Centre universitaire de santé McGill | McGill University Health Centre

Technology Assessment Unit of the McGill University Health Centre

TAU Annual Report

April 2013-2014

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Mission Statement

- To advise the hospital in difficult resource allocation decisions, using an approach based on sound, scientific technology assessments, and a transparent, fair decision-making process.
- To publish its research in peer-reviewed journals when appropriate, and contribute to the training of personnel in the field of health technology assessment.

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This publication was compiled and edited by Lorraine Mines of the Technology Assessment Unit of the McGill University Health Centre (MUHC TAU). This document is available in PDF format on our website:
http://www.mcgill.ca/tau/publications/annual

TAU Reports

NOTE: Projects are researched and drafts prepared by members of the MUHC TAU, referred below as "the authors". They are assisted by expert consultants appointed for each project. Draft reports are then circulated, reviewed, amended and finally approved by the full TAU Policy Committee who thereby take ownership of the recommendations made.

The following reports have been completed during the year.

RITUXIMAB

Title:	**The effectiveness and safety of rituximab (anti-CD20) in neurologic autoimmune diseases.**
Requestor:	Céline Dupont, Secretary of the MUHC Pharmacy and Therapeutic committee (P&T)
Publication date:	August 30, 2013
Authors:	Sinclair A., Nicolau I., Xie, X., Dendukuri N., McGregor M.
Background:	Rituximab is a chimeric monoclonal antibody directed at the B-cell surface marker CD201. Its exact mechanism of action is unclear, but its biological effect is to deplete B-lineage white cells that express CD20 (pre-B cells to lymphoplasmacytic cells), through a combination of direct signaling, complement dependent cellular cytotoxicity and antibody dependent cellular cytotoxicity1. For most patients, depletion lasts 6 to 12 months. Rituximab is effective in the treatment of B-cell malignancies2,3, but has also received regulatory approval for the treatment of refractory

rheumatoid arthritis (RA), Wegener's granulomatosis and microscopic polyangiitis. It has been used off-label in the treatment of a number of other autoimmune diseases4,5, particularly in patients whose disease is unresponsive to or who have unacceptable toxicity from prednisone and immunosuppressants.

The Technology Assessment Unit (TAU) was asked by Céline Dupont, Secretary of the MUHC Pharmacy and Therapeutic committee (P&T) to review the efficacy and costs of use of rituximab in four rare autoimmune diseases (myasthenia gravis, neuromyelitis optica, dermatomyositis, and chronic inflammatory demyelinating polyneuropathy) and to develop recommendations concerning its use in the MUHC.

Conclusions:

The available evidence is based on case series and case reports involving small numbers of subjects, and therefore should be interpreted with caution. However, the rarity of these disorders means that higher quality data may never be obtained.

Efficacy

Myasthenia gravis

☐ There is a small but consistent body of evidence from uncontrolled studies that suggests that patients with severe MG that is refractory to standard treatment, or who cannot tolerate standard treatment, may respond to rituximab, with in some cases marked clinical improvement to the point of remission.

☐ There is a small but consistent body of evidence from uncontrolled studies that suggests that patients with MG who require very frequent dosing (eg, weekly) with IVIg and/or PE to avoid deterioration may be able to abolish or reduce

their dependence. In such cases, use of rituximab may result in savings in cost and reduction in need for resources.

Neuromyelitis optica

☐ NMO is a distinct disease entity with a more severe prognosis than multiple sclerosis. Recurrent relapses early in the disease result in rapid accumulation of disability.

☐ There is a small but consistent body of evidence from uncontrolled studies that patients with NMO experience less frequent relapses following rituximab treatment (although a few may suffer exacerbations). On the basis of this evidence, rituximab with corticosteroids has entered guidelines and practice as first-line treatment.

Dermatomyositis

☐ In a randomized placebo-phase trial of rituximab in dermatomyositis (adult and juvenile) and polymyositis there was no difference between groups in the primary endpoint of time to improvement. By the end of the 44-week trial, most patients in both groups had reached the pre-defined measure of improvement. The evidence from a small number of case series for improvement is inconsistent. Some patients have experienced a modest improvement.

Chronic inflammatory demyelinating polyneuropathy

☐ There is an extremely small body of evidence from uncontrolled studies that suggests rituximab can produce improvement in patients with CIDP, with results ranging from modest improvement to remission.

Safety

Adverse events were reported for all the MG, DM and CIDP case series, and all the full-length reports of NMO case series. On-treatment deaths were reported for patients with NMO

and DM, and hospitalizations due to infection were reported for patients with MG, NMO, and DM. The small size of the dataset means that it is difficult to assess increased risk of adverse events due to rituximab.

Recommendations: The data are of insufficient quantity and quality to support a recommendation for the routine use of rituximab in any of these four conditions.

There is sufficient evidence to support the use of rituximab in the treatment of a limited number of patients, as described below.

Myasthenia gravis

There is sufficient evidence to support temporary and conditional approval of rituximab in the treatment of patients with myasthenia gravis under the conditions outlined below:

☐ Hospitalized patients whose disease is refractory to other therapies

☐ Hospitalized patients whose treatment options are limited due to intolerance or contraindications to more accepted therapies.

☐ Patients who require very frequent use (more frequently than 10 days) of IVIg or PE

☐ The number of new patients treated per year be limited to 10.

Since the present evidence concerning the use of rituximab is sparse, all relevant patient data should be collected and maintained in a regularly updated registry. In particular this should contain: Diagnostic data, reason for treatment, symptomatic status before and after treatment, dosage, adverse events.

The registry should be examined whenever appropriate, and at the latest in two years, at which time the question of permanent approval should be considered.

Neuromyelitis optica

There is sufficient evidence to support temporary and conditional approval of rituximab in the treatment of patients with neuromyelitis optica under the conditions outlined below.

☐ Patients diagnosed with NMO who have positive NMO-IgG and have experienced one or more severe relapses.

☐ The number of new patients treated per year be limited to a maximum of three.

Since the present evidence concerning the use of rituximab is sparse, all relevant patient data should be collected and maintained in a regularly updated registry. In particular this should contain: Diagnostic data, reason for treatment, symptomatic status before and after treatment, dosage, adverse events.

The registry should be examined whenever appropriate, and at the latest in two years, at which time the question of continued/permanent approval should be considered.

Dermatomyositis

There is insufficient evidence to justify the use of rituximab in dermatomyositis other than in the context of a formal research study.

Chronic inflammatory demyelinating polyneuropathy

There is insufficient evidence to justify use of rituximab in CIDP other than in the context of a formal research study.

General Recommendation

To treat patients with rare diseases such as MG and NMO without collecting, coordinating, and publishing the results would constitute a serious waste of opportunity and resources. Accordingly, every effort should be made to enlist colleagues at associated institutions to share in a treatment and reporting protocol that would allow significant information concerning the benefits and indications for the use of rituximab to be accumulated and published.

Renal Denervation

Title:	**Renal Denervation for Resistant Hypertension**
Requestor:	Dr. Sonny Dandona, Cardiology Division, Department of Medicine, MUHC.
Publication date:	August 30, 2013
Authors:	Nicolau I., Dendukuri N.
Background:	Renal denervation is used to control blood pressure in patients with resistant hypertension. The objective of this report is to summarize the literature on efficacy, effectiveness and safety of renal denervation for treatment of resistant hypertension, and to estimate the budget impact of this technology from the perspective of the MUHC.
Conclusions:	☐ The evidence reviewed in this report was largely derived from a comprehensive systematic review, one RCT, and one cohort study. ☐ The available evidence consistently demonstrates that in patients with resistant hypertension, renal denervation is followed by a lowering (not necessarily a normalisation) of blood pressure for periods of at least 6 months and possibly up to 2 years. Longer term results are not yet available.

☐ A few manageable complications are reported, but the number of observations is still too small to be able to evaluate the frequency and severity of complications.

☐ Four HTAs have recommended the acquisition of additional evidence of high quality with a longer follow up and outcomes that reflect clinically meaningful reductions in cardiovascular adverse events.

☐ There is therefore a need for further research to verify the expected benefits of this procedure, to establish that they are long-lasting, and to better estimate the rate and severity of complications. Such research is reported to be taking place

Recommendations: It is recommended that this technology receive temporary and conditional approval as follows:

☐ There is agreement by the applicant and the divisional head that this technology be only applied in the context of a formal research study designed to further evaluate its efficacy or effectiveness and safety. The study should meet associated requirements of ethics committee approval and informed consent of subjects.

☐ Although this research is partly sponsored by the manufacturer, the applicant should retain the rights of publication of any data generated.

☐ Renal denervation procedures should be limited to a maximum of 20 per year and subsidized by the manufacturer as indicated above.

☐ The question of permanent approval be reconsidered at a maximum of two years after the first procedure is completed.

TAVI

Title:	**Transcatheter aortic valve implantation (TAVI) in patients with aortic stenosis. Update of Report No. 45**
Requestor:	Mr. Gary Stoopler, Administrative Director, MUHC
Publication date:	August 31, 2013
Authors:	Sinclair A., Xie X., McGregor M.
Background:	Calcific aortic stenosis is a disease of the elderly, characterised by progressive narrowing of the aortic valve. Once symptoms (angina, heart failure, blackouts) develop, prognosis becomes extremely limited. The only treatment that will prolong life is replacement of the defective valve by an artificial valve, a procedure that is traditionally carried out at open surgery under cardiac arrest. However, since 2002, procedures have been developed by which a prosthetic valve can be installed by catheterisation, via the femoral or subclavian arteries or the cardiac apex. These procedures are called transcatheter aortic valve implantation or TAVI. A 2009 review carried out by the Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC) concluded that1: ☐ This is an effective technology that should continue to be funded by the MUHC. ☐ Since this is a relatively new procedure, and one in which both the selection of patients and its execution are crucial for success, the Cardiovascular Division should maintain a registry, including follow-up, of all cases. ☐ The registry should be examined by the MUHC in approximately one year at which time the decision to continue funding should be reviewed.

The present report, carried out at the request of Mr. Gary Stoopler, Administrative Director, MUHC, consists of an update of the current literature on the TAVI procedure, and a review of the MUHC experience since 2009.

At present, two TAVI devices (valve and implantation assembly) have been granted a Class IV license in Canada, the Edwards SAPIEN valve on June 22, 20112, and the Medtronics CoreValve on August 1, 20123. In both cases, the approved indication is for severe, symptomatic aortic stenosis in a patient considered inoperable (having ≥50% risk of death or irreversible morbidity from surgical aortic valve replacement)

Conclusions:

☐ Symptomatic severe aortic stenosis carries a grave prognosis, with survival rates of approximately 50%, 35% and 20% at one, two, and three years with medical treatment, including valvuloplasty.

☐ In inoperable patients there is evidence of benefit from aortic valve replacement by TAVI, with marked functional improvement and survival rates of the order of 95%, 69.3%, and 56.7% at 30 days and one and two years respectively, based on data from the PARTNER B trial. There is wide consensus that for such patients TAVI is appropriate treatment.

☐ In high-risk operable patients it is unclear whether TAVI has an advantage over surgical valve replacement. Survival and complication rates are comparable, with the exception that TAVI resulted in more paravalvular regurgitation (moderate to severe in 12.2% versus 0.9% at 30 days [PARTNER A], with apparently little progression for up to 3 years) and stroke (4.7% versus 2.4% at 30 days, and 6.0% versus 3.1% at one year, respectively).

	☐ Costs. From the perspective of the MUHC, the procedure cost for TAVI versus SAVR is $29,755 versus $17,395 respectively (a difference of $12,360). Comparison of costs in TAVI versus medical management in inoperable patients is less certain, since it is difficult to estimate the cost of medical management precisely.
Recommendations:	☐ For patients with reduced life expectancy due to severe symptomatic aortic stenosis, in whom surgery is considered not to be an option, if age and comorbidity are such that a continuing life of adequate quality can be anticipated, valve replacement by the TAVI procedure should now be considered standard of care. ☐ For patients for whom surgery is an available option, SAVR should normally be the chosen procedure. ☐ The practice of sharing responsibility for patient selection by a multidisciplinary team, of recording that this has been done, and of recording all relevant clinical material in a registry, as recommended by INESSS, should continue.

Sutureless Aortic Valve

Title:	**Surgical aortic valve replacement with the ATS Enable® sutureless aortic valve for aortic stenosis**
Requestor:	Mr. Gary Stoopler, Administrative Director, MUHC
Publication date:	September 2, 2013
Authors:	Sinclair A., Xie X., McGregor M.
Background:	Surgical implantation of a bioprosthetic valve is the standard treatment for symptomatic severe aortic stenosis. Use of stented bioprostheses, which are designed to remain in position without the need for suturing, can reduce the length and invasiveness of surgery. We were requested by Mr. Gary

	Stoopler to review the evidence for one such valve, the ATS Enable Sutureless Bioprosthesis Model 6000
Conclusions:	☐ The evidence for the use of the 3f ATS Enable valve in aortic stenosis is provided by uncontrolled case series involving a relatively small number of published cases (~400 patients), with approximately 1 year follow-up. ☐ MUHC surgeons report that use of SuAVR facilitates partial sternotomy with associated reductions in operation time which may result in improved patient outcomes in selected cases. Optimal patient selection, side effect profile (particularly relative to the more established alternatives), and durability beyond ~1 year remain to be defined. ☐ From the perspective of the MUHC, use of SuAVR via mini-sternotomy instead of SAVR via standard sternotomy will have an increased budget impact of $3,750 per case. Offset savings may result in some increased efficiency
Recommendations:	☐ There is insufficient evidence to support the general introduction of the sutureless aortic valve. ☐ However, there is sufficient evidence of the safety and short term efficacy of the sutureless aortic valve to justify its use for selected patients in a cardiac surgical centre in an academic hospital such as the MUHC. Accordingly, it is recommended that this device receive temporary, conditional approval for use in those patients in whom a conventional surgical procedure is deemed to be high risk but in whom the overall surgical risk is still acceptable. ☐ Since it is a relatively new procedure a registry including the reasons for case selection, and all pertinent data including operation times and length of hospital stay with follow-up should be maintained, and reviewed in approximately one year.

☐ Patients should be informed in writing of the lack of information on long-term risks of the sutureless valve.

Diffusion

- Our reports are indexed in the international database for the Center for Reviews and Dissemination, York University, UK. http://www.crd.york.ac.uk/crdweb/
- Our reports are diffused from our website (www.mcgill.ca/tau) .

TAU Related Activities

TAU staff members represent TAU at quarterly meetings of hospital-based technology assessment units in Quebec that are organized at INESSS.

Dr. Nandini Dendukuri and Dr. James Brophy developed a 2-credit course EPIB 670: Introduction to Health Technology Assessment, that was taught at, Department of Epidemiology, Biostatistics and Occupational Health, McGill University

Dr. James Brophy selected to join the board of governors of Institut national d'excellence en santé et en services sociaux (INESSS) 2010-

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Presentations
Oral

Dendukuri, N. Introduction to mini-case studies for the breakout sessions and case study of regional/hospital HTA in practice. CADTH, Hospital/Regional HTA Symposium: Local evidence-based decisions for health care sustainability. November 18-19, 2013, Ottawa, Ontario

McGregor, M. Hospital/Regional HTA: Perspectives and Practices from across Canada. CADTH, Hospital/Regional HTA Symposium: Local evidence-based decisions for health care sustainability. November 18-19, 2013, Ottawa, Ontario

Dendukuri, N. Evaluation of a diagnostic test in the absence of a gold-standard reference test in the context of a meta-analysis". Centre of Clinical Epidemiology, Jewish General Hospital, Montreal. April 2013.

Dendukuri, N. Diagnostic meta-analysis of a gold-standard reference test". Symposium on 'Methods for Evaluating Medical Tests & Biomarkers' organized by The Cochrane Collaboration, Birmingham, UK. July 2013.

Selected Peer-Reviewed Publications Related to Technology Assessment Activities (* denotes students and staff)

Sinclair A , Xie X , Teltscher M , Dendukuri N, "Systematic review and meta-analysis of a urine-based pneumococcal antigen test for diagnosis of community-acquired pneumonia caused by Streptococcus pneumoniae.", Journal of Clinical Microbiology 2013 Jul;51(7):2303-10

Steingart KR, Schiller I*, Horne DJ, Pai M, Boehme CC, Dendukuri N. Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev. 2014 Jan 21;1: PubMed PMID: 24448973.

Zhou Y*, Dendukuri N. Statistics for quantifying heterogeneity in univariate and multivariate meta- analyses of binary data: The case of meta-analyses for diagnostic accuracy. Statistics in Medicine. Article first published online: 19 FEB 2014.

Awards

THE MAURICE MCGREGOR AWARD

In 2014 CADTH established the *Maurice McGregor Award* to recognize rising HTA stars early in their careers. The award is open to individuals with the potential to be leaders in the field, from graduate students to those who have been working in HTA for a maximum of 10 years. The Award is named in honour of Dr. Maurice McGregor, Past Chair of the Technology Assessment Unit of the McGill University Health Centre and Professor Emeritus of McGill University. Dr. McGregor was also appointed Officer of the Order of Canada for having pioneered and championed the field of HTA in Canada and for his leadership in medical education and cardiology.

Dr. Maurice McGregor was honored with the **CADTH Anniversary Medal** which honors individuals whose hard work and dedication helped establish and maintain the technology assessment (HTA) as an essential component of a system effective health care. In 2014, the CADTH Anniversary Medal focuses on the recognition of individuals who have played a key role in the establishment and promotion of the use of ETS in Canada, policy makers, producers and users ETS. Dr. Maurice McGregor is is one of the preeminent figures in this important field of health policy analysis. As the founding President of the Conseil d'évaluation des technologies de la santé du Québec and a founding CCOHTA Board member, he was instrumental in building the framework for the use of HTA in Canada.

Grants

Principal Investigator: .Dr Nandini Dendukuri , NSERC "Bayesian Methods for Epidemiologic Studies. Total amount: $55,000, 2013-2018

Principal Investigator: .Dr James Brophy, Co-investigator: Dr. Nandini Dendukuri, CIHR**, "**Comparative effectiveness research for the drug treatment of atrial fibrillation." Total amount: $141,548, 2013-2015

Postscript

The TAU attempts to adjust the services we offer to conform to the resources available in a transparent, logical, fair, and consistent fashion. While some of our recommendations have not supported the acquisition of a technology, and have thus "saved money", others have supported new developments because they have identified the benefits, and found them to be sufficient to justify the increased expenditure. Our sincere thanks are due to the many members of the MUHC who have assisted with data collection, to those who have served as Consultants, and to the members of the Committee who have dedicated many hours to the consideration of these problems. *Maurice McGregor*.