Harnessing the innate immunity to modulate autoimmunity and cancer

IVIG; The myth and reality

Yehuda Shoenfeld

MD, FRCP

CONPO Barcelona 2013

Yehuda Shoenfeld, MD, FRCP (Hon.)
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Definitive way of preparation; produced by 25 pharmaceutical companies (very expensive).

Clinical applications: treatment of severe immune deficiency diseases and a variety of autoimmune conditions.

Pooled IgG (immunoglobulin G) from 6,000-20,000 blood donation.
Intravenous Immunoglobulin - IV Ig

- Pooled IgG (immunoglobulin G) from 6,000-20,000 blood donation (representing the Innate Immune repertoire)
- Definitive way of preparation; produced by 25 pharmaceutical companies (very expensive)
- Clinical applications: Treatment of severe immune deficiency diseases and a variety of autoimmune conditions

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IVIg THERAPY

- High-dose: 2-g/kg body weight IVIg.
- The preparation: Octapharma, MedImmune, Sclavo, BPL, tegeline, endobuline, gammagard, ZLB, Omrix
- A 5-days schedule.
- A monthly interval.
- Every patient received 1-6 treatment courses.

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Paul Imbach

IVIG

Wiskott Aldrich


*IVIG in ITP*

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Immune thrombocytopenia (ITP)

ITP is an autoimmune disease due to autoantibody to endogenous platelets.

Causes platelet destruction by macrophages and bleeding.
Successful IVIG treatment in autoimmune diseases

- ITP
- Autoimmune hemolytic anemia
- Viral-associated red-cell aplasia
- Guillain-Barre syndrome
- Myastenia gravis
- Polymyositis
- Dermatomyositis
- Kawasaki disease
- ANCA-positive systemic vasculitis
- Antiphospholipid syndrome
- Recurrent spontaneous abortions
- Multiple sclerosis

- Felty’s syndrome
- Juvenile RA
- SLE
- GVHD
- Multiple sclerosis
- IDDM
- Steroid-dependent asthma
- Steroid dependent severe atopic dermatitis
- Crohn’s disease
- Chronic Inflammatory Demyelinating Polyneuropathy

Yehuda Shoenfeld, MD,FRCP (Hon.)
A study of 20 SLE patients with intravenous immunoglobulin clinical and serologic response

Yair Levy, Yaniv Sherer, Alaa Ahmed, Pnina Langevitz, Jacob George, Fabizio Fabbrizzi, Jeff Terryberry, Martyna Meissner, Margalit Lorber, James B Peter, Yehuda Shoenfeld.

Lupus 8, 705-712, 1999

- A beneficial clinical response following IVIg treatment was noted in 17 out of 20 patients (85%).
- Some clinical manifestations responded more to treatment: arthritis, fever, thrombocytopenia, and neuropsychiatric lupus.

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Successful treatment of early secondary myelofibrosis in SLE with IVIG.


Reduced proteinuria following repeated courses of IVIG

![Graph showing urinary protein extraction over time](image)
A Comparison Between Prednisone Doses used for the Treatment of SLE Patients Before and After IVIg
2. Anti-idiotypic Abs

Anti-Id Abs modulates the immune system by suppressing auto-Abs production
AIM:
To evaluate the efficacy of the anti-dsDNA anti-idiotype enriched IVIG

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Affinity purification of anti-dsDNA anti-ID from IVIG

Loading dialyzed IVIG
16 hours at 4°C

Elution with HCl-glycine

Anti-dsDNA-Sepharose

anti-dsDNA anti-ID

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Treatment of NZB/W F1 mice with IVIG-ID

Three weekly injections to the tail vein of NZB/W F1 mice:

IVIG-ID: 2 mg/kg = 60 µg/mouse
IVIG: 400 mg/kg = 12 mg/mouse

Yehuda Shoenfeld, MD, FRCP (Hon.)
Proteinuria in NZB/W F1 mice treated with SUPERIVIG and IVIG

Yehuda Shoenfeld, MD, FRCP (Hon.)
Prevention of mesangial mouse IgG deposits in NZB/W F1 mice treated (early treatment) with:

IVIG-αID  IVIG  NON-TREATED

Yehuda Shoenfeld, MD, FRCP (Hon.)
Cumulative number of deaths with concomitant proteinuria in NZB/ W F1 mice

Yehuda Shoenfeld, MD,FRCP ( Hon.)

Shoenfeld Y, Rauova L, Gilburd B, Kvapil F, Goldberg I, Kopolovic J, Rovensky J, Blank M.

Int Immunol. 2002;14:1303-11
Autoimmune Disease Specific IVIg: Low Dose, High Efficacy

Antiphospholipid syndrome

Anti-β2GPI

Antiphospholipd syndrome

Pemphigus vulgaris

Myasthenia Gravis

Anti-dsDNA

Anti-AChR

Special types of IVIg for autoimmune diseases

Yehuda Shoenfeld, MD, FRCP (Hon.)
I.V.I.G Treatment of Cancer

Cancer and Autoimmunity
Yehuda Shoenfeld
M. Eric Gershwin
Editors

Elsevier
Reactivity of the human IVIG with a panel of human cell line

Human bladder carcinoma cell line T24, human glioma cell line U-138MG, human head-and-neck cancer cell line PCI-13, human lymphoid cell line LG2 and human melanoma cell lines 501, 553B, 836, 1379, Colo38 and Mel-1386 at 4oC for 2 hours.

Reactivity of the humanized antibody IVIG with a panel of cell lines

<table>
<thead>
<tr>
<th>Cell lines</th>
<th>IVIG</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>T24</td>
<td>1.0</td>
<td>0.1</td>
</tr>
<tr>
<td>836</td>
<td>1.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Colo38</td>
<td>1.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Mel-1386</td>
<td>1.6</td>
<td>0.4</td>
</tr>
<tr>
<td>DAM-MB-231</td>
<td>1.8</td>
<td>0.5</td>
</tr>
<tr>
<td>553B</td>
<td>2.0</td>
<td>0.6</td>
</tr>
<tr>
<td>293/KDR</td>
<td>2.2</td>
<td>0.7</td>
</tr>
<tr>
<td>1379</td>
<td>2.4</td>
<td>0.8</td>
</tr>
<tr>
<td>PCI-13</td>
<td>2.6</td>
<td>0.9</td>
</tr>
<tr>
<td>LG2</td>
<td>2.8</td>
<td>1.0</td>
</tr>
<tr>
<td>501</td>
<td>3.0</td>
<td>1.1</td>
</tr>
<tr>
<td>U-138MG</td>
<td>3.2</td>
<td>1.2</td>
</tr>
</tbody>
</table>

OD at 450nm
IVIg: Prevention of Melanoma Metastases

Gamma-globulin inhibits tumor spread in mice
Yehuda Shoenfeld and Pnina Fishman
*International Immunology*
11: 1247 - 1251, 1999

Yehuda Shoenfeld, MD, FRCP (Hon.)
Effect of IVIg (I.V.) on the Development of Melanoma Metastases

![Graph showing the effect of IVIg treatment on melanoma metastases]

- **Control**: P < 0.001
- **Days of IVIg treatment**: P < 0.001
IVIg Prolongs the Survival of Tumor Bearing Mice

Sarcoma

a - Sarcoma

% survival

Days after amputation

Treated
Control

b - Melanoma

% survival

Days after amputation

Treated
Control

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IIVIg: Prevention of Tumor foci the Peritoneum

Shoenfeld, MD, FRCP (Hon.)
IV Ig: Prevention of Lung Sarcoma Metastases

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Inhibitory effect of IVIg on in vitro CT26 cell proliferation

Time course and dose response

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Effect of IVIg on CT26 cell invasiveness

The invasive capacity of CT26 cells was decreased by IVIg

(time- and dose-dependent effect)

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Dose Dependent Effect of IVIg on the Proliferation of Human Colon Carcinoma, HCT-116 Cells

![Graph showing the dose-dependent effect of IVIg on [H3] Thymidine incorporation (% of inhibition) for different IVIg Concentrations (mg/ml)]

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Human Experience

Shrinkage of Melanoma Metastases Following High dose Intravenous Immunoglobulin Treatment
Shoenfeld Y, Levy Y, Fishman P.
*IMAJ* 3; 698-699, 2001
Total remission of thymus carcinoma after treatment with intravenous immunoglobulin


42 year-old woman with myasthenia gravis associated with a malignant thymoma. A complete remission of the thymoma was confirmed by FDG-PET after four cycles of immunoglobulins.
IV Ig as a natural anti-cancer agent

Mechanisms
IVIG Exerts Apoptotic Effect on Nb2-11c Lymphoma cells

IVIG 25mg/ml

Control
**IVIG Inhibits MMP-9 mRNA expression in mouse Melanoma cells**

IVIg as an anti-angiogenic agent?

ANTI-VEGF ACTIVITY OF IVIg

Diagram showing the interaction between IVIg and VEGF receptors (VEGFR-1 and VEGFR-2), as well as other agents like anti-VEGF antibodies, soluble VEGF receptors, and small-molecule VEGFR TK inhibitors.
Binding of IVIg to the recombinant VEGF

Anti-VEGF activity in an IVIg preparation (ELISA)

IVIg samples were loaded onto 12% SDS-PAGE and blotted on to nitrocellulose membranes

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Competition of MAV and IVIg for binding to the VEGF in an immunoblot

Lane 1: Binding of IVIg (2mg/ml) to the VEGF pre-incubated with MAV (10 µg/ml)
Lane 2: Binding of MAV (10µg/ml) to the VEGF pre-incubated with IVIg (2mg/ml)
Lane 3: Direct binding of IVIg (2mg/ml) to the VEGF
Lane 4: Direct binding of MAV (10 µg/ml) to the VEGF

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Injection of bFGF

IVIG as an anti VEGF

Arei Solomon @Y Shoefled
Anti-VEGF activity of IVIg *in vivo*

IVIG inhibits VEGF-induced blood perfusion in mouse hind-limb ischemia

**Blood flow recorded by Laser Doppler Perfusion Imaging**

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Effect of IVIg on colon carcinoma primary tumor growing potential

Corneal insemination of CT26 colon carcinoma cells

After 10 days

Control

A rich vascular bed and the growing tumor mass.

IVIg treated

Complete eradication of tumor mass.

Inhibits tumor angiogenesis


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Mechanisms for IVIg as Anti-metastatic Agent

- Increased secretion of IL-12
- Increased activity of NK
- Induction of apoptosis in tumor cells
- Direct binding - cytostatic (cytotoxic)? - c’ dependent?
- Anti-MMP-9, Cathepsin D
- Anti – VEGF
- Anti – Blyss (BAFF)

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Gamma-globulins from an IVIg preparation contain a sub-fraction of anti-VEGF Abs with a possible anti-angiogenic activity.

VEGF specific activity of IVIg may suggest a new action mechanism by which IVIg may suppress cancer and some autoimmune diseases.
Immunomodulation with subcutaneous Ig

Long-term therapy with high doses of subcutaneous immunoglobulin in multifocal motor neuropathy
Thomas Harbo, Henning Andersen and Johannes Jakobsen
Neurology 2010;75;1377
DOI 10.1212/WNL.0b013e3181f735ce

Contents lists available at ScienceDirect
Autoimmunity Reviews 2010

journal homepage: www.elsevier.com/locate/autrev

Review
Subcutaneous immunoglobulin in polymyositis and dermatomyositis: A novel application
Maria Giovanna Danieli a,*, Lucia Pettinari a, Romina Moretti a, Francesco Logullo b, Armando Gabrielli a

a Clinica Medica, Dipartimento di Scienze Mediche e Chirurgiche, Università Politecnica delle Marche & Ospedali Riuniti, Ancona, Italy
b Clinica Neurologica, Università Politecnica delle Marche & Ospedali Riuniti, Ancona, Italy

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BAFF, a New Target for Intravenous Immunoglobulin in Autoimmunity and Cancer


- The excess in serum level and/or tissue production of BAFF in:
Nonglycosylated recombinant BAFF, glycosylated affinity-purified BAFF, and recombinant APRIL (but not TNFalpha), were recognized by certain IgG in IVIg, and their F(ab')(2) fragments.

The presence of anti-BAFF and anti-APRIL Abs in IVIg.
IVIG as Anti BLISS (BAFF) (Functional)

A

B

C

Figure 3

J Clin Immunol 2007
Anti-Mechanisms of IVIG

- Modulation of B-cell repertoire, regulation of Ab production
- Neutralization of Ab by anti-Ids
- Apoptosis
- Activation & Proliferation
- Antibody-dependent cellular cytotoxicity
- Inhibition of maturation and functions, activating and inhibitory FcR-mediated signaling
- Anti-inflammatory cytokines
- Complement-mediated damage

IL-2, IL-1β, IFN-γ
ADVERSE EFFECTS AND VIRAL SAFETY OF INTRAVENOUS IMMUNOGLOBULIN THERAPY IN 56 PATIENTS WITH AUTOIMMUNE DISEASES

Yaniv Sherer, Yair Levy, Pnina Langevitz, Fabrizio Fabbrizzi, Yehuda Shoenfeld

Department of Medicine ‘B’ and Center of Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, and Sackler Faculty of Medicine, Tel-Aviv University, Israel

Pharmacology 2001; 62: 133-137
CONCLUSIONS:
IVIg- the myth and reality

- IVIG is effective in autoimmune conditions—multiple mechanisms
- IVIG anti-cancer effects in; melanoma, carcinoma, sarcoma and lymphoma
- IVIG representing the innate immune system affect tumors by diverse mechanisms
Five Jews change the way we see the world:

Moses: "the Law is everything."

Jesus: "Love is everything."

Marx: "Money is everything."

Freud: "Sex is everything."

Einstein: "Everything is relative."