INESSS
LE SAVOIR PREND FORME

OCTOBER 2022

Optimal use of immunoglobulin in fertility, cardiology and other indications

English summary

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

Québec

SUMMARY

Optimal use of immunoglobulin in fertility, cardiology and other indications

Introduction

Non-specific human immunoglobulins 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 several areas of medicine, including infectious diseases. Providing a framework for the use of non-specific human immunoglobulins is therefore one of the concerns of Québec's Comité consultatif national de médecine transfusionnelle (CCNMT), which has called attention to the lack of recommendations regarding their use for indications in specialties other than neurology.

At the CCNMT's suggestion, the Ministère de la Santé et des Services sociaux (MSSS) therefore asked the Institut national d'excellence en santé et en services sociaux (INESSS) to develop clinical recommendations regarding the use of human immunoglobulin for indications in hematology, clinical immunology, dermatology, rheumatology, infectious diseases, solid organ transplantation and other indications, in the form of optimal use guides. At the completion of this project, which should bring this major undertaking to a close, INESSS developed clinical recommendations for the optimal use of human immunoglobulin administered intravenously (IVIg) or subcutaneously (SCIg) to treat nine indications that were not covered in the previous projects.

Methodology

The literature search was conducted by a scientific information advisor (librarian) in collaboration with a scientific professional. The main concepts selected for developing the strategy were immunoglobulins and fertility or other indications. The MEDLINE, Embase, and Cochrane Database of Systematic Reviews bibliographic databases were queried in November and December 2021. In addition, a manual search of the gray literature was performed by consulting, among others, the websites of learned societies specializing in the field related to the topic of interest. These searches were supplemented by consulting the product monographs for Health Canada-approved immunoglobulins, Health Canada and U.S. Food and Drug Administration (FDA) advisories, and a report on transfusion-related incidents and accidents published by the Institut national de santé publique du Québec (INSPQ). Details of the strategy are presented in Appendix A of the document entitled "Annexes complémentaires".

Items were selected and retrieved and methodological quality assessed independently by two scientific professionals, and the assessment of the scientific evidence and the analysis of the data collected were performed by one professional and validated the other.

The efficacy results are accompanied by a statement of evidence to which an overall level of scientific evidence was assigned according to a four-level scale (high, moderate, low, insufficient). The safety data were synthesized in narrative form.

Contextual utilization data for Québec were documented using a report on their use produced by the Institut national de santé publique du Québec based on data extracted from the TraceLine™ database. Health Canada's website was consulted for the approval status of intravenous immunoglobulins.

Lastly, the clinician perspective was documented in collaboration with the advisory committee consisting of Québec experts and is presented in summary form in a table.

The assessment of the scientific and contextual data and the clinician perspective enabled us to structure the argument leading to the development of the recommendations. Only those recommendations for which there was a consensus among the experts were selected. The nine indications were divided into four use categories: IVIg recommended, IVIg a possible treatment option, IVIg not recommended, and insufficient data.

Results

Scientific data on the efficacy of intravenous immunoglobulin were available for most of the indications of interest. They provide a level of evidence considered moderate to insufficient that it is effective in preventing recurrences of neonatal hemochromatosis in women who have had a previous pregnancy affected by this disorder and in improving the clinical and paraclinical signs in children with myocarditis.

With a low level of evidence, the scientific data suggest that intravenous immunoglobulin would be effective in improving the clinical and paraclinical signs in adults with fulminant myocarditis or peripartum cardiomyopathy, or in women who experience unexplained, repeated miscarriages.

The level of scientific evidence regarding the efficacy of immunoglobulin in improving clinical outcomes in individuals experiencing unexplained, repeated implantation failure or in preventing the recurrence of seizures in individuals with systemic capillary leak syndrome was considered low or insufficient.

The available scientific data suggest that intravenous immunoglobulin is not effective in improving clinical outcomes in individuals with obstetrical antiphospholipid syndrome (with a level of evidence considered moderate or insufficient) or dilated cardiomyopathy (with a level of evidence considered low to insufficient).

Lastly, the level of scientific evidence regarding the efficacy of immunoglobulin in improving the clinical and paraclinical signs of hypogammaglobulinemia due to plasmapheresis treatment was considered insufficient.

The scientific safety data indicate that most of the transfusion reactions that occur after intravenous immunoglobulin administration are not serious. Nevertheless, various serious reactions have been reported in the scientific literature or to Québec's hemovigilance system, but these events are rare. Two of these reactions, thromboembolic reaction and

hemolytic reaction, have been the subject of studies and of Health Canada and the Food and Drug Administration advisories in the past few years.

According to the selected clinical practice guidelines, immunoglobulin is recommended or can be considered a treatment option for neonatal hemochromatosis and systemic capillary leakage syndrome. Most of the clinical practice guidelines do not recommend or have not examined the use of immunoglobulin for unexplained recurrent miscarriages, recurrent implantation failure in the context of assisted reproduction, obstetric antiphospholipid syndrome, dilated cardiomyopathy, or myocarditis. The selected clinical practice guidelines have not considered or do not make any recommendations concerning peripartum cardiomyopathy or post-plasmapheresis hypogammaglobulinemia. In the latter case, the recommendations concerning secondary hypogammaglobulinemia, for which immunoglobulin may be contemplated as a treatment option, were considered while acknowledging their indirectness.

A search of the scientific literature and clinical practice guidelines did not yield any studies that have published efficacy or safety data on subcutaneous immunoglobulin or recommendations concerning its use for the indications of interest. It was therefore the perspectives of the stakeholders consulted, gained from their expertise and clinical experience, that were used to make the recommendations for use included in the optimal use guide.

Recommendations

Based on an assessment of the scientific and contextual data and on the clinician perspective, the following recommendations have been made:

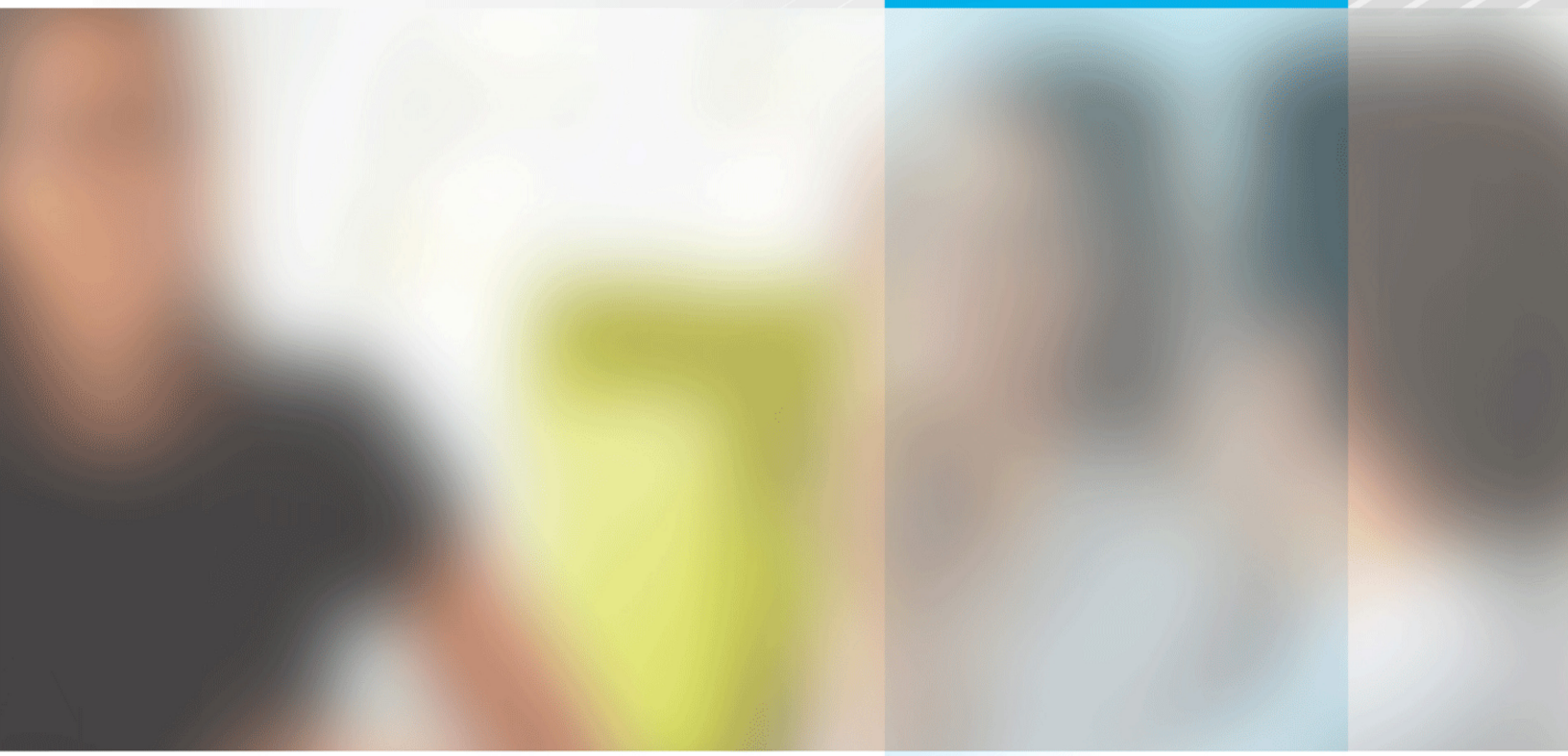
- INESSS recommends the use of IVIg or SCIg in pregnant women who have had a previous pregnancy affected by neonatal hemochromatosis and to prevent the recurrence of life-threatening attacks in individuals with a confirmed diagnosis of systemic capillary leak syndrome;
- INESSS recommends that IVIg or SCIg be considered a treatment option for second-line therapy or in special situations for certain women who experience unexplained, repeated miscarriages or repeated implantation failure in the context of assisted reproduction, for acute myocarditis in children and fulminant myocarditis in adults, and for certain cases of post-plasmapheresis hypogammaglobulinemia;
- INESSS does not recommend the use of IVIg for obstetrical antiphospholipid syndrome, dilated cardiomyopathy or peripartum cardiomyopathy, or for non-fulminant myocarditis in adults;
- Because of insufficient available scientific data on the treatment of an acute attack in a patient with systemic capillary leak syndrome, INESSS was not able to make any recommendations regarding this indication.

Conclusion

In conclusion, the recommendations made in the optimal use guide on the use of immunoglobulin in fertility, cardiology and other indications are in addition to those in the previous guides for neurology, hematology, clinical immunology, dermatology, rheumatology, infectious diseases and solid organ transplantation, all of which are intended to reduce the inappropriate use of this resource.

Update

The need to update the optimal use guide will be assessed in 4 years, that is, in 2026, based on the advancement of the scientific data, the listing or introduction of new therapies or technologies, practice changes, and INESSS's needs with regard to future work.



Siège social

2535, boulevard Laurier, 5e étage
Québec (Québec) G1V 4M3
418 643-1339

Bureau de Montréal

2021, avenue Union, 12e étage, bureau 1200
Montréal (Québec) H3A 2S9
514 873-2563
inesss.qc.ca

Institut national d'excellence en santé et en services sociaux
Québec