based on the findings of the CORD I trial.

Subgroup analyses

Subgroup analyses for moderate and severe disease showed negligible differences in QALYs gained between strategies. The main driver was the cost of treatment. As PNF is the cheapest option, it became the preferred strategy in terms of cost-effectiveness.

Sensitivity analyses

In the majority of scenarios, LF remained the preferable option. However, base-case findings were found to be sensitive to a number of uncertain parameters and assumptions. Collagenase was the preferred option when it could achieve a success rate of 77%. Where only one joint was affected, PNF became the most cost-effective option, and cost-effectiveness of collagenase improved. The probabilistic sensitivity analyses suggested that at a WTP for a QALY gained of £20,000, the chances of collagenase, PNF and LF being the most cost-effective treatment strategy were 0.2%, 35.5% and 64.3%, respectively. The case for cost-effectiveness of LF increased to 71.4% and 72.1% at threshold values of WTP of £30,000 and £50,000.

The cost-effectiveness results were primarily driven by treatment effectiveness. LF appeared to provide the most favourable cost-effectiveness estimates, owing to more favourable success and recurrence rates compared with PNF and collagenase. The model results were also driven by the incremental costs, including the incremental costs of first-line treatment, which were lowest in PNF and highest for collagenase. Higher failure and a higher recurrence would have subsequent knock-on effects on costs, through more patients progressing for further second- and third-line treatments. However, the success and recurrence rates for LF were sufficient to offset the extra 'up-front' costs of LF relative to the lower 'up-front' costs of PNF.

Discussion

Strengths, limitations of the analyses and uncertainties

Strengths

The methods used to conduct this assessment were detailed and thorough and the economic model was populated using the best available data for DC.

Limitations

The main limitations were the lack of comparative evidence on collagenase versus surgery, the small evidence base for estimating the effects of LF and PNF, and the inconsistencies in reporting across included studies, which hampered any reliable comparison of data. Many included studies were observational and, therefore, prone to the risk of bias associated with this type of study design. The economic model was built from a naive indirect comparison and was hampered by a dearth of suitable data. No studies had long-term follow-up data for costs, recurrence and quality of life that tracked patients post treatment. There was considerable uncertainty regarding the appropriateness of many model assumptions and inputs, and so the model outputs should be viewed with caution.

Uncertainties

Long-term data regarding rate of recurrence, complications and impact of repeated treatment after collagenase are lacking. Similarly, indications for second-line treatment after unsuccessful collagenase injections or certain surgical procedures (i.e. PNF) are not clearly defined. No quality-of-life data are available.

There was substantial uncertainty surrounding the values for many of the variables in the model and, therefore, the estimated ICERs should be interpreted with caution. Estimates of utilities for health states in the model were indirectly derived from a recently published discrete choice experiment rather than directly measured from a preference-weighted quality-of-life instrument. Thus, the extent to which changes in quality of life have been adequately captured is unknown. Although the deterministic and probabilistic analyses tackled some of these uncertainties, there was an underlying weakness in the clinical effectiveness evidence base that could not fully be addressed.

Conclusions

No RCTs or high-quality comparative studies of collagenase versus any surgical procedure are available. At present, there is no evidence to suggest that collagenase represents a cost-effective use of NHS resources. Based on the assumptions used within the model, LF appears to be the most cost-effective strategy. As the analyses were built on a naive indirect comparison of clinical effectiveness, the estimates should be interpreted with caution.

Implications for service provision

There was no evidence to suggest that collagenase is a cost-effective use of NHS resources for the treatment of patients with moderate to severe disease who are candidates for surgery.

Suggested research priorities

Large, well-designed RCTs are needed to compare the efficacy and safety of collagenase with surgical interventions, especially PNF and LF. Ideally, such trials would include a clear and agreed definition of recurrence, objective measurements of efficacy, longer follow-ups and quality-of-life measurements.

There is also a need for studies assessing specifically second-line treatments (revision procedures).

Further research should also try to identify resource use for people receiving DC treatments in order to assess if there is variability between strategies in health-care resource use over time.

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