RESEARCH IMPACT CASE STUDY

Canadian Blood Services
BLOOD PLASMA STEM CELLS ORGANS & TISSUES

Making IVIg treatment safer for patients

What was achieved?

Research at Canadian Blood Services has provided critical insights and reshaped our understanding of the impact of intravenous immunoglobulin (IVIg) on the patients who use it. IVIg products contain the pooled antibodies of thousands of plasma donors and are used to treat patients with a range of conditions, from those who don't have enough antibodies of their own to those whose antibodies are harmfully overactive. In Canada, IVIg is provided to hospitals by Canadian Blood Services and demand for this product keeps growing. Although hailed as a wonder drug, IVIg is not without its challenges. One of the rare side effects associated with IVIg is hemolysis, a condition in which the introduced antibodies find a marker on the patient's red blood cells and attack them, causing the cells to rupture.

Scientists at Canadian Blood Services have been working to find the causes and predictors of these hemolytic reactions, as well as alternative treatments to IVIg that have a lower risk of hemolysis. Much work has been done to understand IVIg — how it works, when it works best, and why it works better for some patients than others (Tong, et al., 2020).

How was this achieved?

Researchers at Canadian Blood Services discovered that patients often experience hemolysis after IVIg therapy, even more so than previously thought, and their reactions can be severe (Pendergrast et al., 2021). They found that the risk of hemolysis wasn't related to the reasons patients were receiving IVIg treatment, the duration of treatment, or patient characteristics like sex or weight. However, the risk was lower when patients took other medicines that weakened their immune system (immunosuppressants).

Looking deeper, researchers learned that a specific type of ABO antibodies (also called ABO isoagglutinins), which naturally occur in the donor plasma used to make IVIg, was related to hemolysis (Pendergrast et al., 2021). Importantly, researchers found that the greater the strength (titre) of these ABO antibodies, the more severe the hemolytic reaction in the patient (Pendergrast et al., 2021). Researchers also found a specific ABO genotype that causes IVIg-associated hemolysis (Branch et al., 2018).

Drawing on this knowledge, Canadian Blood Services researchers have begun testing a new product to reduce the risk of hemolysis: isoagglutinin-reduced IVIg. This version of IVIg has lower anti-A and anti-B antibody titres. Testing has shown it should work as well as standard IVIg and cause less IVIg-associated hemolysis, which could make it a safer product for those needing this essential therapy (Cen & Branch, 2020).

ABO antibodies are only part of the story. To better understand what causes IVIg-associated hemolysis, scientists adapted a monocyte monolayer assay test known as a phagocytosis assay. The original version of the test was developed by Canadian Blood Services scientists. The test was further modified to assess the activation of a patient's monocytes, which are white blood cells involved in IVIg-associated hemolysis (Tong et al., 2020). This test may predict whether a patient will experience a hemolytic reaction.

Researchers have discovered that a cytokine — a type of small protein that is secreted by cells and can signal a particular action in other cells — named

IL-1ra can indicate a higher risk that a patient will experience a hemolytic reaction (Pendergrast et al., 2015). Researchers have also examined the role of microparticles as markers showing the existence of an inflammatory condition in the patient before they receive IVIg, which could help predict the risk of a hemolytic reaction (Acker, Almizraq, Millar & Maurer-Spurej, 2018).

What was the impact and outcome?

These findings have had several notable impacts and outcomes:

Deeper understanding: This research has significantly improved our understanding of IVIg, including how it works, the risk factors for hemolysis, and the role of ABO antibodies and genetic variants.

We now have a deeper understanding of how to reduce the risk of IVIg-associated hemolysis and are better prepared to consider risks and possible conditions associated with transfusion.

New predictive tools: New predictive tools such as the phagocytosis assay and the identification of cytokine markers can help assess the risk of hemolytic reactions in patients receiving IVIg.

Safer alternatives: This research led to the development of potentially safer alternatives to IVIg, such as isoagglutinin-reduced IVIg. We also better understand how the dose level affects treatment, and what dose ranges may be suitable for at-risk patients.

This research has contributed to making IVIg treatment safer and more effective for a wide range of patients, and to advancing scientific and medical knowledge in the field of immunoglobulin therapy.

Bibliographies

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