MALAYSIAN HEALTH TECHNOLOGY ASSESSMENT SECTION

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GB-0998 FOR UNEXPLAINED RECURRENT MISCARRIAGE

Keywords: abortion, immunoglobulin, recurrent pregnancy loss, infertility

SUMMARY OF TECHNOLOGY

Immunoglobulin (also referred to as immune globulin or gamma globulin) is a sterile, purified blood product pooled from the plasma of thousands of healthy donors. Immunoglobulin may be used as a replacement therapy for patients with primary or secondary antibody deficiency, as an immunomodulatory agent, or for treatment or prophylaxis of systemic inflammation. Immunoglobulin contains Aβ-antibodies, which help patients regain normal immunoregulation and immune homeostasis, and immunoglobulin may be administered as intravenous immunoglobulin (IVIG) or as subcutaneous immunoglobulin (SCIG). This therapy has long been applied to a variety of immune-mediated diseases such as immune thrombocytopaenic purpura, Kawasaki's disease, Guillain−Barre syndrome, and myasthenia gravis.[1]

GB-0998 (also known as venoglobulin-IH) is an intravenous immunoglobulin (IVIG) from polyethylene glycol-treated human IgG, developed by Mitsubishi Tanabe Pharma. Immunoglobulins precipitated by polyethylene glycol (PEG) under conditions defined to prevent or precipitate aggregates.[2] PEG-treated IgG was claimed to possess some anticomplementary activity and to cause adverse reactions in immune-deficient patients.[2] The proposed dosage is 400 mg/kg of IVIG daily for five consecutive days starting at 4−6 weeks of gestation.[3]

It was extensively studied in systemic sclerosis[4], myasthenia gravis[5], Guillain-Barré Syndrome[6], polymyositis and dermatomyositis[7]. GB-0998 was approved in 2011 covered by the Japanese National Health Insurance system for the indication of decreased muscle strength due to corticosteroid-resistant polymyositis or dermatomyositis.[8]

There are several USFDA-approved intravenous immunoglobulin G includes Asceniv, Bivigam, Carimune R NF, Flebogamma DIF 5% and 10%, Gammagard Liquid, Gammagard S/D, Gammaplex 5% & 10%, Gamunex-C, Octagam, Panzyga and Privigen.[9]

Intravenous immunoglobulin (IVIG) is increasingly used as a treatment for recurrent pregnancy loss (RPL) despite lack of clear evidence on efficacy.[10]

INNOVATIVENESS

Novel, completely new	
Incremental improvement of the existing technology	/
New indication of an existing technology	

DISEASE BURDEN

Spontaneous abortion is the loss of pregnancy naturally before twenty weeks of gestation. Colloquially, spontaneous abortion is referred to as a 'miscarriage' to avoid association with induced abortion. Early pregnancy loss refers only to spontaneous abortion in the first trimester. Recurrent abortion is defined as three or more consecutive pregnancy losses.[11]

Recurrent pregnancy loss (RPL) is a multifactorial condition that may be due to genetic, anatomic, endocrine, antiphospholipid antibody syndrome, immunologic, and environmental factors.[12] However, the aetiology of >50% of RPL is unknown and is therefore designated as unexplained RPL. Only about 2 percent of pregnant women have two consecutive pregnancy losses. Up to 50 percent of patients with RPL have no clearly defined aetiology.[12]

Currently, there is a prevailing conviction that immunological aberrations may be at fault in women with RPL, as it is evident that the maternal immune system needs regulation to avoid rejection of the semi-allogenic fetus. Among the different immunological aberrations potentially associated with RPL are changes in levels of regulatory T cells and Natural Killer (NK) cells, NK cell cytotoxicity, ratios of T helper cells and the presence of excessive autoimmune reactivity to self-antigens. Auto-antibodies that have been associated with RPL include anti-thyroid, antiphospholipid, lupus anticoagulant, anticardiolipin, antinuclear, anti-ssDNA, anti-dsDNA, and anti-histone. Furthermore, there is compelling evidence showing that women with RPL have significantly elevated T1 (proinflammatory) to T2 (anti-inflammatory) ratios and reduced levels of regulatory T cells compared to normal fertile controls. More recently, a study showed that women with RPL have significantly increased activated peripheral blood NK cell levels compared to normal fertile controls.[10] Intravenous immunoglobulin (IVIG) treatment has been broadly applied to suppress excessive immune activation in autoimmune diseases. IVIG has been shown to inhibit the pathological-activity of a large number of disease-associated autoantibodies, to downregulate NK cell killing capacity, and to inhibit T1 cytokines.[10]

CURRENT OPTIONS FOR PATIENTS

The management of people with RPL is multifactorial and should include lifestyle modification, psychological support and specific treatment of any identified cause.[13] Referral to recurrent miscarriage clinic and expert advice help to improve the reproductive outcome.[14] The treatment of RPL should be directed towards the underlying treatable cause.[12]

Women with thyroid conditions, diabetes, obesity, and other medical problems should be treated as medically appropriate.[12]

In couples with chromosomal abnormalities, the first step is a referral to genetic counseling. Couples should be educated on the potential likelihood of having fetal chromosomal abnormalities in future pregnancies. They may choose to proceed with prenatal genetic testing, such as preimplantation genetic diagnosis, chorionic villus sampling, or amniocentesis to identify genetic anomalies in the fetus and decide about further treatment options. Although embryos with unbalanced chromosomal arrangements can theoretically be screened out, preimplantation genetic testing (PGT) is not routinely advised since the likelihood of a pregnancy with an unbalanced karyotype surviving into the second trimester is low.[12]

Congenital and acquired uterine abnormalities causing RPL could be managed surgically which includes hysteroscopic septum resection, lysis of adhesions, myomectomy, or repair of a bicornuate uterus.[12]

Patients with antiphospholipid antibody syndrome and RPL are generally treated with aspirin and heparin, and it appears to improve pregnancy outcomes.[12] However, in women with thrombophilia, this treatment may improve maternal outcomes but does not prevent RPL.[12]

A 2019 Cochrane review also suggested that progesterone supplementation for RPL may reduce the rate of pregnancy loss in further pregnancies.[13]

Women with unexplained recurrent miscarriage have an excellent prognosis for future pregnancy outcome without pharmacological intervention if offered supportive care alone in the setting of a dedicated early pregnancy assessment unit. These women can be reassured that the prognosis for a successful future pregnancy with supportive care alone is in the region of 75%. However, the prognosis worsens with increasing maternal age and the number of previous miscarriages.[14] Aspirin alone or in combination with heparin is being prescribed for women with unexplained recurrent miscarriage, with the aim of improving pregnancy outcome.[14]

A Cochrane systematic review and meta-analysis has shown that the use of various forms of immunotherapy, including paternal cell immunisation, third-party donor leucocytes, trophoblast membranes and IVIg, in women with unexplained recurrent

miscarriage provides no significant beneficial effect over placebo in preventing further miscarriage.[15,16]

POTENTIAL IMPACT OF TECHNOLOGY

a. Clinical Impact

Systematic search was conducted from scientific databases such as Medline, EBM Reviews, EMBASE via OVID, PubMed and from the general search engines [Google Scholar and US Food and Drug Administration (US FDA)] on GB-0998 for the treatment of recurrent miscarriage.

There was only one published scientific evidence on effectiveness of IVIG (GB-0998) for the treatment of unexplained recurrent pregnancy loss.

Efficacy

A double-blind randomised placebo-controlled phase II trial (NCT02184741) conducted in Japan recruited primary RPL of unexplained aetiology (n=102 participants aged 42 years old with ≥4 RPLs excluding biochemical pregnancy loss in the count of miscarriages) who were randomly assigned to receive IVIG (n = 53) or placebo (n = 49) in the intention-to-treat population. The intervention group were given 400 mg/kg of IVIG daily for five consecutive days starting at 4−6 weeks of gestation. The primary outcome was the ongoing pregnancy rate at 22 weeks of gestation. The live birth rate was defined as secondary outcomes. The ongoing pregnancy rate at 22 weeks of gestation (62.0%) in the IVIG group was higher than that (34.7%) in the placebo group in the ITT population (odds ratio [OR] 3.07, 95% CI; 1.35 to 6.97; p=0.009). The live birth rate (58.0%) in the IVIG group were higher than that (34.7%) in the placebo group (OR 2.60, 95% CI; 1.15 to 5.86; p =0.03). However, the rates of ongoing pregnancy and live birth were not statistically different between IVIG (47 women) and placebo (38 women) groups in the modified-ITT population. The IVIG-to-placebo hazard ratios for the ongoing pregnancy were 0.47 (95% CI; 0.26 to 0.82; p=0.007) in the ITT population and 0.52 (95% CI; 0.27 to 0.98; p=0.04) in the modified-ITT population, respectively.[3]

b. Cost

There was no retrievable evidence on cost or cost-effectiveness study on GB-0998. As for rough estimation, the IVIG costs roughly $110 (RM513; 1 USD= 4.66 MYR) per gram, with patients needing an average of 20 grams for a total medication cost of around $2200 (~RM10263).[17]

c. Societal/ethical

There was no retrievable evidence on societal or ethical issue on GB-0998.

d. Safety

The IVIG-to-placebo hazard ratios for the ongoing pregnancy were 0.47 (95% CI; 0.26 to 0.82; p =0.007) in the ITT population and 0.52 (95% CI; 0.27 to 0.98; p =0.04) in the modified-ITT population, respectively. The gestational age at delivery was earlier in the IVIG group than the placebo group, and the rates of preterm delivery (44.8% vs. 15.9%) and fetal growth restriction (34.5% vs. 0%) were higher in the IVIG group compared with the placebo group. Four new-borns in the IVIG group and none in the placebo group had congenital anomalies (p=0.28). Although preeclampsia was observed in four (8.0%) of 50 women, in the IVIG group and one (2.0%) of 49 women in the placebo group (p=0.36), there were no thromboembolic events. Twenty-three (46.0%) of 50 women receiving IVIG had mild adverse events including elevated liver enzymes in nine (18.0%), headache in four (8.0%), skin rash in four (8.0%), and fever in two (4.0%) women, while a total of three (6.1%) of 49 women in the placebo group had adverse events.[3]

CONCLUSIONS

In conclusion, very limited evidence has shown that IVIG treatment has tolerable safety profile and has the potential to significantly increased rates of ongoing pregnancy at 22 weeks of gestation and live birth. The rates of preterm delivery and fetal growth restriction were also noticeably higher in the IVIG group. Therefore, further research among larger population with its cost-effectiveness study is highly recommended.

EVIDENCE

Yamamoto H, Suzuki H. Intravenous immunoglobulin treatment in women with four or more recurrent pregnancy losses. EClinicalMedicine. 2022;52:101601.

REFERENCES

1. Arumugham VB, Rayi A. Intravenous Immunoglobulin (IVIG). StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Appaji Rayi declares no relevant financial relationships with ineligible companies.: StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC.; 2023.
2. Radosevich M, Burnouf T. Intravenous immunoglobulin G: trends in production methods, quality control and quality assurance. Vox Sanguinis. 2010;98(1):12-28.
3. Yamamoto H, Suzuki H. Intravenous immunoglobulin treatment in women with four or more recurrent pregnancy losses. EClinicalMedicine. 2022;52:101601.
4. Clinicaltrials.gov. Efficacy and Safety Study of GB-0998 for Treatment of Systemic Sclerosis. 2010. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT00348296. Accessed on 20 june 2023.

5. Clinicaltrials.gov. Efficacy and Safety Study of GB-0998 for Treatment of Generalized Myasthenia Gravis. 2010. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT00515450?term=gb0998&draw=2&rank=5. Accessed on 20 June 2023.
6. Clinicaltrials.gov. Efficacy and Safety Study of GB-0998 for Guillain-Barré Syndrome. 2016. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT02342184?term=gb0998&draw=2&rank=3. Accessed on 20 June 2023.
7. Clinicaltrials.gov. Efficacy and Safety Study of GB-0998 for Treatment of Steroid-resistant Polymyositis and Dermatomyositis (PM/DM). 2014. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT00335985?term=gb0998&draw=2&rank=4. Accessed on 20 June 2023.
8. Miyasaka N, Hara M, Koike T, et al. Effects of intravenous immunoglobulin therapy in Japanese patients with polymyositis and dermatomyositis resistant to corticosteroids: a randomized double-blind placebo-controlled trial. Modern rheumatology. 2012;22(3):382-393.
9. (USFDA) USFDA. Immune Globulins. 2023. Available from: https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/immune-globulins. Accessed on 21 June 2023.
10. Habets DHJ, Pelzner K, Wieten L, et al. Intravenous immunoglobulins improve live birth rate among women with underlying immune conditions and recurrent pregnancy loss: a systematic review and meta-analysis. Allergy, Asthma & Clinical Immunology. 2022;18(1):23.
11. Alves C, Rapp A. Spontaneous Abortion. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Amanda Rapp declares no relevant financial relationships with ineligible companies.: StatPearls Publishing
Copyright © 2023, StatPearls Publishing LLC.; 2023.
12. Pillarisetty LS, Mahdy H. Recurrent Pregnancy Loss. StatPearls. Treasure Island (FL) relationships with ineligible companies. Disclosure: Heba Mahdy declares no relevant financial relationships with ineligible companies.: StatPearls Publishing
Copyright © 2023, StatPearls Publishing LLC.; 2023.
13. Chester MR, Tirlapur A, Jayaprakasan K. Current management of recurrent pregnancy loss. The Obstetrician & Gynaecologist. 2022;24(4):260-271.
14. Regan L, Rai R, Saravelos S, et al. Recurrent MiscarriageGreen-top Guideline No. 17. BJOG : an international journal of obstetrics and gynaecology. 2023.
15. Regan L, Rai R, Saravelos S, et al. Recurrent MiscarriageGreen-top Guideline No. 17. BJOG: An International Journal of Obstetrics & Gynaecology.n/a(n/a).
16. Wong LF, Porter TF, Scott JR. Immunotherapy for recurrent miscarriage. The Cochrane database of systematic reviews. 2014;2014(10):Cd000112.
17. Fertility C. IVIG Therapy. 2023. Available from: https://www.cnyfertility.com/ivig-therapy/. Accessed on 20 June 2023.

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