Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

IVIG

Evidence Summary

Low brain penetrance and inconsistent clinical data suggest it is unlikely to prevent dementia. Lower doses, while safer, are less likely to achieve beneficial anti-inflammatory effects.

Neuroprotective Benefit: Unclear mechanisms of action, limited evidence, and inconsistent effects in trials suggest minimal potential to benefit in CNS.

Aging and related health concerns: Anti-inflammatory and anti-fibrotic effects in patients with autoimmune disease. Unclear if it promotes or inhibits thromboembolism and atherosclerosis.

Safety: Severe risks are very rare, based on decades of clinical use in at-risk populations. Low-dose use may be safer, but may also have less potential benefit.

What is it? Intravenous immunoglobulin (IVIG or IVIg or IGIV) is a concentrated extract of IgG antibodies prepared from plasma pooled from 10,000 or more human donors. There are four subclasses of IgG (1-4), with IVIG levels mimicking that of plasma with mainly IgG1 & 2. Depending on the preparation and the batch, the amount of non-IgG material can vary with ingredients like IgA, IgM (Schwab & Nimmerjahn 2013), soluble LRP, soluble CD4, TGF-β1 & TGF-β2 (Loeffler 2013) as well as additives like salt or sugar-based product stabilizers (Schwab & Nimmerjahn 2013, Nimmerjahn Ravetch 2008).

At low doses (300-500 mg/kg), IVIG is used as a replacement therapy for people who suffer from diseases that suppress immune function, such as primary immunodeficiencies like common variable immune deficiency (CVID), HIV infection, bone marrow transplants, B cell lymphocytic leukemia, and multiple myeloma.

At higher doses (2 g/kg), IVIG is used as an anti-inflammatory therapy for many conditions. On-label uses include chronic inflammatory demyelinating neuropathy (CIDP), Kawasaki disease, Guillain-Barre syndrome, and idiopathic thrombocytopenia purpura. Off-label use is common for chronic inflammatory diseases like multiple sclerosis, systemic vasculitis, rheumatoid arthritis, autoimmune diseases, and sepsis. The purported mechanism of action varies across these different conditions (Schwab & Nimmerjahn 2013; Lunemann 2015).

Neuroprotective Benefit: Unclear mechanisms of action, limited evidence, and inconsistent effects in trials suggest minimal potential to benefit in CNS.

Types of evidence:

- 1 Phase II trial on MCI patients; several Phase II & one Phase III on Alzheimer's patients
- 1 retrospective case-control
- Numerous laboratory studies
- Data for CNS penetrance (or lack thereof)

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

Despite early success in pilot trials, IVIG preparations failed to help Alzheimer's patients in Phase II and III clinical trials with either Gammagard or Octagam. Enthusiasm following the trials was lowered not

just because of the lack of efficacy on cognition but because, contrary to the earlier pilot studies, no effects were seen on beta-amyloid levels in cerebrospinal fluid and plasma (reviewed in Loeffler 2014).

The use of IVIG for prevention has been less well-studied. In a small clinical trial of 50 patients, IVIG treatment appeared to temporarily protect against brain atrophy and conversion to dementia in mild cognitive impairment (MCI patients), with significance at 12 months but not 24 months (e.g. conversion to dementia was 72% in IVIG group vs 75% in placebo group at 24 months, but 33.3% and 58.3% respectively at 12 months). Enthusiasm for these results is dampened by unusual fluctuations in the placebo group that appeared to drive the results, for example with worse atrophy in the placebo group measured at 12 vs 24 months (Kile 2017). The lack of error bars also reduces enthusiasm for the analyses. The treatment itself had been 0.4 g/kg of 10% IVIG every 2 weeks (total 5 infusions).

A retrospective case-control study (Fillit 2009) reported a lower risk of Alzheimer's and related dementia in people who had previously been given one or more IVIG therapies (Hazard ratio (HR): 0.577, 95% CI 0.359 to 0.930). However, these results rely on claims data, which suffers from serious concerns around data validity and underreporting of dementia.

Mechanisms of action for neuroprotection identified from laboratory and clinical research

The original rationale for IVIG use in Alzheimer's was that IVIG may contain antibodies against phosphorylated tau and beta-amyloid, which might in turn pull such molecules out of circulation (Loeffler 2013). Ig molecules have very little penetration across the blood brain barrier, with an estimated 0.009% of systemically administered IVIG reaching the cortex of mice (St-Amour 2013), which makes it unlikely that tau antibodies will block tau-related pathology in the brain. In theory, clearance of peripheral beta-amyloid aggregates might create a "sink" that increases clearance from the brain by homeostatic mechanisms (Loeffler 2013). This theory has yet to be proven.

Anti-inflammatory properties may also be relevant to neurodegeneration. However, chronic high dosing is reportedly needed to achieve anti-inflammatory effects (1-2 g/kg) in the periphery (Nimmerjahn & Ravetch 2008). Given the low brain penetrance of IgG, it seems rather unlikely that anti-inflammatory effects occur within the brain. Nevertheless, putative anti-inflammatory effects may be dependent on a specific type of IgG (with a terminal sialic acid in the Fc region) that is present in only 1-3% of IVIG molecules (Loeffler 2013). For Alzheimer's disease, its suppression of the complement pathway through C3 and C5a (e.g. Gong 2014) are often discussed, possibly acting through the Fab regions of the antibodies (Schwab & Nimmerjahn 2013). Other mechanisms have been proposed such as antibodies to proinflammatory cytokines and chemokines, improved glucocorticoid receptor binding (Gelfand 2012),

and non-IgG content such as soluble lipoprotein receptor related protein (LRP), soluble CD4, TGF-β1 & TGF-β2 (Loeffler 2013). Pro-inflammatory mechanisms have also been identified, particularly at low doses of IVIG, specifically complement activation and IgG binding to FcγR (Gelfand 2012)

APOE4 interactions: APOE4 carriers were reportedly more likely to benefit from IVIG treatment in a randomized trial on Alzheimer's patients (Relkin 2014). Preclinical studies also suggest that IVIG may help to treat atherosclerosis (Basta 2014), which in turn is a risk of APOE4 carriers.

Aging and related health concerns: Anti-inflammatory and anti-fibrotic effects in patients with autoimmune disease. Unclear if it promotes or inhibits thromboembolism and atherosclerosis.

IVIG has been used in a wide range of conditions with varying purported (often unclear) mechanisms of action depending on the health condition and dose. When considering the evidence, it is essential to consider whether the effect reported in a specific patient population would be likely to occur in other, healthier people. At high doses, IVIG is used to blunt chronic inflammation in a variety of illnesses. In theory, it could be very helpful in aging individuals who battle immunosenescence and chronic low-grade inflammation in addition to several pertinent age-related diseases. However, it remains unclear whether low-dose therapies could modulate the immune system in aging adults, particularly because some data suggests that low-dose IVIG is pro-inflammatory.

Infection risk

IVIG reduces the risk of infection in the immunodeficient patients who receive it as an IgG replacement therapy. In theory, it could also reduce the risk of infections in non-immunodeficient people, particularly the elderly. However, epidemiological data on the risk of infection in patients given high-dose IVIG for inflammatory conditions was not readily available. Note that IVIG reduces the serum half-life for other antibodies by about 40% (Lunemann 2015) and can suppress vaccine responses (Silvergleid & Perez 2017), presumably by providing an antibody-based response to infection that does not elicit the creation of new antibodies.

Thromboembolism (ischemic stroke, venous thromboembolism, or acute myocardial infarction):

IVIG and thromboemboli have a complicated history. It seems likely that IVIG therapy can slightly increase risk in the short-term, although this might be prevented by manufacturing to avoid Factor XIa (FX1a).

A long history of case studies suggests that IVIG use carries a rare but real risk of thromboembolism, with more case studies continuing to emerge even in younger people (Nakano 2016, Chang 2014, Lorenzana 2014). A 2016 systematic review and meta-analysis of 31 RCTs, totaling 4129 participants, reported a null effect (Odds ratio (OR): 1.10, 95% CI 0.44 to 2.89) (Ammann 2016), however the ability to detect such a rare risk is hampered by the typically small size and duration of the RCTs and by the RCT participants, who were mostly younger adults at lower risk (mean age 47 years, range 29-70).

Milan Basta from BioVisions argued in 2014 that the epidemiological data suggests lower risk, not higher risk, from IVIG use. Using CDC data on the average frequency of stroke, he showed that the prevalence of stroke is roughly 4 times lower in patients with primary immunodeficiency disorder (PID) than the general population, despite the standard use of low-dose IVIG to treat PID (Basta 2014). However, there are some concerns with his interpretation. He reports that of 443 cases of thromboemboli reported within 42 days of an IVIG infusion, 269 were within 24 hours. In other words, 60% of all thromboemboli in these patients occur within 24 hours of a low-dose IVIG infusion. Second, IVIG therapy in PID patients is typically restoring appropriate IgG levels in these immunosuppressed patients – the effects of IVIG may be quite different than in people with normal baseline levels.

Another study supports the idea of a temporarily increased risk of thromboemboli within 48 hours of infusion (overall risk was 1.27, 95% CI 0.67 to 2.41; risk for arterial events was HR: 3.40, 95% CI 1.25 to 9.25). No effect on risk (positive or negative) was seen at days 16-30 after IVIG use (HR: 0.88, 95% CI 0.43 to 1.81) and the net risk over 1 year showed a miniscule increase of 1.0 % (95% CI -0.2 to 2.7%) (Ammann 2016). In specific patient populations, however, like antiphospholipid syndrome, IVIG therapy appears to reduce the risk of thrombosis (Tenti 2013, Sciascia 2012).

Possible mechanisms related to thromboembolism: With respect to increased risk for thromboembolism, the most commonly suggested mechanism is increased serum viscosity and platelet aggregation following IVIG, possibly via residual amounts of coagulation factor Xia (FXIa) in high doses. Newer manufacturing methods may avoid this risk of FXIa (Germishuizen 2014, Park 2017) and the short temporal link between infusion and thromboemboli supports the idea that a molecule with a shorter half-life like FXI (45-52 hours) is more likely to be causing the risk than an IgG (half-life ~20 days). However, uncertainties remain. According to Milan Basta from BioVisions, an increase in blood viscosity has rarely been reported after IVIG infusion, and indeed was refuted in a small study on seven patients (Basta 2014). Other harmful mechanisms of action might include antiphosphlipid antibodies, arterial vasospasm, vasoactive cytokines, or clotting factors (listed in Nakano 2016).

Other mechanisms of action suggest that IVIG could protect from thromboembolism, particularly from the complications of stroke. In laboratory models, IVIG has been reported to decrease MAPK and NF-kB during ischemic conditions, possibly reducing inflammasome activity (Fann 2017). IVIG can influence complement pathways through several mechanisms (Lunemann 2015) which might also blunt inflammation and stroke pathology. Effects on inflammatory pathways and complement appear to be dose-dependent, typically requiring higher doses in the clinic (Nimmerjahn Ravetch 2008, Machimoto 2010) although few clinical studies have carefully examined dosing (e.g. Kerr 2014). Overall, these potential mechanisms of action suggest that IVIG might mitigate damage from stroke, but they are less likely to be relevant to reducing stroke risk, given that blood-brain barrier penetrance of IVIG is likely to be extremely low except under abnormal conditions like stroke. An exception is atherosclerosis – if IVIG does protect from atherosclerosis (see below), it might reduce risk of thromboembolism (Basta 2014).

Fibrosis: Since fibrosis is a common component of age-related pathologies, a reduction in fibrosis could help promote healthy longevity. IVIG has been shown in pilot clinical studies to reduce fibrosis but only in specific health conditions with abnormal fibrosis like systemic sclerosis (Sanges 2017, Dalakas 2014). Whether such benefits occur in people with normal aging remains unclear.

Atherosclerosis: The antibodies found within IVIG may either promote or inhibit atherosclerosis. While the antibodies to oxidized LDL are expected to reduce atherosclerosis, autoantibodies against beta-2 GPI is expected to foster their development. Which action dominates is uncertain, which may perhaps explain why this line of research slowed, with almost all studies predating 2009 (van Leeuwen 2009, Matsuura 2005).

Neuropathies: IVIG is approved for chronic inflammatory demyelinating polyneuropathy (CIDP) and Guillain-Barre, an acute autoimmune disease, which causes demyelination of peripheral nerves. For CIDP, IVIG is one of several possible therapies with similar efficacy (Eftimov 2013). These effects are dose-dependent. For example, effects on dendritic cell activation can go in opposing directions at high vs low doses (Durandy 2009)..

Safety: Severe risks are very rare, based on decades of clinical use in at-risk populations. Low-dose user may be safer, but may also have less potential benefit.

Types of evidence:

- UpToDate review

- 2 reviews
- 2 retrospective cohorts & several case studies per: atherosclerosis

IVIG has been widely used at varying doses for decades in a variety of patient populations. Adverse reactions are reported to occur in 5-15% of IVIG infusions, affecting 20-50% of IVIG recipients. Most adverse reactions occur at higher doses or during the first infusion of a specific IVIG brand. These are usually mild, with headache, chills, flushing, fatigue, nausea, chills, chest pain, and aseptic meningitis. Most of these respond to a break in infusion followed by a slower rate of infusion. Skin reactions can also occur, starting 2-5 days after infusion and continuing up to 30 days. Subsequent response to vaccination can be impaired. (Lunemann 2015; Silvergleid & Perez 2017).

Potentially serious reactions include thrombosis (very small risk – see above), renal dysfunction and acute renal failure. Allergic reactions can occur, particularly in IgA deficient individuals (Note: IgA deficiency is sometimes asymptomatic). The risk of adverse reactions can be increased by advanced age and a variety of morbidities like infection at baseline, "coronary artery disease, hypertension, smoking, hyperlipidemia, diabetes mellitus, age greater than 65, sepsis, immobility, and concomitant use of estrogens or nephrotoxic agents" and kidney disease. There is also a miniscule risk for transmission of infectious disease (e.g. Creutzfeldt-Jakob disease) but no cases have been reported after safety standards were improved following an outbreak of hepatitis C in the 1990's (Silvergleid & Perez 2017).

Clinically, a variety of strategies are used to reduce the risk of adverse events, but it is unclear whether they are protective. They include adequate hydration before treatment, the use of subcutaneous or intramuscular administration instead of IV, testing for the risk of hemolytic reaction in the patient (for high-dose use in at-risk patients), slow infusion rates with gradual stepwise increases, and preloading with NSAIDs to help prevent headaches (Silvergleid Perez 2017).

Putative causes of the adverse events vary. Factor Xia (unrelated to IgG) has been suggested to cause the temporarily increased risk of thrombosis. Complement activation, specific antibodies (e.g. those that react to A, B, or Rh(D) red blood cell antibodies), infusion rate are also associated with adverse reactions (Silvergleid & Perez 2017).

Sources and dosing:

Dosing for IVIG is somewhat complicated by a dearth of dose-response curve studies and by data gathered from highly variable patient populations (Kerr 2014, Lunemann 2015). Typically, low-dose

therapy is used as replacement therapy in IgG deficient patients (300-500 mg/kg to achieve serum levels of 500 mg/dl) while a high-dose therapy of 1-3 g/kg (leading to serum IgG of 2500-3500 mg/dl) is used to achieve anti-inflammatory effects, typically in auto-immune or chronic inflammatory diseases (Nimmerjahn Ravetch 2008, Gelfand 2012). In patients who respond to IVIG, maintenance doses of roughly 1 g/kg per month might be given (Lunemann 2015). The precise clinical dose needed to suppress complement inflammatory pathways is unclear but one small observational cohort does suggest that higher doses are more effective yet lower doses (e.g. 0.4 – 1 g/kg) has some temporary efficacy (that some temporary suppression is seen even at the lower range of doses (Machimotor 2010). Generally, treatment must be repeated every 3-4 weeks to maintain the serum level. Subcutaneous formulations might achieve more stable levels in between dosing (see below).

A variety of patented preparations are available. Variation in additives and stabilizing agents like sucrose affect the risk of adverse events in specific patient groups (Silvergleid Perez 2017). Most IVIG is produced, with only slight modifications, using techniques developed in the 1940's – 1950's (Nimmerjahn Ravetch 2008).

Research underway: There are no ongoing studies for dementia, however, research continues on other health indications. Many groups are also working on other formulations or synthetic substitutes.

Subcutaneous formulations of Ig have become increasingly popular in recent years. Although primarily driven by the ease of administration compared with IV, subcutaneous injection may also achieve more stable concentrations in between infusions (Shabaninejad 2016, Berger 2011). A newer subcutaneous formulation combines Ig with hyaluronidase, with improved bioavailability (Bonilla 2016).

Several companies are working to develop replacement therapies for IVIG, for example with a recombinant antibody preparation that blocks neonatal FcRn to alter Ig half-life, multimeric antibody or IgG Fc preparations, and sIVIg (Lunemann 2015).

Search terms:

Pubmed:

- IVIG + stroke, thromboembolism, Alzheimer, cognition, dementia, lifespan, mortality

Google or other sites:

- IVIG, pneumonia (or infection) risk in CIDP
- IVIG safety

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