INESSS
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Optimal use of immunoglobulin in solid organ transplantation

English summary

Une production de l'Institut national d'excellence en santé et en services sociaux (INESSS)

Québec

SUMMARY

Optimal use of immunoglobulin in solid organ transplantation

Introduction

Nonspecific human immunoglobulins (Igs) are stable products derived from human plasma. Their cost is high, their supply variable, and their use in Québec has been steadily increasing for many years in a number of areas of medicine, including solid organ transplantation. The framework for the use of nonspecific human immunoglobulins is therefore one of the concerns of Québec's *Comité consultatif national de médecine transfusionnelle*, which has called attention to the lack of recommendations concerning their use for most solid organ transplantation indications.

At the suggestion of the *Comité consultatif national de médecine transfusionnelle*, the *Ministère de la Santé et des Services sociaux* asked the *Institut national d'excellence en santé et en services sociaux* to develop clinical recommendations concerning the use of nonspecific human immunoglobulins in solid organ transplantation, in the form of an optimal use guide. At the completion of this project, INESSS had developed clinical recommendations for the optimal use of nonspecific human intravenous immunoglobulin (IVIg) in solid organ transplantation to prevent or treat eight different infections and to prevent or treat transplant rejection in pediatric or adult solid organ transplant recipients (kidney, heart, lung, liver, pancreas or small intestine).

Methodology

In response to the mandate from the *Ministère de la Santé et des Services sociaux*, the *Institut national d'excellence en santé et en services sociaux* used a collaborative approach known as "knowledge mobilization". This approach consists of analyzing and assessing scientific and contextual data as well as the perspectives of clinicians.

Scientific data

To assess the efficacy and safety of Igs in children and adults for each of the selected solid organ transplantation indications, we conducted a systematic review for each one in several bibliographic databases from the date of their inception to June 2021 to identify all the primary studies and systematic reviews with a meta-analysis published on the subject. The official product monographs for Health Canada-approved Igs, Health Canada and U.S. Food and Drug Administration advisories, and a transfusion accident and incident report published by the *Institut national de santé publique du Québec* were consulted to complete the search concerning safety.

To document the conditions of Ig use, we conducted a systematic literature review to identify guidance documents, clinical practice guidelines and any other items containing clinical recommendations, published between January 2011 and June 2021, for all of the indications of interest. The grey literature and the official product monographs for Health Canada-approved immunoglobulins were also consulted to complete the search concerning the conditions of Ig use.

Documents were selected according to predefined exclusion and inclusion criteria, and their quality was assessed using the appropriate tools. These steps were carried out independently by two professional scientists. The data were then extracted by one scientist and validated by the other. The results are presented in tables and summarized in the form of an analytical narrative synthesis. The main efficacy results reported in the selected studies are expressed as brief statements of scientific evidence, and an overall level of scientific evidence was assigned to each statement of evidence according to a four-level scale (high, moderate, low, insufficient).

Lastly, to determine the main characteristics of each of the indications of interest in the optimal use guide on immunoglobulins in solid organ transplantation, we explored the scientific literature and clinical practice guidelines.

Contextual data and the clinician perspective

The number of persons treated and the quantity (expressed in grams) of Igs administered in Québec in 2018 and 2019 were documented from a report on their use prepared by the *Institut national de santé publique du Québec* using information extracted from the TraceLine™ system database. Health Canada's website was consulted to check the approval status of IVIg.

Recommendations were drawn up in collaboration with the advisory committee consisting of Québec experts.

In general, the information on contextual data and the perspectives of the consulted clinicians are presented in narrative form and summarized in tables.

Process of constructing recommendations

The analysis and synthesis of the scientific and contextual data as well as the clinician perspective enabled structuring of the arguments leading to the formulation of the recommendations. Only those recommendations for which there was a consensus among the experts were retained. The solid organ transplantation indications for preventing or treating eight different infections and for preventing or treating transplant rejection in pediatric or adult solid organ transplant recipients (kidney, heart, lung, liver, pancreas or small intestine) were divided into four use categories: IVIg recommended, IVIg a possible treatment option, IVIg not recommended, and insufficient data.

Results

For the indications of interest, the results of the systematic reviews permit the conclusion, with a level of evidence considered low, that IVIg is effective in treating transplant rejection in solid organ transplant recipients in certain situations. Most of the clinical practice guidelines selected also recommend the use of IVIg to treat transplant rejection. The advisory committee's members therefore determined that IVIg may be recommended as a treatment option for acute humoral transplant rejection in solid organ transplant recipients, but that there is insufficient evidence to recommend IVIg in the context of chronic humoral transplant rejection.

The systematic literature review indicates, with a level of evidence considered moderate to low, that IVIg is ineffective in preventing transplant rejection in solid organ transplant recipients. However, the clinical practice guidelines recommend the use of IVIg to prevent transplant rejection in transplant recipients in specific situations. The advisory committee's members also indicated that IVIg could be considered a treatment option for preventing transplant rejection in hyperimmunized individuals or in cases of HLA- or ABO-incompatible transplants. In the case of liver transplantation, the committee members also indicated that IVIg could be considered a treatment option to prevent transplant rejection in HLA- or ABO-incompatible transplant recipients. However, there is insufficient data regarding the prevention of transplant rejection in hyperimmunized individuals who have received a liver transplant.

The data from the systematic reviews indicate that IVIg is only marginally effective or ineffective for four indications: the prevention of Epstein-Barr virus infections (low level of evidence), the treatment of norovirus infections (low level of evidence), and the prevention and the treatment of polyomavirus BK infections (moderate to low level of evidence). In addition, the systematic literature reviews did not yield any primary studies and have an insufficient level of evidence to draw any conclusions regarding the treatment of Epstein-Barr virus infections or the prevention of norovirus infections. The clinical practice guideline recommendations and the clinician perspective are consistent in not recommending the use of IVIg to prevent Epstein-Barr virus, norovirus or BK polyomavirus infections, or to treat Epstein-Barr virus or norovirus infections. Nevertheless, the experts consulted indicated that IVIg may be considered a treatment option for treating confirmed polyomavirus BK nephropathy in solid organ transplant recipients, particularly if concurrent transplant rejection is suspected in a kidney transplant recipient.

Lastly, the systematic literature reviews did not yield any primary studies and have an insufficient level of evidence to draw any conclusions regarding the treatment or prevention of respiratory syncytial infection or parvovirus B19, West Nile virus, adenovirus or HHV-6 infections. This is because these infections are quite rare. Based on the analysis of all available data, which include the clinical practice guideline recommendations and the clinician perspective, the advisory committee's members indicated that the data are insufficient for recommending or not recommending the use of IVIg to prevent or treat respiratory infections or to treat West Nile virus or adenovirus

infections. In addition, they do not recommend the use of IVIg to prevent parvovirus B19, adenovirus, West Nile virus or HHV-6 infections, or to treat HHV-6 infections. Nevertheless, they indicated, as do the clinical practice guidelines, that IVIg may be considered a treatment option for parvovirus B19 infection in solid organ transplant recipients.

Scientific safety data indicate that most transfusion reactions that occur after IVIg administration are not serious. Nevertheless, different serious reactions have been reported in the scientific literature or to Québec hemovigilance system, but these events are rare. Two of them, thromboembolic event and hemolytic reaction, have been the subject of studies and of communications from Health Canada and the Food and Drug Administration in recent years.

Conclusions

Evidence on the efficacy data of Igs was available for a minority of the indications of interest, and the level of evidence was considered low or insufficient for 17 of these 18 indications.

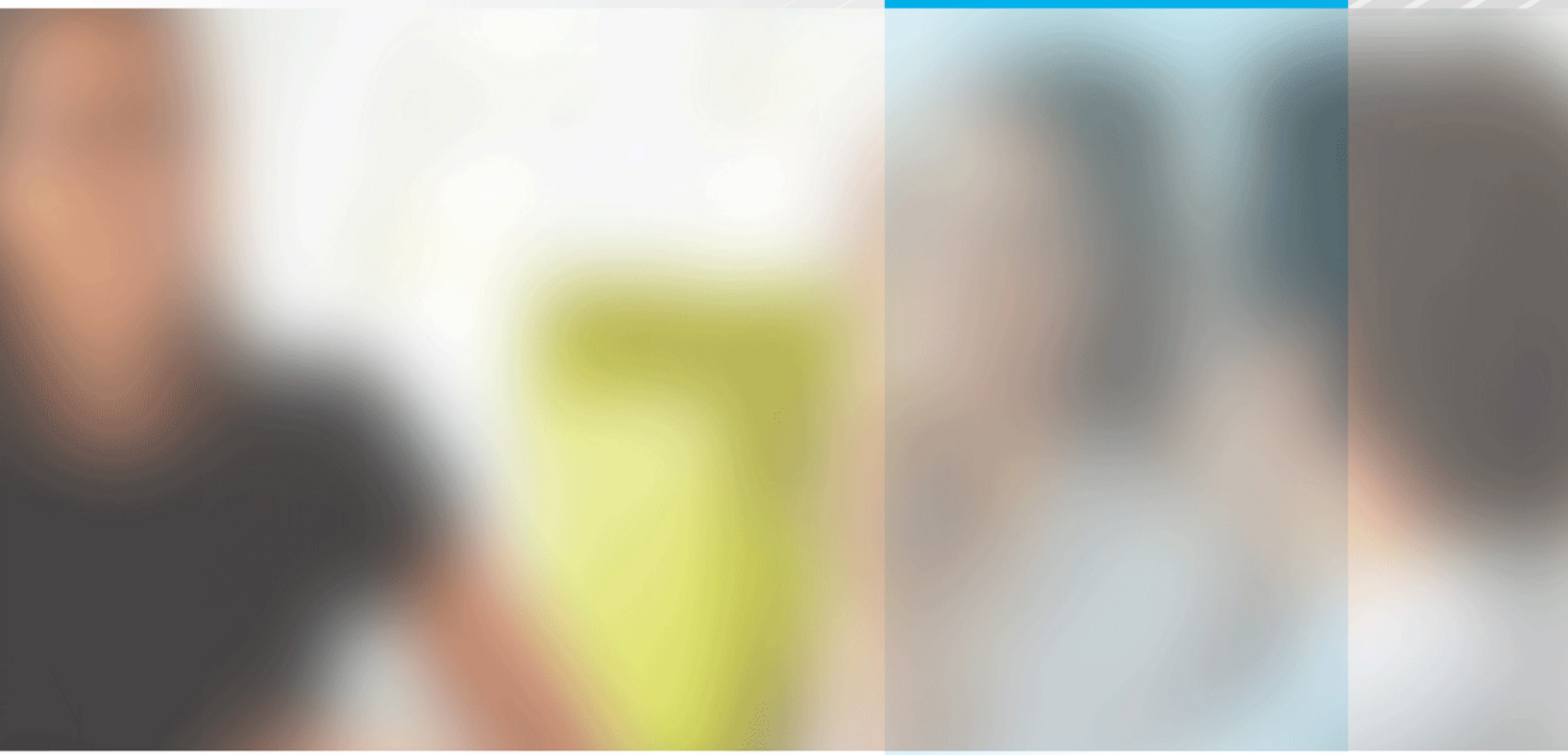
An assessment of the scientific and contextual data and the clinician perspective led to the following conclusions:

- the *Institut national d'excellence en santé et en services sociaux* recommends that IVIg be considered a treatment option, a second-line treatment or, in specific situations, for the treatment of transplant rejection or the prevention of transplant rejection under specific conditions of use in solid organ transplant recipients, and for the treatment of parvovirus B19 or polyomavirus BK infections in solid organ transplant recipients;
- the *Institut national d'excellence en santé et en services sociaux* does not recommend the use of IVIg to prevent Epstein-Barr virus, norovirus, HHV-6, parvovirus B19, polyomavirus BK, adenovirus, or West Nile virus infections or to treat of Epstein-Barr virus, norovirus or HHV-6 infections in solid organ transplant recipients.

Because of insufficient data, the *Institut national d'excellence en santé et en services sociaux* could not make recommendations concerning the use of IVIg to prevent transplant rejection in hyperimmunized individuals who have received a liver transplant, to treat chronic humoral rejection in solid organ transplant recipients, to prevent respiratory syncytial virus infections or to treat respiratory syncytial virus, adenovirus or West Nile virus infections in solid organ transplant recipients.

The use of IVIg may be associated with transfusion reactions, which are usually not serious. Serious transfusion reactions, which are rare, have, however, been reported.

In conclusion, the recommendations in the optimal use guide on nonspecific human immunoglobulins in solid organ transplantation are in addition to those in the previous guides for neurology, hematology, clinical immunology, dermatology, rheumatology, and infectious diseases, which are intended to reduce the inappropriate use of this resource.



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