Apheresis in the Treatment of Idiopathic Dilated Cardiomyopathy

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DISCLOSURE

Relevant Financial Relationship(s)
NONE

Off Label Usage
NONE
Dilated Cardiomyopathy

- Chronic progressive biventricular enlargement and contractile dysfunction.
- Patient Population: 20 to 60 years of age
- Incidence and prevalence: stable incidence after 20 with increasing prevalence until age 60 to 70
- Presentation: CHF and/or symptoms related to arrhythmia, conduction disturbance, or thrombotic complications. May also present with sudden death.

Images courtesy of William Edwards M.D., Mayo Clinic, Rochester MN
Dilated Cardiomyopathy

- Causes:
  - **Idiopathic** - 50%
  - **Myocarditis** - 9%
  - **Ischemic heart disease** – 7%
  - **Infiltrative disease** – 4%
  - **Hypertension** – 4%
  - **HIV** – 4%
  - **Connective tissue disease** – 3%
  - **Substance abuse** – 3%
  - **Doxorubicin** – 1%
  - **Other** – 10%

- “Other” includes: Lyme disease, Chaga’s disease, nutritional deficiencies, sleep apnea, endocrine abnormalities, and inherited syndromes.

Idiopathic Dilated Cardiomyopathy

- Incidence: 36 per 100,000/yr in the United States
- 50% of cases of dilated cardiomyopathy
  - 15% of heart failure in the elderly
  - 50% of heart transplants in the United States
- Medical Treatment:
  - Angiotensin converting enzyme inhibitors
  - Angiotensin II receptor blockers
  - β-adrenergic receptor blockers
  - Aldosterone inhibitors
  - Diuretics
  - Digitalis
Idiopathic Dilated Cardiomyopathy

- Pathophysiology
  - Susceptibility
  - Autoimmunity
    - Higher prevalence of autoimmunity than the general population.
    - Family members have a higher prevalence of autoimmunity including:
      - Psoriasis
      - Thyroid disease
      - Rheumatoid arthritis
      - Warm autoimmune hemolytic anemia
  - HLA association
    - HLA-DR4 and HLA-DQ4

Idiopathic Dilated Cardiomyopathy

- Pathophysiology
  - Viral Infection
    - Up to 67% have viral genome on endomyocardial biopsy
      - Parvovirus B19 – 36.6%
      - Enterovirus – 32.6%
      - Human herpes virus 6 – 10.5%
      - Adenovirus – 8.1%
    - Clearance associated with LVEF improvement.
    - Presence of viral replication not associated with worse function.
    - No difference in outcomes in those with and without detectable viral genome.


Injury and Innate Immune Response

Initial myocyte injury from pathogen or toxin

Antigen-presenting cells stimulate pathogen-specific T-cell response

Antibodies to pathogens may cross-react with endogenous epitopes (e.g., cardiac myosin and β-adrenergic receptor)

Myocyte cell death from direct viral damage, cytolytic T-cells, or apoptosis

Decreased regulatory T-cells function, activation of cytolytic T-cells, and increased Th1 and Th2 cytokines

Exposure of innate immune system to pathogens and intracellular sequestered antigens

Regulatory T-cell

Recovery or Persistent Cardiomyopathy

Viral clearance and down-regulation of immune response

Ongoing injury with persistent viral infection or immune response
Evidence for the Role of Humoral Autoimmunity in Dilated Cardiomyopathy

• Animal Studies
  • Immunization with M2 acetylcholine receptor or cardiac G-protein receptors induced DCM in rabbits
  • Immunization with the second extracellular loop of the β1-adrenergic receptor induced antibodies and DCM in rats. Transfer of serum induced DCM.
  • Immunization with Troponin-I induced antibodies and DCM in mice. Transfer of serum induced DCM.

Evidence for the Role of Humoral Autoimmunity in Dilated Cardiomyopathy

- **Human Studies**
  - 63 to 80% have detectable cardiac autoantibodies
  - Antibodies eluted from immunoadsorption columns or separated from serum:
    - Lyse rat cardiomyocytes
    - Decrease rat cardiomyocyte contractility
    - Impair rat cardiomyocyte calcium transport
    - Impair chick embryo cardiac function
Evidence for the Role of Humoral Autoimmunity in Dilated Cardiomyopathy

- α-Myosin Antibodies
  - 23 to 66% of patients (0 to 2.5% healthy controls and 4 to 21% with ischemic cardiomyopathy)
  - Worsening left ventricular function and increased diastolic stiffness
  - Cross react with β1-adrenoreceptor

- β1-Adrenoreceptor Antibodies
  - 26 to 46% patients (1 to 10% healthy controls and 10 to 13% with ischemic cardiomyopathy)
  - Depressed myocardial function, greater incidence of severe ventricular arrhythmia, and greater incidence of sudden cardiac death
  - Presence predicts increased risk of all-cause and cardiovascular mortality

Evidence for the Role of Humoral Autoimmunity in Dilated Cardiomyopathy

• Troponin-I Antibodies
  • Increase L-type Ca$^{2+}$ current

• Na-K-ATPase Antibodies
  • Independent predictor of poor systolic function, ventricular tachycardia, and sudden cardiac death.

• M2-Muscarinic Acetylcholine Receptor Antibodies
  • Greater incidence of atrial fibrillation

Mechanism of Autoantibodies

• How can autoantibodies toward diverse myocardial antigens produce a common physiologic effect (reducing calcium transients and cell shortening) and a common clinical syndrome?
  • Cross linking of the target antigen and Fcγ receptor IIa present on cardiomyocytes is necessary!

Mechanism of Autoantibodies

F(ab’)2 fragments and antihuman F(ab’)2 fragments did not induce effect.

F(ab’)2 fragments blocked the effect of intact antibody.

Antibody binding induces a negative inotropic effect.

Fc fragments from normal IgG blocked the effect of intact antibody.

Cardiac Antigen

Sarcolemmal Fcγ Receptor IIa

Apheresis Treatment

- **Immunoabsorption**
  - Antihuman Sheep Polyclonal Immunoglobulin Column (Ig-Therasorb)
  - Antihuman Sheep Polyclonal Immunoglobulin Column (Ig-Adsopak)
  - Staphylococcal Protein A Agarose Column (Immunosorba)
  - β1-adrenergic Receptor Antibody Column (Coraffin)
  - Tryptophan Polyvinyl Alcohol Column (Myosorba/Immusorba)
  - PGAM146 Column (Globaffin)

- **Plasma Exchange**
Antihuman Sheep Polyclonal Immunoglobulin Column (Ig-Therasorb)

- Anti-human sheep Ig bound to matrix
- Centrifugal disk separator
- Glycine HCL
- Waste Bag

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Antihuman Sheep Polyclonal Immunoglobulin Column (Ig-Therasorb)

- Dorffel 1997 – CS 9 patients
  - Treatment on 5 consecutive days
  - Improved cardiac output, index, and stroke volume at 3 months
  - Decreased mean arterial pressure, LV filling pressure, and systemic vascular resistance
  - At 3 years follow-up:
    - 5 alive with no increase in β1-adrenoreceptor antibody titers and continued improvement of LVEF
    - 4 dead, all had increase in β1-adrenoreceptor antibody titers with associated LVEF decline

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Antihuman Sheep Polyclonal Immunoglobulin Column (Ig-Therasorb)

- Muller 2000 – CT 34 patients (17 treated and 17 control)
  - Treatment on 5 consecutive days
  - Improvement at 12 months in:
    - LVEF
    - LV diastolic diameter
    - NYHA class
  - Decrease at 12 months in:
    - Oxidative stress markers
    - β1-adrenoreceptor antibody titers
  - Improved survival at 5 years (82% vs 41%, p=0.00071)
  - Annual cost of treatment was less (€24,857 vs €28,875)
Antihuman Sheep Polyclonal Immunoglobulin Column (Ig-Therasorb)

- **Knebel 2004** – CT 34 patients (17 treated, 17 untreated)
  - Acute increase in LVEF (19.8 to 25.7%)
  - Decreased days of hospitalization (17.2 days versus 4.3 days).
  - Effect lasted beyond 2.5 years
  - Days of hospitalization gradually increased with time after treatment.

- **Lehmkuhl 2005** – CS 108 patients
  - At 2 years – 81% responders, 19% non-responders
  - Increase in LVEF, decrease in LVEDD in responders
  - Lower LVEF at start of therapy in non-responders
  - LVEF and LVEDD changes became more pronounced over time
  - Sustained decline in β1-adrenoreceptor antibody in responders
Antihuman Sheep Polyclonal Immunoglobulin Column (Ig-Therasorb)

- Other studies have found
  - Improved cardiac index, stroke volume, LVEF, and NYHA class at 3 months
  - Decreased systemic vascular resistance at 3 months
  - Decreased desmin gene expression, HLA class II expression, and myocardial lymphocytes on EMB at 3 months
  - Decreased β1-adrenoreceptor antibody titers

- Other key points:
  - Presence of β1-adrenoreceptor antibody did not correlate with response (Mobini 2003)
  - Only patients with cardiodepressant antibodies demonstrated a response (Staudt 2004)
Antihuman Sheep Polyclonal Immunoglobulin Column (Ig-Adsopak)

- Pokrovsky 2013 – RCT 16 patients (9 treated and 7 controls)
  - Not selected for antibody positivity
  - Treatment on 5 consecutive days
  - No IVIG replacement
  - Improvement immediately after treatment:
    - LVEF (not statistically significant)
    - 6 minute walking distance
    - Brain natriuretic peptide (BNP)
    - NYHA class
  - NYHA class improvement persisted at 6 month follow-up
  - LVEF improved at 3 month follow-up but declined at 6 months.

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Staphylococcal Protein A Agarose Column (Immunosorba)
Staphylococcal Protein A Agarose Column (Immunosorba)

Image courtesy of Fresenius KABI
Staphylococcal Protein A Agarose Column (Immunosorba)

- Phase III multicenter trial in Germany and Sweden (NCT00558584)
  - Estimated primary completion date: December 2015
- Staudt 2002 – CT 18 patients (9 SPAA vs 9 AHPI)
  - Treatments on 3 consecutive days then two days every 4 weeks for 3 months.
  - No change in LVEF or cardiac index with SPAA
  - Due to limited IgG3 removal by SPAA
- Staudt 2005 – CT 18 patients (9 modified SPAA vs 9 SPAA)
  - Enhanced IgG3 removal protocol
  - Improved LVEF at 3 months with modified protocol

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Staphylococcal Protein A Agarose Column (Immunosorba)

- **Staudt 2006 – RCT 22 patients**
  - Treatment on 5 consecutive days vs 5 consecutive days every month for 4 months
  - Equivalent LVEF and cardiac index improvement at 6 months

- **Other studies have found**
  - Improved LVEF, VO$_2$, exercise capacity and NYHA class at 3 and 6 months
  - Continued improvement to 12 months
  - Decreased nt-proBNP, nt-BNP, and nt-ANP at 3 months
  - Decreased cardiodepressant antibodies at 6 months with return at 12 months
Staphylococcal Protein A Agarose Column (Immunosorba)

- Other key points
  - Shorter disease course and low affinity Fcγ receptor IIa associated with greater LVEF improvement (Staudt 2009)
  - Only those with cardiodepressant antibody improved (Trimpert 2010)
  - Only those with antibody (β1-adrenoreceptor, Troponin-I) improved (Herda 2010)
  - Shorter disease duration and greater IgG3 reduction associated with greater LVEF improvement (Doesch 2010)
Staphylococcal Protein A Agarose Column (Immunosorba)

• Other key points
  • Treatment associated with increased Treg and decreased Tstim and Tcostim lymphocytes (Bulut 2010)
  • Responders had fewer Treg and more Th17 lymphocytes than non-responders with increase in Tregs in responders (Bulut 2013)
  • Response predicted by the presence of cardiodepressant antibodies and RANBP1, RGS10, UBE3B, and USP22 genes. (Ameling 2013)
    • Inhibitory antibodies correlated with UBE3B and USP22 expression
β1-adrenergic Receptor Antibody Column (Coraffin)

0.9% NaCl

PDCM075 peptide column

Plasma Pump

Whole Blood Pump

Waste Bag
β1-adrenergic Receptor Antibody Column (Coraffin)

PDCM349 (loop 1-peptide): 14mer peptide
PDCM075 (loop 2-peptide): 18mer peptide

Image and graphics courtesy of Fresenius KABI
β1-adrenergic Receptor Antibody Column (Coraffin)

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- Wallukat 2002 – CS 8 patients
  - β1-adrenoreceptor antibody positive
  - Treatment 5 consecutive days
  - Increased LVEF
  - Decreased LV diameter, β1-adrenoreceptor antibody titer, and oxidative stress at 12 months
β1-adrenergic Receptor Antibody Column (Coraffin)

• Dandel 2010 – CT 105 patients (54 SPAA vs 51 β1-receptor column)
  • β1-adrenoreceptor antibody positive
  • Improved LVEF and decreased LV diameter in both
  • Similar response (78.4% SPAA vs 75% β1-adrenoreceptor column)
  • No difference at 3 and 5 years
  • 8.6% with β1-adrenoreceptor antibody recurrence and decreased function
Tryptophan Polyvinyl Alcohol Column (Myosorba/Immusorba)
Tryptophan Polyvinyl Alcohol Column (Myosorba/Immusorba)

Image courtesy of Asahi Kasei

Image courtesy of Leslie Cooper, M.D., Mayo Clinic, Rochester MN
Yazaki 2009 – CS 2 patients
  • Improved LVEF and decreased BNP in one patient at 3 months

Baba 2010 – CS 18 patients
  • β1-adrenoreceptor or M2-muscarinic acetylcholine receptor antibody positive
  • LVEF, 6 minute walk test, and BNP improved
  • LVEF improved greater at 3 months if cardiodepressant antibody disappeared

Nagatomo 2011 – CS 16 patients
  • Improved LVEF and 6 minute walk test at 3 and 6 months
  • Decreased BNP at 3 and 6 months

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GAM146 Column (Globaффin)

- Synthetic peptide binds immunoglobulin non-specifically
- Cannot be regenerated
- Limited published reports on use in DCM
  - Dandel 2012

Image and graphics courtesy of Fresenius KABI
Comparison of Immunoabsorption Devices

• Dandel 2012 – CT 182 patients

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<tr>
<th>Column</th>
<th>N</th>
<th>Response Rate</th>
<th>LVEF Pre</th>
<th>LVEF Post</th>
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<tr>
<td>Coraffin</td>
<td>23</td>
<td>78.3%</td>
<td>23.8±6.3%</td>
<td>32.3±7.8%</td>
<td>91.3±5.9%</td>
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<td>Globaffin</td>
<td>24</td>
<td>79.2%</td>
<td>24.4±5.4%</td>
<td>33.6±6.2%</td>
<td>86.0±8.5%</td>
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<td>Ig-Therasorb</td>
<td>25</td>
<td>80.0%</td>
<td>24.0±6.0%</td>
<td>30.7±12.4%</td>
<td>78.8±8.4%</td>
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Plasma Exchange

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- Torre-Amione 2010 – CS 8 patients
  - 1 plasma volume
  - Albumin replacement
  - 5 treatments every other day
  - Improved LVEF and NYHA class
  - Decreased Ig deposition on EMB

- Remaining case reports treated patients with β1-adrenoreceptor antibody in whom SPAA was contraindicated or not available
  - Improved LVEF and NYHA class
Other Points

• Studies have excluded patients with familial DCM, which represent 20% of iDCM and are due to inherited cytoskeletal abnormalities.
• Patients on optimum medical therapy with a minimum disease duration of 6 months.
• Most protocols treated NYHA class II to IV patients with some treating only NYHA class II or III.
• Role of cardiac autoantibody assays is unclear though bioassays indicating cardiodepressant antibodies have been associated with response.
• In most SPAA and AHPI column protocols, IVIG (0.5 g/kg) has been administered.
  • SPAA: 471 vs 4 patients
  • AHPI: 142 vs 37 patients
• Published reports of plasma exchange have administered IVIG (0.5 g/kg).
• Tryptophan polyvinyl alcohol, β1-adrenoreceptor column, and AHPI (Ig-Adsopak) protocols have not administered IVIG.
2013 ASFA Guidelines

• Immunoadsorption
  • ASFA Category: II (NYHA class II to IV)
    ➢ Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.
  • Recommendation Grade: 1B
    ➢ Strong recommendation, can apply to most patients in most circumstances without reservation.

• Plasma Exchange
  • ASFA Category: III (NYHA class II to IV)
    ➢ Optimum role of apheresis therapy is not established. Decision making should be individualized.
  • Recommendation Grade: 2C
    ➢ Very weak recommendation; other alternatives may be equally reasonable.

References

Antihuman Polyclonal Immunoglobulin Column (Ig-Therasorb)


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Staphylococcal Protein A Agarose Column (Immunosorba)


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Tryptophan Polyvinyl Alcohol Column (Myosorba/Immunosorba)


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Ig-Adsopak
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Plasma Exchange


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Background


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Review Articles