REVIEW

Review on IVIG Therapy in Dermatomyositis: Can the MAC Pathway Be Suppressed?

Melissa Payne
Department of Biology, University of Minnesota Duluth

Abstract

Myositis encompasses different idiopathic inflammatory myopathies (IIMs) which contain a subset of diseases that are regulated through an irregular autoimmune response. A rare form of IIM is Dermatomyositis. Dermatomyositis is mediated by a complement process that results in the destruction of muscle fibers through the membrane attack complex (MAC). When dermatomyositis patients become resistant to fist-line interventions, there is an inadequate response in the patients' health which leads to physical disabilities. When first-line therapies provide insufficient remission states, second-line therapies are administered or paired with the first-line drugs. Intravenous immunoglobulin (IVIG) is an immune-modulating therapy introduced as a second line therapy; it affects the immune system at multiple levels. In dermatomyositis, IVIG therapy has been shown to diminish the formation of MAC depositions through inhibiting the assembly of *C5B-9* B cells on capillaries and muscle fibers. Inhibition of MAC through the Fc receptor on IgG antibodies disrupts multiple polymerization steps through the complement pathway. The impact IVIG has on dermatomyositis exhibits significant impacts on muscle strength and skin lesions, improving and prolonging remission states seen in dermatomyositis patients.

INTRODUCTION

Myositis is a term used to categorize different inflammatory myopathies which are idiopathic, meaning they have no known cause. Idiopathic inflammatory myopathies (IIMs) are a group of autoimmune diseases in humans, and they and promote inflammation of proximal skeletal muscles (Dalakas 2003). Inflammation of skeletal muscle leads to muscle weakness and fatigue, which can result in difficulty walking, swallowing, and/or breathing (Dalakas et al. 1993). Eventually, everyday tasks require assistance. IIMs are autoimmune disorders where the body mistakenly attacks healthy tissues; the body's white blood cells attack blood vessels, normal muscle fibers, and connective tissues in organs, bones , and joints (Troyanov et al. 2005).

A rare form of IIM is Dermatomyositis (DM). DM affects fewer than 11 per 100,000 subjects in the United States (Steiner 2009). DM is characterized by the shared features of proximal muscle weakness and inflammation with a characteristic skin manifestation known as Gottrons (Findlay et al. 2015). Gottrons is visible on the face, chest, nails, and/or elbows and has a patchy bluish-purple appearance. The clinical features of DM are diagnosed through a series of laboratory tests and diagnostic imagining, as well as through muscle and skin biopsies. Muscle biopsies studied in DM patients show up-regulated depositions of *C5b-9* proteins (Dalakas 2010). This up-regulated *C5b-9* complex provokes formation of the membranolytic attack complex (MAC) on intramuscular capillaries (Basta 1994). MAC is a complex of *C5b-9* fragments that assemble together to form a pore across the cell membrane, allowing the entry of ions and water into the cell. This uninhibited movement of molecules across the cell membrane results in osmotic swelling and cell death (Iaccarino et al. 2014)

Corresponding Author:
Melissa Payne
payne245@d.umn.edu

The autoimmune mechanism is central to the development of DM, providing a rationale for treating DM patients with immunosuppressive drugs or immunomodulatory therapies (Dalakas et al. 2003). Intravenous immunoglobulin is a unique immune-controlling therapy used in inflammatory myopathies. The mechanism of IVIG in DM is a well-studied therapy in regards to different IIM states.

IVIG diminishes the activity of MAC depositions on capillaries and muscle fibers, the expression of adhesion molecules, and cytokine production (Basta et al. 1994). Through binding the constant fragment site (Fc) of the IVIG's immunoglobulin G (**IgG**) to potentially harmful complement fragments, IVIG blocks the deposition of harmful fragments onto target cells. This blocking prevents immune damage that stems from cellular destruction and excessive inflammation (Durandy et al. 2009). The reduction of complement fragments in the blood inhibits the release of cytokines, further preventing the formation of MAC. When the complement cascade and inhibited MAC depositions are repressed, DM patients exhibit significant improvement in muscle strength and skin lesions - 100% from IVIG treated vs 42.9% from Corticosteroid treated (Marie et al. 2011).

IgG: A type of antibody found in IVIG therapy

The primary objective of this review is to assess and cross analyze different findings on IVIG. This paper does so by reviewing the different current mechanistic effects of IVIG therapy on MAC in DM patients. Additionally, this review briefly covers the assembly and roles of different MAC proteins, in order to understand the full mechanism of treatment and how IVIG works at a molecular level.

THE HUMAN IMMUNE SYSTEM

The human immune system has two levels of immunity which are essential for the human body's survival against potentially dangerous microbes. The two levels of immunity are considered specific and non-specific, and both function in a normal immune state to eliminate foreign material from the body. Non-specific immunity defends the body against pathogens. In doing so, white blood cells known as phagocytes surround the pathogen, take it in, and neutralize it. Specific immunity includes white blood cells, called natural killer (NK) cells, which are vital to the specific immune response. Two common forms of NK cells are T cells and B cells (Hunt 2016). The specific immunity is a complement to the function of phagocytes in the non-specific immunity. Using a **target response**, plasma B cells tag pathogens with antibodies on their cell membranes, allowing the body to defend itself against these pathogens (Hunt 2016).

Target response: A cell affected by a particular agent, such as a virus or drug

Complement System

The complement system is a known pathway of the immune system that helps eliminate foreign material from the body. In a healthy immune response, the complement system conducts an enzyme cascade that defends against pathogens (Luo et al. 2014). The response is driven by B cells which circulate in the blood as inactive precursors, waiting to be stimulated by foreign material like pathogens. When these precursor B cell molecules are triggered, **proteases** cleave specific proteins to release cytokines and initiate an amplifying cascade known as MAC on pathogenic cell membranes (Figanelle-Branger et al. 2003). Cytokines are secreted by cells in the immune system and range in both their specificity and their effects on cells (Delves 2014).

Proteases: An enzyme used to break down proteins and peptides

Dermatomyositis begins when antibodies against endothelial cells activate the complement system cascade MAC. This cascade promotes MAC depositions on healthy cells instead of pathogenic cells (Brouwer et al. 2001). The MAC pathway activation is led

by the stimulation of *C3* molecules. *C3* leads into the formation of MAC through *C5b-9* fragments, creating a pore across the cell membrane (Dalakas et al. 2003) as seen in Figure 1. The formation of MAC deposits on capillaries sequentially leads to the muscle weakness and inflammation seen in DM patients.

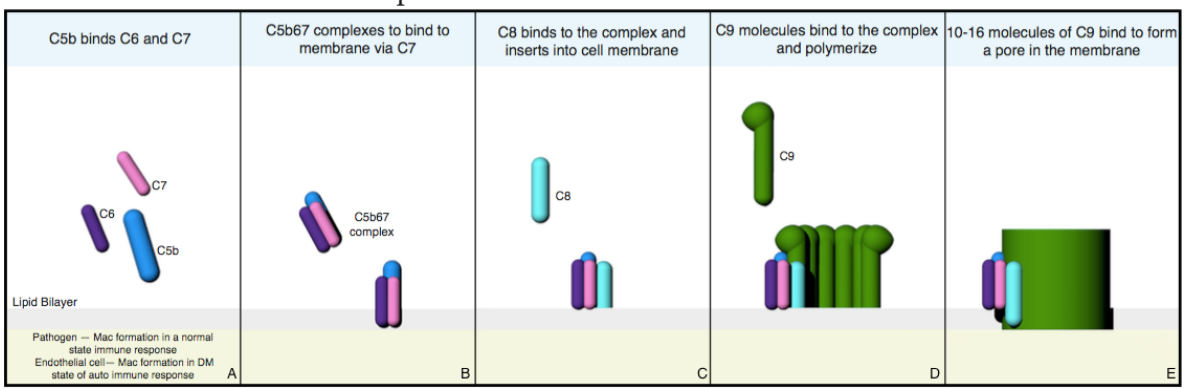

Figure 1. Formation of MAC by the terminal components of the complement system. Forming a visible pore across the cell membrane, causing the cells to lyse. A) *C5b* cleaves from *Cb* and induces binding of *C6*, allowing *C7* to then bind to the subunit. *C7* undergoes conformational change which attaches the complex to the membrane of the cell. B) *C8* can now bind and attach to the membrane as well. This is known as the *C5b-8* complex. C) The *C5b-8* complex induces binding of *C9* molecules. D) *C9* molecules polymerize to form a pore through the cell membrane wall, allowing ions and water molecules to pass from the extracellular space through the lipid bilayer and into the intracellular space. This causes the cell to lyse and then die. Adapted from Podack and Tschopp (1984).

MAC DEPOSITIONS; ASSEMBLY OF THE PORE

The formation of a MAC trans membrane channels disrupts the phospholipid bilayer of target cells, leading to cell lysis and cell death (Triantafilou et al. 2013). In DM, MAC targets healthy endothelial cells of endomysial capillaries, weakening them through micro infarcts. Micro infarcts are small localized areas of dead muscle tissue that result from lack of blood supply within muscle fascicles (Nagaraju et al. 2000). These micro infarcts ultimately lead to the destruction of the perifasicular tissue situated around a muscle fiber bundle (Figure 2).

Muscle damage is caused by the attachment of the *C5b-9* proteins within the membrane of endomysial cells (Nagaraju et al. 2005). MAC proceeds in two stages: first, through the membrane insertion of *C5b-7* and the binding of *C8*, and second by the polymerization of *C9*. The addition of the *C9* fragment to the *C5b-8* complex allows formation of a pore through the cell's membrane (Figure 1) (Bhakdi et al. 1982). Both of these methods require the **amphiphilic** transition of hydrophilic precursor proteins for membrane insertion (Vattemi et al. 2014).

Amphiphilic: A hydrophilic and lipophilic chemical compound

MAC forms as a cylindrically structured molecule that is generated by five hydrophilic proteins. These proteins are IgG and IgM macrophages, along with the B cells *C5b-9*. These B cells act as an antigen presenting cell, and these cells also internalize offending antigens through the pore created in the cell's membrane. When the *C5b-8* complex binds to *C9*, the new complete complex acts as a catalyst in the polymerization of *C9* (Tegla et al. 2011).

IVIG THERAPY IN DERMATOMYOSITIS

IVIG is a second-line or add-on therapy used with other immune-modulating medications. The primary therapy for patients with DM are corticosteroids, methotrexate and/or azathioprine (Cherin et al. 1991). The major drawbacks of long-term corticosteroid

treatments are adverse side effects and insufficient efficacy. Side effects are seen in 41% of all DM patients where long-term studies show disability was associated with corticosteroid use (Nzeusseu et al. 1999). DM patients exhibiting resistance and adverse effects to these immunosuppressive drugs are recommended for IVIG infusion treatment (Choy et al. 2002).

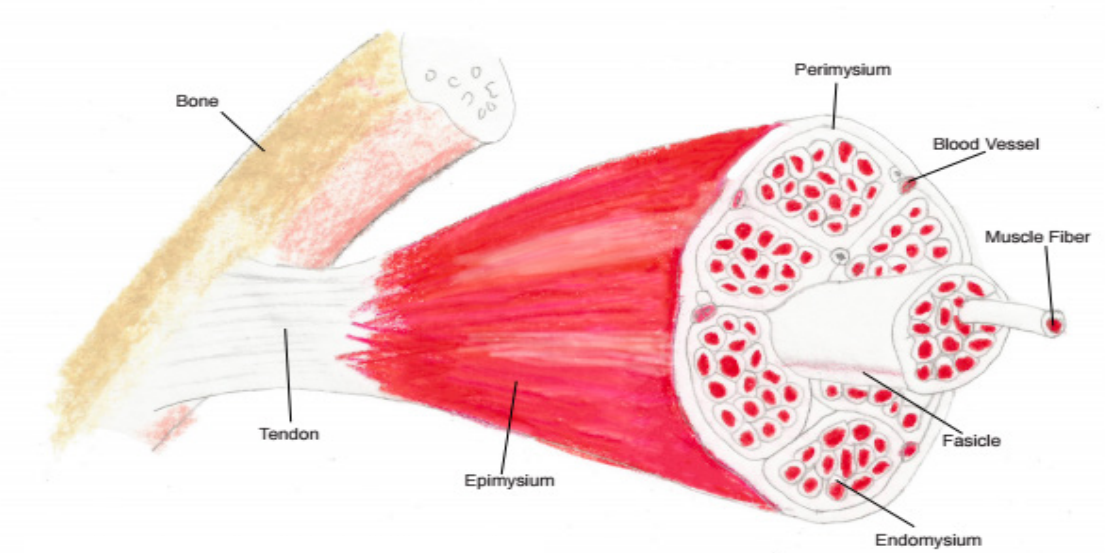

Figure 2. Structure of a Skeletal Muscle All tissue in the human body depends on a blood supply, and the blood supply depends on endothelial cells, which form the lining of blood vessels. Endothelial cells create an adaptive life-support system through extending and remodeling blood vessels, tissue growth and tissue repair. In DM patients, muscle biopsies show MAC depositions on endomysial capillaries, which causes the degeneration of the muscle fiber due to cell lysis. In IVIG treatment, MAC depositions on endomysial cells are inhibited, allowing regeneration and tissue remodeling. Adapted from Marieb et al. (2013).

The use of IVIG therapy to treat autoimmune and inflammatory diseases as an add-on therapy works to reduce potentially harmful immunosuppressive drugs. Using IVIG as a second-line therapy increases remission states and prolongs high quality of life in patients with immunodeficiencies (Bohan 1988). Undesirable effects from IVIG therapy occur in less than 5% of patients (Scheinfeld et al. 2016). Although IVIG therapy has a high success rate, its use has to be rationalized and prioritized due to its high cost. Jordan et al. (2006) calculated an approximate cost of $25,000 to $26,000 for 2g/kg IVIG therapy.

The complement system enhances the ability of antibodies and NK cells (B cells and T cells) to maintain a stable defense against pathogens in a normal immune state. In autoimmune diseases, abnormalities in antibodies and NK cells develop (Albrecht et al. 2015). Mutated NK cells create auto-antibodies instead of antibodies. This mutation attacks healthy body parts such as cells, tissues, and organs (Hunt 2016). Auto-antibodies produced by B cells stimulate complement fragments through the release of cytokines initiating an amplified cascade and assembly of MAC on healthy endothelial cells (Jain 2011).

To combat this autoimmune attack, IVIG therapy adds Fc receptors on macrophages, and suppresses inflammatory mediations, cytokines and chemokines (Scheinfeld et al. 2016). The addition of these Fc receptors regulates the complement system and activates the suppression of antibodies (Hartung 2008). This proportional regulation, as seen in autoimmune diseases, occurs through binding of the Fc region on IgG antibodies (Hartung 2008). By disrupting the steps in the complement system cascade, IVIG therapy down-regulates the formation of MAC, stabilizing the immune response seen in immunodeficiencies (Lunemann et al. 2016).

Dermatomyositis is generated by an uncontrolled activation of the complement cascade through auto-antibody initiation. Auto-antibodies increase the polymerization of *C9* fragments, which in turn increase the formation of MAC on targeted muscles (Suber et al. 2008). The up-regulated activation of complement fragments in autoimmune diseases allow the MAC complex to form on intramuscular cells and capillaries (Dalakas et al. 2003). MAC depositions on muscle endothelial cells cause destruction of capillaries within the muscle fiber, and also causes areas of restricted blood flow to the muscle. Restricted blood flow results in microinfarcts which decrease the oxygen and glucose supply in the muscle tissues needed for cellular metabolism. When muscle tissues get inadequate oxygen and nutrients, they begin to break down (Coley 2012). Pathology is more pronounced in the outer layer of the fascicles due to this inadequate supply of oxygen and blood, known as hypo-perfusion. Hypo-perfusion results in the atrophy of the perifascicular layer surrounding muscle bundles (Figure 2).

MAC INHIBITION BY WAY OF IgG BINDING SITE

IVIG contains approximately 95% unmodified IgG from the plasma of 10,000 or more donors (Lunemann et al. 2015). IgG antibodies present in IVIG reduce the pathogenic auto-antibodies found in DM patients. Unmodified IgG molecules can be divided into two important subunit molecules: the antigen-binding fragment (Fab) and the Fc region (Muhlen et al. 1995). These two subunits act as binding regions for either specific immunity antigens or non-specific immunity antigens. The antigen-binding subunits, Fc and Fab, are important in the role of IVIG by mediating activity of MAC in DM (Patrick et al. 1991). Fc and Fab regions on IgG antibodies bind to immune cell membranes (Quick et al. 2011), allowing NK cells to recognize and lyse marked auto-antibodies.

NK cells destroy these pathogenic auto-antibodies marked by IVIG through antibody-dependent cellular cytotoxicity. Antibody-dependent cellular cytotoxicity is an immune defense where an effector cell of the immune system actively lyses a target cell. This cell-mediated immune defense actively lyses cells with membrane-surface antigens bound by specific antibodies (Quick et al. 2011).

The Fc-dependent effector functions as a binding unit to complement proteins in order to manage their production. With regulated complement proteins through the Fc subunit binding, IVIG depresses the autoimmune response to a level the body can tolerate, reducing host tissue damage. This response includes modifications of complement activations through suppression of various antibodies and cells, such as cytokines and chemokines, that provoke inflammation (Scheinfeld et al. 2016).

Fc receptors on IgG antibodies in IVIG therapy are the primary mechanism of action for decreasing MAC deposits on muscle fibers. Through IVIG, significant muscle recovery is detected and remission states are notable (Casiola-Rosen et al. 2005). This significant change is a result of the diminished lysis of cells that prevents the degradation process of the muscle fibers. IVIG inhibits MAC formation and complement mediated tissue damage by binding to active plasma components *C3b* and *C4b* through IgG's Fc interaction region (Campo et al. 2007). When the Fc region interacts with complement fragments *C3b-8*, IgG molecules restrict the polymerization of *C9* fragments, thus inhibiting MAC formation. The binding of *C3-4b* in the binding site of Fc prevents the deposition of *C3-4b* on the membrane surface of intramuscular capillary cells (Scheinfeld et al. 2016). These interactions between plasma proteins and the Fc unit on IgG molecules cause a decrease in plasma levels of MAC. This interaction is due to the prevention of *C3b* and *C4b* binding to the extracellular surface of the cell, which in turn blocks MAC formation.

OVERVIEW: IVIG THERAPY RESEARCH IN DERMATOMYOSITIS PATIENTS

IVIG's effectiveness as a DM therapy has been studied through double-blind and placebo-controlled studies. Dalakas et al. (1993) conducted a double blind placebo-controlled study on DM patients who exhibited resistance to other immunosuppressive drugs. Comparing IVIG treated patients to placebo-treated patients, Dalakas et al. (1993) found a marked improvement in muscle strength in patients who had received IVIG for three months. The inhibited complement activation seen in IVIG treated patients demonstrates IVIG's beneficial effects through the reduction of the MAC depositions that are visible on muscle biopsies.

Basta and Dalakas (2010) studied in vitro IVIG treatment, with *C3* uptake assay, examining coded sera from 55 patients with DM and from 5 patients with other non-complement-mediated neuromuscular diseases. Results were recorded before and after IVIG treatment in 60 patients. As MAC deposition decreased, atrophy and degradation of the muscles also decreased (Cherin et al. 1991). IVIG therapy's regulation of complement-dependent tissue damage in patients with DM shows enhanced muscle strength and short term recovery.

Basta et al. (1994) showed that high-dose IVIG treatment can effectively regulate the complement-dependent damage caused in DM (Table 1). IVIG diverts the complement protein fragments *C3b* and *C4b* from target cells. This diversion prevents destruction by MAC deposits. This diversion is relevant to the beneficial effect of IVIG in patients with DM when a MAC-mediated destruction of the endomysial capillaries is the major pathogenic event. The formation of MAC in DM is through the function of *C5* convertase formation, for which incorporation of *C3b* is essential. *C3b* acts as an anchor on the membrane of the cell, and this anchoring starts the formation of MAC channels through the cell membrane (Fig 1a) and any changes in this protein effect the formation of MAC exponentially (Cherin et al. 1991).

Table 1. Comparison of related IVIG studies

	Dalakas et al. (1993)	**Basta et al. (1994)**	**Cherin et al. (1991)**
Study design	Randomized, cross-over, open label	Double-blind placebo-controlled crossover	Double-blind placebo-controlled crossover
Patients Methods	15 DM - Prednisone-IVIG (2g/kg/month) VS. Prednisone	13 DM - Prednisone-IVIG (2g/kg/2days) - Placebo	20 DM - IVIG with elevated intact IgG molecules -1g/kg/day for 2 days in 13 patients 0.4g/kg/day during 5 days for 7 patients
Results	At 3 month follow-up: In the IVIG-treated group, significant improvement of: - Muscle strength - Neuromuscular symptom score - Activity of daily living score - CK level - Muscle Biopsy findings	Post-IVIG: - IVIG sera inhibited C3 uptake (hours after IVIG) - C5b-9 complex production were normalized after IVIG - Prevented MAC formation through interception of C3 into C5 convertase	Post-IVIG: - Strength tests taken between every IVIG infusion - 16 patients showed muscle strength improvement - CK levels decreased and became normalized ($p<0.01$)

CK: Creatine kinase

IVIG: Intravenous immunoglobulin

DM: dermatomyositis

CONCLUSION

IVIG is a useful treatment for DM patients who have built up a resistance to corticosteroids and immunosuppressants such as methotrexate. IVIG's numerous modes of activation that are relevant to autoimmune disorders have shown repression of the MAC depositions normally found in DM patient muscle biopsies. IVIG therapy has also shown to improve skin manifestations, such as Gottrons rash. IVIG therapy interrupts several steps in the complement activation cascade through disruption of MAC protein fragments.

IVIG has been shown to inactivate and silence autoimmune disorders through numerous modes of action. The effect that the IgG antibodies in IVIG have on B-cells is well studied and is thought to down-regulate the production of pathogenic auto-antibodies. Their interference of IgG antibodies, through the Fc cell surface receptor, block the activity of the B-cell fragments, *C3b* and *C4b*. Through this interaction, the inactive B-cells can no longer initiate the complement cascade MAC. This disruption of MAC fragments restores the imbalance and also restores degraded intramuscular capillaries. The entire process predominantly restores muscle strength and decreases inflammation in muscle fibers. The absence of MAC depositions allows predisposed patients the chance to live active lives with adequate muscle function.

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BIOGRAPHY

Melissa Payne is a senior at the University of Minnesota Duluth where she is pursing her B.A. in biology with a minor in chemistry. After graduation, she plans to pursue a career in Nutrition. In her free time she enjoys training for marathons, hiking, and yoga.

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