

The role of hepatitis B immunoglobulin in hepatitis B related liver transplantation: Canadian Transplant Centre Position Paper

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ABSTRACT

Introduction. Hepatitis B virus (HBV) related liver transplant (LT) recipients face a high risk of HBV reinfection in the absence of continuous post-operative HBV prophylaxis. Combination HBV prophylaxis with hepatitis B immune globulin (HBIG) and nucleos(t)ide anti-viral agents prevents HBV recurrence in 90 to 100% of patients who undergo transplantation for hepatitis B and is considered the standard of care in Canada. Post liver transplant HBV prophylaxis protocols vary with regard to the dosing, duration and routes of HBIG administration. All Canadian transplant centres managing liver transplant patients were surveyed as to their HBV transplant protocols. **Results.** Results of the survey showed that the majority of the Canadian transplant centres use an oral antiviral in combination with long term or indefinite HBIG for prevention of HBV recurrence post liver transplantation. Studies were done to test new protocols using lower HBIG doses given intramuscularly or subcutaneously alone or in combination with antiviral agents. **Conclusion.** Long term HBIG administration post transplantation in combination with antiviral agents is an integral part of Canadian HBV related liver transplant protocol.

Key words. Hepatitis B. Immunoglobulin. Liver transplantation. Canada.

INTRODUCTION

Currently, hepatitis B virus (HBV) infection accounts for approximately 5% of liver transplant related activity in Canada, through the treatment of end-stage liver disease or hepatocellular carcinoma.¹ The overall prevalence of HBV is between 0.1 and 1%, but is much higher in the Inuit and the much larger Canadian Asian community with an estimated prevalence upwards of 25%. In the absence of post liver transplant HBV prophylaxis, HBV-related disease was once considered a contraindication for liver transplantation, with 5 year patient survival < 20%.² As of 1996, the advent of Hepatitis B Immunoglobulin (HBIG) enabled successful transplantation and combination of HBIG plus a nucleos(t)ide anti-

viral has become the standard of care to prevent disease recurrence.³⁻⁵ A large number of studies have shown that HBIG in combination with antiviral therapy has been effective in decreasing hepatitis B recurrence and improving patient survival, such that the outcomes post-transplant for HBV are superior for many other chronic liver diseases.^{6,7}

The mechanism whereby HBIG protects the transplanted liver against HBV reinfection is not well understood. HBIG may protect naive hepatocytes against infection by neutralizing HBV by forming immune complexes with any circulating virus, and by blocking HBV receptors on liver cells (hepatocytes). Presumably, this intercepts virus sequestered in extra-hepatic tissues post transplantation and prevents the new liver hepatocytes from being infected.⁸ There is also the possibility, supported by in-vitro experiments, that the endocytosis of HBIG by hepatocytes impairs the release of hepatitis B surface antigen and active virus.⁹ Regardless of mechanism, recurrence rates thus decreased from 100% with a 5 year survival of < 48%, to patient and graft survival comparable to non-viral liver disease and reinfection rates of < 10%.^{10,11}

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CANADIAN PERSPECTIVE

The use of HBIg in combination with antiviral agents post HBV-related liver transplant for prevention of HBV recurrence is considered standard of care in Canada. Currently in Canada two HBIg products are available, HepaGam B® (Cangene Corporation, Winnipeg MB, Canada) and HyperHEP B™ S/D (Talecris Biotherapeutics Inc., Research Triangle Park NC, USA). Despite the success of HBIg combined with antiviral therapy, neither of these products were licensed for use in the post-transplant setting in North America until approval of HepaGam B by Health Canada and the US FDA in 2007. HepaGam B has undergone a Phase III, multi-center, open-label clinical trial, and several single center cohort studies in North America which demonstrated excellent efficacy and safety results.^{12,13} Initial HBIg protocols consisted of high dose regimens utilizing 10,000 IU of IV HBIg in the anhepatic phase of transplantation and daily for one week. Thereafter, further dosing was administered as needed to maintain hepatitis B surface antibody (HBsAb) titers of > 1,000 IU/mL as per the Terrault protocol.¹⁰ A lower dose, intramuscular protocol in combination with lamivudine, was pioneered in Canada with equivalent results and is the origin of current patterns of practice.¹⁴ In August of 2010, prior to an HBIg forum to discuss the current and future role of HBIg for prevention of HBV recurrence following liver transplantation, eight Canadian centres managing liver transplant patients were surveyed as to their HBV transplant protocols. Results of the survey based on response from seven out of eight centres were presented and discussed among representatives from Canadian Centres managing liver transplant patients.

RESULTS OF SURVEY. CANADIAN STANDARD OF CARE¹⁵

- **Anhepatic.** All centres administer HBIg once the diseased organ has been removed in the operating room. Dosing ranges from 2,170 IU to 20,000 IU, with the majority using 10,000 IU.
- **Maintenance.** In the first week, daily HBIg dosing was the consensus but dosing ranged from 2,170 IU to 10,000 IU, thereafter dosing and HBsAb titer goals were stratified as to the risk of recurrence depending on the patient's pre-transplant disease activity.
- **Adjuvant therapy.** Nucleos(t)ide analogue medications have revolutionized HBV therapy, and

they are universally added to the pre and post transplant regimes if available. All Canadian Transplant Centres utilize nucleos(t)ide analogues to further decrease the risk of recurrence as is the standard of care worldwide.

- **Long-term follow-up.** After the first year, a small minority (1) centre discontinues the HBIg therapy, and all continue the use of the nucleos(t)ide analogues, checking the patient's HBsAb titer approximately monthly and HBV serology yearly.
- **Recurrence.** Overall recurrence is not documented, however centres estimated a rate of < 2%, with one centre documenting 6 viral breakthroughs in patients who had stopped HBIg therapy.

DISCUSSION

Overall there was consensus among participants of the HBIg forum on using an oral antiviral in combination with long term or indefinite HBIg for prevention of HBV recurrence post liver transplantation. HBIg will always have a place in the HBV related post transplant prophylaxis regimen as it rapidly clears circulating HBV and provides an alternate mechanism to minimize the risk of mutations & HBV recurrence. In general, HepaGam B is the HBIg product utilized by liver transplant centers surveyed. Canadian centres will continue to use HBIg due to concerns of nucleos(t)ide resistance, cost and as a guard against intermittent non-compliance. If patients miss a dose of the antiviral agent (either inadvertently or because of non-compliance to therapy), the HBIg is present to prevent recurrence.

The use of nucleos(t)ide analogues alone or in combination is being evaluated at non-Canadian centres.¹⁶⁻¹⁸ Although very potent antivirals exist, there are concerns with their use in isolation. Viral breakthrough rates have been studied for lamivudine, adefovir and entecavir, with breakthrough rates of 71, 29, and 16% at 5 years for each agent respectively. Additionally these medications will have a significant impact on the provincial drug formularies that provide financial coverage for these patients.¹⁹⁻²¹ Cost implications are also high for HBIg-based protocols which include not only drug acquisition costs but also nursing administration and monitoring costs, however, as discussed, optimizing patient outcomes, access and adherence to these therapies favors HBIg use. Focus has therefore shifted to investigate alternate dosing schedules in order to maximize cost-effectiveness and optimize long-term use.

Considerable variability was noted among Canadian centres with regard to the dosing, duration and routes of administration of HBIg. Collaborative research initiatives are underway after pilot projects in Vancouver and London looking at novel routes of administration. Outpatient subcutaneous or intramuscular administration has been shown to be effective, well tolerated and cost beneficial.^{13,22} Ongoing Canadian research initiatives to individualize dosing and administration of HBIg through intramuscular and subcutaneous routes will likely improve patient outcomes and decrease costs.

CONCLUSION

Hepatitis B viral infection contributes to a significant portion of liver transplant activity in Canada, and will likely grow due to the demographics of immigration to Canada. The advent of HBIg and introduction of antiviral agents were a major breakthrough in management of HBV related liver transplant patients. Long term HBIg administration post transplantation in combination with antiviral agents is an integral part of successful HBV related liver transplantation.

DISCLOSURES

The Canadian Transplant HBIg Forum was sponsored by Cangene Inc, Winnipeg Manitoba, Canada. Drs. Levstik, Greanya and Yoshida provided lectures at the Forum and were paid honoraria for their contributions. Drs. Levstik, Wong, Greanya and Yoshida have not been paid for their work on this paper.

The Canadian Transplant HBIg Forum included representatives from: the University of British Columbia, Vancouver, BC; the University of Calgary, Calgary AB; the University of Manitoba, Winnipeg MN; the University of Western Ontario, London ON; the University of Toronto, Toronto ON; McGill University, Montreal QC; Dalhousie University, Halifax NS.

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