Mechanisms of action of IV Ig: What do we really know?

Alan H. Lazarus, PhD

Canadian Blood Services
St. Michael’s Hospital
University of Toronto
Outline

• How does IVIg work in autoimmunity?

• There are too many theories to explain how IVIg works!

• Present evidence against:
  • FcRn
  • Fc³RII B
  • IgG sialylation

• Evidence for immune complexed IgG acting on Dendritic cells via activating Fc³R ɵDC-SIGN
Intravenous Immunoglobulin

IV Ig is IgG

Fc

F(ab’)2
Mechanisms of IV Ig

How does IV Ig work in autoimmunity?

- ITP (murine passive ITP)
- Inflammatory arthritis (murine kn serum transfer)
- EAE (M urine model of MS)
IV Ig Beneficial - Yes/likely

- CIDP
- ITP and HIV-ITP
- Hypogammaglobulinemia
- Guillain-Barré syndrome
- Kawasaki disease
- Kidney transplantation: HLA sensitization
- Toxic epidermal necrolysis, Stevens-Johnson syndrome
- Dermatomyositis, polymyositis
- Autoimmune uveitis
- Stiff-person syndrome

- Fetal/neonatal alloimmune thrombocytopenia
- Post transfusion purpura
- A autoimmune neutropenia
- Multifocal Motor Neuropathy
- Demyelinating Polyneuropathies associated with IgG or IgA monoclonal gammopathies
- A cute exacerbations in Myasthenia Gravis
- Lambert-Eaton M yasthenic syndrome

Source: Immunoglobulin Therapy
Most mechanistic studies in murine ITP

Platelet count

Time post serum injection

Yippee!

Good idea?

IV Ig?

Harrington-1951
Immune thrombocytopenia (ITP)
The first demonstration that IV Ig has ameliorative effects in an autoimmune disease
How does IVIg work?
We don’t know how IVIg works and the IVIg puzzle has been difficult to solve with results that often seem to be in conflict with each other.
The players

Block Fc receptors (RES blockade)
Anti-idiotypic antibodies
complement
Neonatal Fc receptor
Fc$^3$RIIB (Inhibitory)
Fc$^3$RIII (Activating)

Immune complex
Dendritic cells
DC-SIGN
Fc sialylation
T regulatory cells
The players: There are too many

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What is the FcRn and how does it work?

FcRn protects IgG from degradation in adults

From, Roopenian et al, Nature Reviews Immunology 7, 715-725
Hypothesis

IVIg works (at least in part) by saturating FcRn, thereby increasing catabolism of all IgG antibodies, including pathogenic IgG.
FcRn deficient mice are protected from ITP to the same extent as wild-type mice.
FcRn: Conclusion

IVIg can ameliorate murine ITP in the absence of FcRn or 2M (required for functional FcRn expression).

Brief report

The neonatal Fc receptor (FcRn) is not required for IVIg or anti-CD44 monoclonal antibody–mediated amelioration of murine immune thrombocytopenia

Andrew R. Crow,1-3 Sara J. Suppa,2,3 Xi Chen,2,3 Patrick J. Mott,2,3 and Alan H. Lazarus1-4

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The players: There are too many

- Immune complex
- Dendritic cells
- DC-SIGN
- Fc sialylation
- T regulatory cells

- Neonatal Fc receptor
- Fc$^3$RIIB (Inhibitory)
- Fc$^3$RIII (Activating)
What is the major signaling pathway involved in FcγRIIB inhibitory function?

Not SHIP, SHP-1, or Btk
Reversal of immune thrombocytopenia in mice by cross-linking human immunoglobulin G with a high-affinity monoclonal antibody

Renée Bazin, Réal Lemieux and Tony Tremblay

1Department of Research and Development, Héma-Québec, and 2Department of Biochemistry and Microbiology, Laval University, Quebec, QC, Canada

2006 British Journal of Haematology, 135, 97–100

Brief report

Mouse background and IVIG dosage are critical in establishing the role of inhibitory Fcγ receptor for the amelioration of experimental ITP

Danila Leontyev, Yulia Katsman, and Donald R. Branch

1Research & Development, Canadian Blood Services, Toronto, ON; and 2Department of Medicine, University of Toronto, Toronto, ON

Blood. 2012;119(22):5261-5264
<table>
<thead>
<tr>
<th>Genotype</th>
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<tr>
<td>Fc³RIIB⁺⁺⁺</td>
<td>yes</td>
<td>yes</td>
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Intravenous immunoglobulin ameliorates ITP via activating Fcγ receptors on dendritic cells

Vinayakumar Siragam¹², Andrew R Crow¹², Davor Brinc¹², Seng Song², John Freedman¹³ & Alan H Lazarus¹³

(NZW x BXSB) F1 male mice
Expression of the autoimmune Fcgr2b NZW allele fails to be upregulated in germinal center B cells and is associated with increased IgG production

ZSM Rahman¹, H Niu², D Perry², E Wakeland³, T Manser¹ and L Morel²
Intravenous immunoglobulin does not increase FcγRIIB expression levels on monocytes in children with immune thrombocytopenia

M. Shimomura, S. Hasegawa, Y. Seki, R. Fukano, N. Hotta and T. Ichiyama
Department of Pediatrics, Yamaguchi University Graduate School of Medicine, Ube, Yamaguchi, Japan

“There were no significant differences in the percentages or numbers of CD14+CD32B+ monocytes, or in the percentage of CD14+CD32B+ monocytes present in (20) children with ITP before and after IVIG therapy.”
The players: There are too many

Immune complex
Dendritic cells
DC-SIGN
Fc sialylation
T regulatory cells

Fc$^3$RIIB (Inhibitory)
Fc$^3$RIII (Activating)
Anti-Inflammatory Activity of Immunoglobulin G Resulting from Fc Sialylation

Yoshikatsu Kaneko,* Falk Nimmerjahn,* Jeffrey V. Ravetch†

Identification of a receptor required for the anti-inflammatory activity of IVIG

Robert M. Anthony, Fredrik Wermeling, Mikael C. I. Karlsson, and Jeffrey V. Ravetch

DC-SIGN $\xrightarrow{Fc^3RIIB (M\uparrow)}$ IL-4 $\rightarrow$ Baso $\rightarrow$ IL-33
Sialylation-independent mechanism involved in the amelioration of murine immune thrombocytopenia using intravenous gammaglobulin

Danila Leontyev, Yulia Katsman, Xue-Zhong Ma, Sylvia Miescher, Fabian Kösermann, and Donald R. Branch

Enrichment of Sialylated IgG by Lectin Fractionation Does Not Enhance the Efficacy of Immunoglobulin G in a Murine Model of Immune Thrombocytopenia

Theresa Guhr¹, Judith Bloem², Ninotska I. L. Derksen¹, Manfred Wuhrer³, Anky H. L. Koenderman², Rob C. Aalberse¹, Theo Rispens¹

Dissecting the Molecular Mechanism of IVIg Therapy: The Interaction between Serum IgG and DC-SIGN is Independent of Antibody Glycoform or Fc Domain

Xiaojie Yu¹, Snezana Vasiljevic¹, Daniel A. Mitchell², Max Crispin¹ and Christopher N. Scanlan¹

Andrew R. Crow, Seng Song, John W. Semple, John Freedman, and Alan H. Lazarus

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DC-SIGN \[\rightarrow\] Fc³RIIB (M₁) \[\rightarrow\] IL-4 \[\rightarrow\] Baso \[\rightarrow\] IL-33
The players: There are too many

Immune complex
Dendritic cells
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Fc sialylation
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Fc<sup>3</sup>R<sub>III</sub> (Activating)
The players: There are too many

Immune complex
Dendritic cells
DC-SIGN

Fc$^3$RIII (Activating)

T regulatory cells

Block Fc receptors (RES blockade)
Cell-associated (anti-D like effect)

Soluble

IgG1 and IVIg induce inhibitory ITAM signaling through FcγRIII controlling inflammatory responses

Meryem Aloulou,1,2 Sanae Ben Mkaddem,1,2 Martine Biarnes-Pelicot,1,2 Tarek Boussetta,1,2 Hervé Souchet,1,2 Elisabetta Rossato,1,2 Marc Benhamou,1,2 Bruno Crestani,2-4 Zhou Zhu,5 Ulrich Blank,1,2 Pierre Launay,1,2 and Renato C. Monteiro1,2,6

Vinayakumar Siragam,1,6 Davor Brnic,1,6 Andrew R. Crow,1,6 Seng Song,1 John Freedman,1,2,3 and Alan H. Lazarus1,2,3
Endogenous soluble antigens

![Graph showing the effect of various treatments on platelet count. The x-axis represents time (0-4) with treatment indicated at 2. The y-axis represents platelet count (x10^9/L). The graph compares IVIG, anti-albumin, anti-transferrin, and non-immune IgG treatments. The legend indicates significant differences at certain time points.](image)

Intravenous immunoglobulin ameliorates ITP via activating Fcγ receptors on dendritic cells

Vinayakumar Siragam¹,²,⁴, Andrew R Crow¹,²,⁴, Davor Brinc¹,², Seng Song², John Freedman¹−³ & Alan H Lazarus¹−³
Proposed model of IVIg action in murine ITP

Siragam et al, J Clin Invest 2005
Aloulou et al, Blood 2012
Siragam et al, Nat Med 2006
Huang et al, Blood 2010
Proposed model of IVIg action in ITP

Tha-In et al, Blood 2007
Ephrem et al, Blood 2008
Aubin et al, Blood 2010
Conclusions (IVIg)

- IVIg has beneficial effects in a large number of seemingly unrelated autoimmune diseases and inflammatory states

- Evidence against the concept that IVIg requires the neonatal Fc receptor (FcRn) for its function

- Evidence against the concept that IVIg interacts or requires the inhibitory Fc receptor (Fc³RIIB) for its function

- Evidence against a simple role of Fc sialic acids in mediating IVIg effects

- IVIg may interact with activating FcRs on dendritic cells in the initiation of its effects
Acknowledgements

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Derry Ropenian
John Semple
Steve McKenzie
Mike Reilly

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CIHR
Health Canada
IV Ig effectiveness and pharmacology in a model autoimmune disease

A. IV Ig; standard single dose
B. IV Ig; maximal continuous dosing
C. IV Ig; single dose with decay
D. IV Ig; low cont. Infusion
E. IV Ig; 2/week