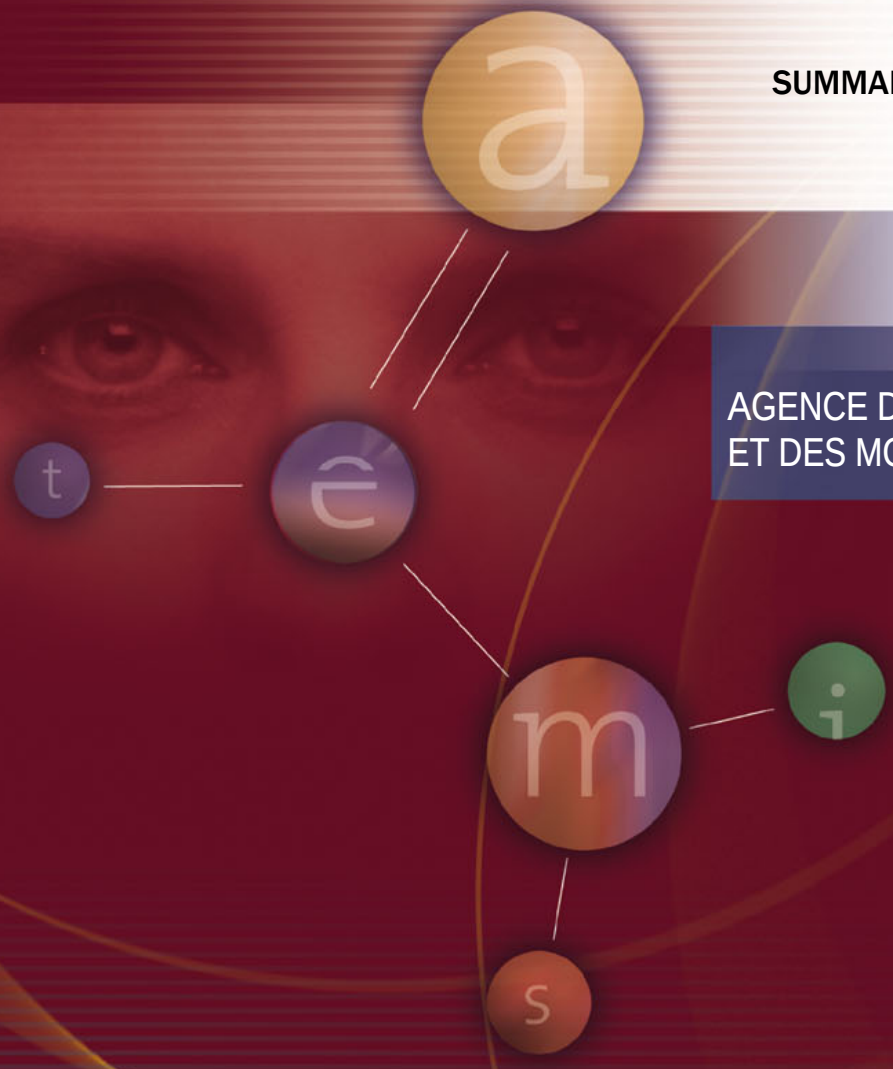
Viscosupplementation for the Treatment of Osteoarthritis of the Knee

SUMMARY



AGENCE D'ÉVALUATION DES TECHNOLOGIES
ET DES MODES D'INTERVENTION EN SANTÉ

Québec

Viscosupplementation for the Treatment of Osteoarthritis of the Knee

Report prepared for AETMIS by

Pierre Dagenais and Alicia Framarin

July 2007

Agence d'évaluation des technologies et des modes d'intervention en santé
Québec

The content of this summary was translated from an official French publication of the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS). Both the original report, entitled *La viscosuppléance pour le traitement de la gonarthrose* and the English summary are available in PDF format on the agency's Web site.

Scientific revision
Dr. Alicia Framarin, Scientific Director

Translation
Jocelyne Lauzière, MA, C. Tr.

Editorial Supervision
Suzie Toutant

Page layout
Sylvie Houle

Proofreading
Suzie Toutant

Bibliographic verification
Denis Santerre

Coordination
Lise-Ann Davignon

Coordination of external readers
Valérie Martin

Information specialists
Fleurette Grégoire
Pierre Vincent

Communications and dissemination
Diane Guilbault
Richard Lavoie

For further information about this publication or any other AETMIS activity, please contact:

Agence d'évaluation des technologies et des modes d'intervention en santé
2021, Union Avenue, Suite 10.083
Montréal (Québec) H3A 2S9

Telephone: 514-873-2563
Fax: 514-873-1369
E-mail: aetmis@aetmis.gouv.qc.ca
www.aetmis.gouv.qc.ca

How to cite this document:

Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS). Viscosupplementation for the Treatment of Osteoarthritis of the Knee. Report prepared for AETMIS by Pierre Dagenais and Alicia Framarin (AETMIS 07-06). Montréal: AETMIS, 2007, xv–67 pp.

Legal deposit
Bibliothèque nationale du Québec, 2007
Library and Archives Canada, 2007
ISBN: 978-2-550-50495-5 (PDF)

Mission

The mission of the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS) is to help improve the Québec health-care system. To this end, it advises and supports the Minister of Health and Social Services and decision-makers in the health-care system with regard to the assessment of health services and technologies. The Agency makes recommendations based on scientific reports assessing the introduction, diffusion and use of health technologies, including technical aids for the disabled, as well as the methods of providing and organizing services. The assessments examine many different factors, such as efficacy, safety and efficiency, as well as ethical, social, organizational and economic issues.

Foreword

Osteoarthritis of the knee is a degenerative joint disease affecting nearly 15% of people aged 60 years and older, and its incidence is expected to increase with the aging of the Québec population. Treatment involves a variety of therapeutic, physical, pharmacological and surgical approaches, such as total knee replacement. That procedure alone is already monopolizing a fair share of the health-care system's human and financial resources.

Viscosupplementation, a therapeutic option available for treating osteoarthritis of the knee, involves draining the affected joint then injecting it with hyaluronic acid, which is meant to reduce joint pain and stiffness. The clinical effectiveness of this treatment remains controversial, and its benefits in terms of relieving pain or delaying total knee replacement continue to be hypothetical. That is one of the reasons this treatment is not currently covered by Québec's public health insurance plan. Upon application by a drug manufacturer for public coverage of its viscosupplement product, the Ministère de la Santé et des Services sociaux asked AETMIS to evaluate the effectiveness, safety and cost-effectiveness of this treatment for osteoarthritis of the knee.

Analysis of the scientific evidence revealed considerable heterogeneity in the number of subjects per trial and in the methodological quality, often mediocre, of the studies used to perform the meta-analyses and economic analyses.

This report presents the results of our assessment of the clinical effectiveness and cost-effectiveness of this treatment for osteoarthritis of the knee.

Juan Robert Iglesias, MD, MSc, President and Chief Executive Officer

Executive summary

Osteoarthritis (OA) of the knee is a degenerative disease that frequently results in the need for total knee replacement. This disease has been absorbing an ever-growing share of the human and financial resources of Québec's health-care system.

Considered by some to be an alternative to surgery, viscosupplementation involves draining the affected knee then injecting it with hyaluronic acid. The clinical effectiveness of this procedure, which is intended to relieve pain and improve joint mobility, remains controversial.

After examining a series of meta-analyses and assessment reports on the different types of viscosupplements available, we concluded that viscosupplementation offers clinically modest relief from the symptoms of knee OA over a period that could last up to several weeks. It is furthermore a safe short-term treatment. Of note, these conclusions are based on secondary analyses of a multitude of small primary studies of poor methodological quality.

Available data did not help distinguish differences in the effectiveness of any one product over the others. It was equally impossible to identify patient subgroups more likely to benefit from this treatment compared with other currently available therapeutic modalities.

The cost-effectiveness of this treatment could not be established owing to discrepancies among the clinical data used and the methodological limitations of the economic studies examined. Funding this treatment would lead to a cost increase of some tens of millions of dollars per year and would command significant professional resources at a time when the health system is experiencing a labour shortage.

Consequently, AETMIS considers that, given the modest effectiveness of this therapeutic treatment compared with its relatively high cost and the additional professional resources required to administer it, it is not currently justified to contemplate funding viscosupplementation for all patients with OA of the knee.

It nonetheless raises the possibility that this product could be offered as a last-resort treatment to patients who do not achieve pain relief from conventional therapies or for whom these are contraindicated.

The recommendation not to cover this treatment does not exclude the fact that the MSSS may examine the possibility of exceptionally offering it to people who have failed to achieve pain relief from recognized conventional treatments, as do some other third-party payers.

AETMIS therefore recommends that granting agencies should encourage universities to pursue clinical research on viscosupplementation as part of the research areas or programs dedicated to musculoskeletal diseases and focused on either osteoarthritis or chronic pain.

Acknowledgements

This report was prepared by **Dr. Pierre Dagenais**, specialist in rheumatology, PhD (cell biology), MSc (clinical sciences), MSc (health technology assessment and management), research consultant, and **Dr. Alicia Framarin**, MSc (health administration), scientific director, at the request of the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS). AETMIS thanks **Chantale Lessard**, MSc (pharmaceutical sciences), doctoral candidate in public health who helped draft an earlier report that served as the basis for this one.

AETMIS would also like to thank the external reviewers whose many comments helped improve both the quality and the content of this report.

Dr. Nicolas Duval
Orthopedic surgeon, Clinique orthopédique Duval, Laval (Québec)

Dr. Bruno Fautrel
Professor of rheumatology, Université Pierre et Marie Curie – Paris VI, Groupe hospitalier Pitié-Salpêtrière, Paris (France)

Dr. Diane Lacaille
Assistant professor, Division of Rheumatology, University of British Columbia, and research scientist, Arthritis Research Centre of Canada (British Columbia)

Dr. Pierre Ranger
Orthopedic surgeon, associate clinical professor, Department of Surgery, Université de Montréal, Montréal (Québec)

DISCLOSURE OF CONFLICTS OF INTEREST

None to be declared.

Summary

Osteoarthritis (OA) of the knee is a chronic degenerative disease characterized by the gradual loss of cartilage. It presents with joint pain frequently associated with local swelling, and eventually results in loss of mobility affecting the autonomy of those with this disease. It is a common condition with a prevalence ranging from 10% to 15% in people aged 60 years and older. With the aging of the Québec population, the number of patients suffering from OA is expected to rise over the next decades.

Treatment initially involves analgesics or anti-inflammatory drugs followed by physical therapy or surgery. When the disease is too advanced, it is often necessary to surgically implant a prosthetic knee, a procedure that has a substantial impact on health-care organization and costs.

Viscosupplementation, one of the treatment options for knee OA, involves injecting into the joint a derivative of a physiological substance—hyaluronic acid—which lubricates and protects the cartilage. This substance, considered a therapeutic device despite the discovery of initially unsuspected pharmacological properties, is the subject of some clinical controversy over its effectiveness for the symptomatic relief of knee OA. In addition, this product, which costs between $300 and $500 (Cdn) per treatment, requires from one to five injections at one-week intervals and is not currently covered by public health insurance.

Since 1992 Health Canada has approved ten viscosupplements for the treatment of knee OA. Most of these products (seven) have a molecular weight of less than 2900 kilodaltons (kDa) and are composed of hyaluronate sodium. Hylan G-F 20 has a molecular weight of 6000 kDa, while Durolane, a non-animal stabilized product, is characterized by a very high molecular weight of over 100 000 kDa.

Upon application by a drug manufacturer hoping to make its viscosupplement more readily available to public health care system beneficiaries, the Ministère de la Santé et des Services sociaux (MSSS) asked Québec's Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS) to assess the effectiveness, safety and cost-effectiveness of viscosupplementation for the symptomatic treatment of knee OA. The end purpose of this request was to establish whether it would be advisable to make this treatment available to all public health care system beneficiaries.

The primary literature search covered a period up to September 30, 2005, with a literature watch until December 2006. Given the large number of secondary studies available, we decided to conduct an assessment of these studies. This assessment scrutinized six meta-analyses considered to be of satisfactory methodological quality. We also reviewed reports published by other health-technology assessment (HTA) agencies on topics such as the budget impact of this treatment on their respective health-care systems. Five economic studies were used to assess cost-effectiveness. Various insurance companies' health coverage policies were also reviewed.

The selected outcome measures varied from one meta-analysis to the other. Considerable heterogeneity was also found in the number of subjects per study and in the

methodological quality, often mediocre, of the studies used to perform these analyses. Our assessment results are presented in terms of the outcome measures that where comparable across the meta-analyses examined.

With regard to the effects of viscosupplementation for relieving pain at rest, the series of meta-analyses showed a statistically significant improvement compared with placebo. The difference between the experimental and control groups was nevertheless modest and generally less than what objective criteria would consider to be clinically significant. Pain relief seemed to occur mostly between the 5th and 13th weeks post-treatment, but it could last longer with hylan G-F 20.

A single meta-analysis showed statistically and clinically significant pain relief during weight bearing and walking. This outcome suggests that hylan G-F 20, which stands out from other products, would deliver more benefits than placebo by the fifth week after injection.

Analysis of the studies on the effects of viscosupplementation on functional impairment (the results of which were very heterogeneous though sometimes very favourable to the treatment) do not allow the conclusion that it has significant beneficial effects.

The patient global assessment outcome measure for relief of clinical symptoms of knee OA was evaluated in only a small fraction of the primary studies and used in only half of the meta-analyses examined for this report. For Hyalgan or hylan G-F 20, that evaluation did not generally show any clinically significant difference. Two of the meta-analyses reported subject-physician agreement regarding improvement in this outcome measure among the subjects treated with viscosupplementation.

We succinctly examined the comparisons between viscosupplementation and the other therapeutic options for knee OA, excluding total knee replacement. We noted that most of the comparative studies, which had widely differing research designs, were generally not conducive to meta-analysis. When meta-analyses were possible, they did not reveal significant benefits for viscosupplementation over the comparator interventions.

Few adverse effects and no mortality were observed post-treatment.

Although a few of the health economic cost-effectiveness or cost-utility studies reported positive cost-effectiveness, for instance, in terms of the incremental cost ratios between viscosupplementation and placebo or NSAIDs, those favourable outcomes were for the most part weakened by the poor methodological quality of the clinical trials under review. The use of clinical-effectiveness data from poor-quality trials generally very favourable to viscosupplementation may have in fact biased the results.

Budget-impact studies conducted mainly by other HTA agencies, such as the Ontario Health Technology Assessment Committee (OHTAC), showed that public funding of viscosupplementation could lead to additional health-care costs amounting to several tens of millions of dollars per year.

Greater use of these products, if they were covered by public health insurance, would also have an impact on health-care organization by decreasing the availability of musculoskeletal specialists, who would need to spend more time giving this treatment.

Conclusions

- Viscosupplementation relieves the symptoms of osteoarthritis of the knee, and this therapeutic effect may last several weeks. However, it is apparently not much greater than that of placebo and, according to some studies, it barely reaches clinical significance. Its pain-relieving effect seems comparable to that of other non-surgical options. Furthermore, the meta-analyses examined are based on primary studies of poor methodological quality that use widely differing outcome measures to assess therapeutic effect.
- Viscosupplementation is usually well tolerated and causes few adverse effects. This information comes from clinical trials of short duration and often with small sample sizes, which did not have examination of this issue as a primary objective. That is why we cannot comment definitively on the long-term safety of this treatment.
- Discrepancies among the clinical effectiveness outcomes used in the economic analyses and the much more modest ones achieved in the secondary studies, combined with the methodological limitations of the economic or clinical studies we examined to provide an answer about the cost-effectiveness of viscosupplementation, does not allow us to comment definitively on this question.
- Available scientific literature comparing viscosupplements derived from hylan G-F 20 with those derived from hyaluronate sodium do not allow to establish the clear superiority of any one of these products.
- Examination of the evidence did not permit identification of any particular therapeutic indications for subgroups of patients liable to gain clear clinical benefits from the effectiveness or safety of this product. We do not exclude the possibility that clinical research may one day justify such a therapeutic niche.
- The modest clinical benefit of viscosupplementation may never be great enough to outweigh its disadvantages, which include slow onset of action, the need for several weekly injections, the low but present risk of adverse reactions and the relatively high cost of this treatment.
- Moreover, given that its effectiveness is similar to that of other OA treatments, some third-party payers have developed policies that cover or reimburse viscosupplementation for some people who fail to achieve symptomatic pain relief from recognized treatments for OA of the knee. Common treatments mentioned in the literature include regular use of therapeutic doses of different drugs such as acetaminophen or NSAIDs; intra-articular corticosteroid injections; and the pain relief offered by different physical therapy or rehabilitation procedures. Coverage is also offered to patients waiting for knee replacement surgery.

Recommendations

Public health coverage

AETMIS considers that, given the modest effectiveness of this therapeutic treatment compared with placebo, its relatively high cost and the additional professional health resources required to administer it, it is not currently justified to contemplate public funding for viscosupplementation for patients with knee OA in Québec.

However, this treatment could be offered to some people, who would meet strict eligibility criteria similar to those adopted by other third-party payers presented in this report.

Of note, viscosupplementation is not a drug: as such, it cannot be granted exception drug status under the Public Prescription Drug Insurance Plan administered by the Régie de l'assurance maladie du Québec (RAMQ). A viscosupplement is a therapeutic device used in physicians' private practice consultations, which is why it is not covered by hospital budgets. If the MSSS were to consider it reasonable to move in the direction of partial coverage of viscosupplementation for exceptional cases, it would first need to establish very clearly defined administrative terms and conditions applicable to such coverage.

Research into osteoarthritis of the knee

The magnitude of OA of the knee as a chronic disease, which is expected to grow in incidence with the aging of the population, justifies research into new effective and cost-effective treatments.

In the case of viscosupplementation, the plethora of small poor-quality studies hindered the assessment of this treatment. It would be important to understand the mechanisms of action of viscosupplements and to determine their efficacy and safety but primarily their specific clinical indications by means of independent studies. Such studies must be well designed and must examine clinically relevant outcome measures such as pain during weight bearing and walking. The studies should also focus on clinical populations presenting with different severity levels of OA and different medical conditions restricting the use of other medical and surgical interventions, so as to establish the place of viscosupplementation among the therapeutic options for this disease.

AETMIS therefore recommends that granting agencies should encourage universities to pursue clinical research into viscosupplementation as part of the research areas or programs dedicated to musculoskeletal diseases and focused on either osteoarthritis or chronic pain.

Agence d'évaluation des technologies et des modes d'intervention en santé

Québec