ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

Comprehensive Research Plan:

Protocol for systematic review and network meta analysis of treatments for chronic hepatitis B

W. Wong PhD, P. Pechlivanoglou PhD, J. Bielecki BSc, MISt, V. Rac MD, PhD, M. Krahn MD, MSc, FRCPC

Toronto Health Economics and Technology Assessment (THETA) collaborative, University of Toronto, Canada. 144 College st. M5S3M2 ON Toronto

Systematic Review Team

November 11th, 2014

Background

In Canada as in other developed countries, the growing burden of chronic hepatitis B (CHB) infection poses a significant public health concern. It is estimated that at least 136,000, or 0.4% of the population, is infected with hepatitis B virus (HBV) [1]. The exact prevalence of CHB is not known, as CHB is often asymptomatic [2]. Of those infected with CHB, 40% will silently progress to liver cirrhosis and thereby be at risk of dying prematurely of liver failure and/or liver cancer [3].

In the early 2000s, lamivudine (LAM) has been introduced as the first oral therapy for treating CHB [4]. However, LAM turned out to be a treatment option with poor effectiveness due to common antiviral resistance. Since the introduction of lamivudine, other drugs became available for treating CHB including standard and pegylated interferon-alfa, adefovir, entecavir, telbivudine, and tenofovir [4]. Among these treatment options, only standard and pegylated interferon alfa is used as a short-term treatment that when successful, may lead to long-term immune control without the need for further antiviral therapy. For all other treatments, once started, lifelong administration may be required. Initiating therapy with each of these medications involves consideration of drug specific trade-offs such as high and potentially lifelong medication costs, potential side effects including risk of antiviral resistance.

In Canada, two of the most potent drugs, entecavir and tenofovir, with the highest genetic barrier to resistance were approved for treatment for CHB in 2005 and 2008 respectively. Clinical guildlines [4, 5] recommend that both drugs should be used as first-line therapy for CHB. Patients have also expressed the need for new treatments with higher cure rates, higher barrier to resistance, better side effect profiles, and reduced treatment burden, which are affordable and accessible [6]. However, both entecavir and tenofovir are not covered as first-line agents by Onatio Drug Benefit for treating CHB [6]. Thus, providing evidence-informed recommendations for changes to the existing listing of treatments for the Ontario public drug formulary is important.

The objective of this analysis is to identify the available evidence on comparable benefits and harms of the available CHB treatments through a systematic review and synthesize this evidence using network meta-analysis. This network meta-analysis is expected to inform not only clinical but economic and policy decision making as it will serve as input for an economic decision model on the reimbursement of CHB treatment. Results from this analysis will be disseminated through presentations at: i) national and international scientific meetings, such as the CADTH symposium and the American association for the study of liver Diseases meeting; and ii) publication in peer-reviewed journal.

Methods

This systematic review was designed to comply with the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA statement [7]). This systematic review protocol will be registered with PROSPERO.

Eligibility Criteria

The systematic review will include both Randomized Controlled Trials (RCTs and observational studies

(i.e. case-control and cohort studies) that compare at least two CHB treatments or placebo/no treatment in adults patients diagnosed with HBeAg-positive and/or HBeAg-negative CHB. The review will include but not be limited to treatment options such as standard and pegylated interferon-alfa, lamivudine, adefovir, entecavir, telbivudine, and tenofovir as monotherapy or combination therapy. The review will not be limited by language or by year of publication. All studies regardless of their follow-up period will be included in the review. The outcomes of interest that will be investigated include virologic and biochemical response, HBeAg loss, HBeAg seroconversion, HBsAg loss, histologic improvement, and adverse events.

Information sources

Studies will be indentified through a comprehensive literature search designed and carried out by a librarian (JB). The following electronic databases, will be searched from the date of inception, and the same search strategy will be translated as appropriate for each database: MEDLINE (Ovid), EMBASE (Ovid), Web of Science (Thomson Reuters), Cochrane and DARE (Database of Abstracts of Reviews of Effectiveness) databases will be searched. Search terms will include controlled vocabulary (MeSH) and text-words in the following three concept areas: Chronic Hepatitis B (CHB), antiviral agents (standard interferon, pegylated interferon, lamivudine, adefovir, entecavir, telbivudine, tenofovir) and the following published and validated filters will be applied consecutively: Randomized Control Trials (RCTs) [8] or Prognosis studies [9] or Causation (Etiology) studies [10] or Cohort and case-control studies [11]. There will be no language restriction. In addition to electronic database searches additional studies will be identified from i) stakeholder consultations and ii)inspection of reference lists of relevant articles and iii) hand searching of pertinent journals. Detailed search strategy for MEDLINE is provided in the Appendix 1.

Study selection and screening process

Two reviewers will independently screen the titles and abstracts of the studies identified by the search strategy for match with the inclusion criteria, using a hierarchical screening method adapted from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The full text from the studies identified as potentially eligible will be assessed by the same reviewers independently to determine if they meet the inclusion criteria. Disagreements between the two reviewers at any stage of the study selection process will be resolved with discussion. Inter-rater agreement will be measured with a kappa statistic. Clinical experts will be consulted to identify any relevant studies that were not identified through the extraction process.

Data collection

A data extraction form will be constructed and will be used to extract information from the selected studies. Both reviewers will independently extract the data from all identified studies. The extracted information will be cross-checked between the two reviewers and any discrepancies will be resolved through discussion or if necessary after contacting the corresponding authors of the studies.

Data items

Data related to the patient and study characteristics as well as to the outcomes of interest will be extracted from each study. Patient characteristics will include but not be limited to mean age, gender distribution, disease severity, comorbidities, proportion of patients with HBeAg-positive CHB diagnosis,

proportion of patients with HBeAg-negative CHB diagnosis, viral load at baseline etc. Study characteristics will include but not be limited to treatment duration, study design, intervention and comparators, sample size, year of study conduct, year of publication, country of origin. Finally information related to the outcomes of interest (number of patients with i) virologic and biochemical response; ii) HBeAg loss; iii) HBeAg seroconversion; iv) HBsAg loss; v) histologic improvement; and vi) adverse events) will be extracted from every study. The definition of virologic response that will be used in this review is attainment of undetectable levels of HBV DNA as determined by the polymerase chain reaction test for each particular study. Biochemical response is defined as the return of the ALT levels to below the upper limit of normal. HBeAg and HBsAg loss are defined as the absence of HBeAg and HBsAg detection respectively given the threshold used in each study. Histologic improvement of the liver is defined as a 2-point improvement on the Knoddel inflammation score without an increase in fibrosis. Given the anticipated heterogeneity on the treatment related adverse events we will measure the impact of serious adverse events, withdrawals due to adverse events, and any adverse events.

Risk of Bias / Quality Assessment

Risk of bias in the identified RCTs will be assessed independently by both reviewers using the Cochrane risk of bias tool [12]. The risk of bias tool is used to assess certain aspects that can constitute sources of bias. These include the method used in random sequence generation, the method of allocation concealment, the blinding of participants, personnel and assessors of the outcomes, the completeness of outcome data, the presence of selective reporting or any other aspect that may cause concern about the presence of bias. The Newcastle-Ottawa tool [13] will be used to asses the quality of the identified case-control and cohort studies. Using this tool each study will be assessed with respect to the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively.

Synthesis of results

The characteristics of both randomized and non-randomized identified studies will be presented narratively while the patient characteristics of the identified studies will be pooled seperately for RCTs and observational studies to create descriptive summary estimates for the synthesized population. For the patient characteristics that cannot be pooled, the estimates from each study will be narratively described. Risk of bias for each study and bias domain will be also presented.

Network meta-analysis methods will be used to synthesize the evidence from the phase III RCTs identified on relative effectiveness and safety across the treatment options. Binomial NMA models will be applied for binary outcomes while Poisson models will be applied for count data, rates and for outcomes where the follow-up time across studies varies. The network meta-analysis will be conducted within a Bayesian framework using WinBUGS v.1.4.3. (MRC Biostatistics Unit, Cambridge, England) [14]. Under this framework the distribution of each parameter of interest (posterior distribution) will be estimated through a Markov Chain Monte Carlo simulation method. Both fixed and random effect models will be considered based on the data availability in the included studies. Mean estimates for the parameters of interest together with their 95% credible intervals will be constructed from the posterior distributions of the MCMC simulations.

In order to evaluate the presence of between study heterogeneity, subgroup analyses will be performed and, if necessary, network meta analysis models that allow for covariate adjustments will be

implemented. Through subgroup analyses we will investigate the effect of the proportion of patients with HBeAg-positive or HBeAg-negative CHB, high vs low risk of bias etc. Covariates such as mean study age, mean viral load, ALT level etc will be examined using network meta-regression modelling [15]. Consistency between direct evidence and indirect evidence of relative efficacy, safety and tolerability will be assessed in the presence of closed loops. The assessment will be done using the "node-splitting" method [16] which statistically compares the "similarity" of the pooled estimates from the direct evidence to those from indirect evidence. Sensitivity analyses will be performed to assess the impact of assumptions related to the type of model (fixed vs random) and the prior distributions of the model (e.g. informative vs vague, type of distribution assumed etc) on the estimates of relative efficacy and safety.

Competing interests

Dr. Krahn received unrestricted grant from Gilead Sciences during 2009 – 2010.

APPENDIX 1

RANDOMIZED CONTROLLED TRIALS

MEDLINE

Filter: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format from Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Database(s): Ovid MEDLINE(R) 1946 to September Week 4 2014, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations October 08, 2014

Search Strategy:

#	Searches
1	interferon-alpha/ or ((interferon adj5 alpha) or (interferon adj5 alfa) or (peginterferon adj5 alpha) or (ifn adj5 alpha) or alpha-interferon or interferon-alpha or ifn-alpha or leif).mp.
2	Lamivudine/ or LAMIVUDINE (nm) or ("gr 103665" or gr103665 or heptodin or hepivir or "nsc 6207533 nsc6207533" or zefix or 3tc or epivir or (bch189 or "bch 189") or (gr109714x or "gr 109714x") or (hepitec or heptovir or trizivir or zeffix or zidovudine or lamivudine)).mp.
3	(adefovir or hepsera or preveon or pmea or adv or phoshonylmethoxyethyl: or ("gs 0393" or gs0393 or gs840 or "gs 840" or gs0840 or "gs 0840")).mp.
4	(142217-69-4 or 209216-23-9).rn. or (entecavir or baraclude or etv or "bms 200475" or bms200475 or "sq 34676" or sq34676).mp. or (Telbivudine or Epavudine or "LdT 600" or LdT600 or "Nv 02b Nv02b" or Sebivo or tenofovir$).mp. or (3424-98-4 or 147127-19-3 or 147127-20-6).rn. or pmpa.ti,ab.
5	1 or 2 or 3 or 4
6	Hepatitis B Antibodies/ or hepatitis b/ or hepatitis b, chronic/ or Hepatitis B Antibodies/ or hepatitis b antigens/ or hepatitis b core antigens/ or hepatitis b e antigens/ or hepatitis b surface antigens/ or Hepatitis B virus/ or ("hep b" or "hepatitis b" or "type b hepatitis" or "hbv" or (chronic adj2 homologous adj2 serum adj2 jaundice) or (chronic adj2 diffuse adj2 hepatocellular adj2 inflamm:)).mp.
7	(randomized controlled trial or controlled clinical trial).pt. or (randomly or randomized or placebo?).ab. or clinical trials as topic.sh. or trial.ti.
8	exp animals/ not humans.sh.
9	7 not 8
10	5 and 6 and 9
11	remove duplicates from 10

OBSERVATIONAL STUDIES

MEDLINE

Filters:

Prognosis – MEDLINE (Best balance of sensitivity and specificity) from: Wilczynski NL, Haynes RB; The Hedges Team. Developing optimal search strategies for detecting clinically sound

prognostic studies in MEDLINE. BMC Medicine. 2004;2:23 (5 pages).

Causation (Etiology) – MEDLINE (Best balance of sensitivity and specificity) from: Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound causation studies in MEDLINE. Proc AMIA Symp. 2003;719-23.

Cohort and case-control studies – MEDLINE form: The InterTASC Information Specialists' Sub-Group. Search filter resource. http://www.york.ac.uk/inst/crd/intertasc/

Database(s): Ovid MEDLINE(R) 1946 to October Week 1 2014, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations October 08, 2014.

Search Strategy:

#	Searches
1	interferon-alpha/ or ((interferon adj5 alpha) or (interferon adj5 alfa) or (peginterferon adj5 alpha) or (ifn adj5 alpha) or alpha-interferon or interferon-alpha or ifn-alpha or leif).mp.
2	Lamivudine/ or LAMIVUDINE (nm) or ("gr 103665" or gr103665 or heptodin or hepivir or "nsc 6207533 nsc6207533" or zefix or 3tc or epivir or (bch189 or "bch 189") or (gr109714x or "gr 109714x") or (hepitec or heptovir or trizivir or zeffix or zidovudine or lamivudine)).mp.
3	(adefovir or hepsera or preveon or pmea or adv or phoshonylmethoxyethyl: or ("gs 0393" or gs0393 or gs840 or "gs 840" or gs0840 or "gs 0840")).mp.
4	(142217-69-4 or 209216-23-9).rn. or (entecavir or baraclude or etv or "bms 200475" or bms200475 or "sq 34676" or sq34676).mp. or (Telbivudine or Epavudine or "LdT 600" or LdT600 or "Nv 02b Nv02b" or Sebivo or tenofovir$).mp. or (3424-98-4 or 147127-19-3 or 147127-20-6).rn. or pmpa.ti,ab.
5	Hepatitis B Antibodies/ or hepatitis b/ or hepatitis b, chronic/ or Hepatitis B Antibodies/ or hepatitis b antigens/ or hepatitis b core antigens/ or hepatitis b e antigens/ or hepatitis b surface antigens/ or Hepatitis B virus/ or ("hep b" or "hepatitis b" or "type b hepatitis" or "hbv" or (chronic adj2 homologous adj2 serum adj2 jaundice) or (chronic adj2 diffuse adj2 hepatocellular adj2 inflamm:)).mp.
6	prognosis.sh. or diagnosed.tw. or cohort:.mp. or predictor:.tw. or death.tw. or exp models, statistical/
7	1 or 2 or 3 or 4
8	5 and 6 and 7
9	(risk or mortality).mp. or cohort.tw.
10	5 and 7 and 9
11	epidemiologic methods/
12	limit 11 to yr=1966-1989
13	exp cohort studies/ or exp case-control studies/ or (case$ and control$).tw. or controlled clinical trial.pt. or cohort$.tw.
14	12 or 13
15	5 and 7 and 14
16	remove duplicates from 15 (COHORT AND CASE-CONTROL STUDIES Search)
17	remove duplicates from 10 (CAUSATION STUDIES Search)
18	remove duplicates from 8 (PROGNOSIS STUDIES Search)

References

[1] M. Rotermann, K. Langlois, A. Andonov, and M. Trubnikov, "Seroprevalence of hepatitis B and C virus infections: Results from the 2007 to 2009 and 2009 to 2011 Canadian Health Measures Survey," in *Health Reports* vol. 24, ed: Health Analysis Division of Statistics Canada, 2013.

[2] W. W. Wong, G. Woo, E. Jenny Heathcote, and M. Krahn, "Cost effectiveness of screening immigrants for hepatitis B," *Liver Int,* vol. 31, pp. 1179-90, Sep 2011.

[3] Y. S. Hsu, R. N. Chien, C. T. Yeh, I. S. Sheen, H. Y. Chiou, C. M. Chu*, et al.*, "Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B," *Hepatology,* vol. 35, pp. 1522-7, Jun 2002.

[4] M. Sherman, S. Shafran, K. Burak, K. Doucette, W. Wong, N. Girgrah*, et al.*, "Management of chronic hepatitis B: consensus guidelines," *Can J Gastroenterol,* vol. 21 Suppl C, pp. 5C-24C, Jun 2007.

[5] A. S. Lok and B. J. McMahon, "Chronic hepatitis B," *Hepatology,* vol. 45, pp. 507-39, Feb 2007.

[6] M. Sherman and S. S. Lee, "Canadian patients with chronic hepatitis B cannot access appropriate drug treatments: a call for change," *Can J Gastroenterol,* vol. 25, pp. 538-41, Oct 2011.

[7] D. Moher, A. Liberati, J. Tetzlaff, D. G. Altman, and P. Group, "Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement," *Ann Intern Med,* vol. 151, pp. 264-9, W64, Aug 18 2009.

[8] J. P. T. Higgins and S. Green. (2011). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* Available: www.cochrane-handbook.org

[9] N. L. Wilczynski, R. B. Haynes, and T. Hedges, "Developing optimal search strategies for detecting clinically sound prognostic studies in MEDLINE: an analytic survey," *BMC Med,* vol. 2, p. 23, Jun 9 2004.

[10] N. L. Wilczynski, R. B. Haynes, and T. Hedges, "Developing optimal search strategies for detecting clinically sound causation studies in MEDLINE," *AMIA Annu Symp Proc,* pp. 719-23, 2003.

[11] *Cohort and case-control studies – MEDLINE form: The InterTASC Information Specialists' Sub-Group. Search filter resource*. Available: http://www.york.ac.uk/inst/crd/intertasc/

[12] J. P. Higgins, D. G. Altman, P. C. Gotzsche, P. Juni, D. Moher, A. D. Oxman*, et al.*, "The Cochrane Collaboration's tool for assessing risk of bias in randomised trials," *BMJ,* vol. 343, p. d5928, 2011.

[13] G. A. Wells, B. Shea, D. O'Connell, J. Peterson, V. Welch, M. Losos*, et al.* (2000). *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

[14] D. J. Lunn, A. Thomas, N. Best, and D. Spiegelhalter, "WinBUGS-a Bayesian modelling framework concepts, structure, and extensibility.," *Statistics and computing,* vol. 10, pp. 325-337, 2000.

[15] S. Dias, A. J. Sutton, N. J. Welton, and A. E. Ades, "Evidence synthesis for decision making 3: heterogeneity--subgroups, meta-regression, bias, and bias-adjustment," *Med Decis Making,* vol. 33, pp. 618-40, Jul 2013.

[16] S. Dias, N. J. Welton, D. M. Caldwell, and A. E. Ades, "Checking consistency in mixed treatment comparison meta-analysis," *Stat Med,* vol. 29, pp. 932-44, Mar 30 2010.