

IN BRIEF A Summary of the Evidence

Off-Label Use of Intravenous Immunoglobulin (IVIg)

Key Messages

Off-label IVIg for Neurological Conditions:

- Studies suggest that IVIg treatment for neurological conditions is promising, but compelling evidence that IVIg works to improve most neurological conditions is lacking.
- Evidence suggests that IVIg may be better than plasma exchange for the treatment of pediatric Guillain-Barré Syndrome, and IVIg is shown to be more effective than placebo for the treatment of multiple sclerosis in adults.
- IVIg is no better than placebo for Alzheimer disease, encephalitis, or post-polio syndrome.
- The results for epilepsy, myasthenia gravis, and chronic inflammatory demyelinating polyneuropathy are mixed, making it unclear whether or not IVIg is an effective treatment.

Off-label IVIg for Hematological Conditions:

- No evidence was found for aplastic anemia, autoimmune neutropenia, hyperhemolysis after transfusion, and acquired hemophilia.
- A limited amount of evidence was found for blood conditions affecting a fetus or newborn. Overall, the evidence on IVIg for these specific conditions compared with other treatment options was mixed.

Off-label IVIg for Autoimmune or Inflammatory Conditions:

- Evidence indicates that the off-label use of IVIg may be effective in some autoimmune diseases but not in others.
- IVIg improves outcomes for patients with systemic lupus erythematosus, and it improves cardiac outcomes in infants of mothers with antiphospholipid syndrome during pregnancy.
- Limited evidence does not show a benefit with IVIg for dermatomyositis, myasthenia gravis, polymyositis, Kawasaki disease, Sydenham chorea, or cardiac complications of acute rheumatic fever.

Off-label IVIg for Non-neurological Paraneoplastic Disorders:

- No evidence was found, so it is not known whether or not IVIg is effective in treating non-neurological paraneoplastic disorders.

Off-label IVIg for Dermatological Conditions:

- Evidence is scarce and based mainly on non-randomized studies or small randomized controlled studies.
- For Stevens-Johnson syndrome or toxic epidermal necrolysis, IVIg treatment – alone or combined with corticosteroids – did not show survival benefit, but there may be a positive correlation between high-dose IVIg and some clinical benefits.
- For bullous pemphigoid, IVIg reduces the time-to-treatment reduction compared with placebo.
- For polymyositis or dermatomyositis, IVIg with corticosteroids improves muscle strength and the biochemical profile compared with placebo or corticosteroids alone (IVIg alone compared with placebo does not).

Off-label IVIg for Recurrent Spontaneous Abortion:

- Whether IVIg improves the chances of live birth in women who have experienced repeated miscarriage is unclear.
 - Some studies show no difference in live birth rates with IVIg compared with placebo and other treatments.
 - Other studies show a significant improvement in rates of live birth with IVIg compared with no IVIg.
- Studies that included obstetrical, perinatal, and neonatal outcomes found no important differences between groups treated with IVIg and those not treated with IVIg.

Off-label IVIg for Solid Organ Transplant Rejection:

- Limited evidence shows no difference in renal effect with IVIg and rituximab compared with placebo in patients with chronic, antibody-mediated rejection following renal transplant.
- Limited evidence shows an improvement in renal function in patients with chronic, antibody-mediated rejection following renal transplant with IVIg versus methylprednisolone.

Context

Immunoglobulin products delivered intravenously (IVIG) are used to treat patients with immune deficiencies or autoimmune disorders. The approved indications for IVIG treatment in Canada include:

- primary immune deficiency
- immune thrombocytopenic purpura
- secondary immune deficiency states
- chronic inflammatory demyelinating polyneuropathy
- Guillain-Barré syndrome
- multifocal motor neuropathy.

However, IVIG is often used off-label for a wide variety of other conditions that may have an immune-mediated or unknown cause. These off-label conditions may be neurological, hematological, autoimmune or inflammatory, dermatological, paraneoplastic, or may involve solid organ transplant rejection or recurrent spontaneous abortion.

Technology

Antibodies are proteins found in the blood that are made by the body to recognize and fight infections. Serum is the portion of the blood that does not contain blood cells. IVIG is a blood product made up of antibodies and serum. It is prepared using the serum of thousands of donors, resulting in a product with a very high concentration of antibodies to a wide variety of antigens.

Issue

Although Canadian Blood Services supplies IVIG to hospitals at no charge, IVIG treatment is expensive, with each dose costing between \$550 and \$8,000. Because the production of IVIG requires thousands of donors, Canada must purchase IVIG and other blood plasma products from commercial manufacturers in the US. The global demand for IVIG is high, and as Canada is unable to produce enough of its own, there is a risk of shortages and disruptions in supply. The demand for IVIG also continues to increase. Between 1998 and 2006, Canada's per capita use of IVIG grew by 115%, which makes Canada one of the highest consumers of IVIG per capita worldwide. The belief is that much of this growth is attributable to an increase in the off-label use of IVIG. But is the off-label use of IVIG clinically effective? To help answer this question, CADTH undertook a series of reviews of the evidence on the clinical effectiveness of the off-label use of IVIG.

Methods

For each off-label condition, a limited literature search was conducted of key resources, and titles and abstracts of the retrieved publications were reviewed. Full-text publications were evaluated for final article selection according to predetermined selection criteria (population, intervention, comparator, outcomes, and study designs).

Results

Off-label IVIG for neurological conditions: 24 included studies — 16 systematic reviews (five with meta-analyses) and eight randomized controlled trials.

Off-label IVIG for hematological conditions: four included studies — two systematic reviews, one randomized controlled study, and one non-randomized study.

Off-label IVIG for autoimmune or inflammatory conditions: 13 included studies — six systematic reviews, two randomized controlled studies, and five non-randomized studies.

Off-label IVIG for dermatological conditions: eight included studies — four systematic reviews with meta-analysis, one narrative systematic review, and three randomized controlled studies.

Off-label IVIG for recurrent spontaneous abortion: nine included studies — two systematic reviews, three randomized controlled trials, and four non-randomized trials.

Off-label IVIG for solid organ transplant rejection: two included studies — one randomized controlled trial and one non-randomized trial.

Off-label IVIG for non-neurological paraneoplastic disorders: No studies met the eligibility criteria.

Read more about CADTH's reviews of the off-label uses of IVIG at:



www.cadth.ca/ivig.

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