Managing Autoimmune Issues & Primary Immunodeficiency

August 18, 2022
Immune Deficiency Foundation (IDF) education events offer a wide array of educational presentations, including presentations developed by healthcare and life management professionals invited to serve as presenters. The views and opinions expressed by guest speakers do not necessarily reflect the views and opinions of IDF.

The information presented during this event is not medical advice, nor is it intended to be a substitute for medical advice, diagnosis or treatment. Always seek the advice of a physician or other qualified health provider with questions concerning a medical condition. Never disregard professional medical advice, or delay seeking it based on information presented during the event.
MISSION

Improving the diagnosis, treatment, and quality of life of people affected by primary immunodeficiency through fostering a community empowered by advocacy, education, and research.
VISION

IDF seeks to ensure that everyone in the U.S. affected by PI has a fully informed understanding of

1. the PI diagnosis that affects them,
2. all available treatment options,
3. the expected standard of care,
4. all their opportunities for connection and support within the PI community.
Questions?

https://community.primaryimmune.org/s/newask
800-296-4433
Get Connected Groups

https://primaryimmune.org/support-services

Virtual groups exclusively for individuals & families living with PI
THANK YOU TO OUR SPONSORS

- CSL Behring
- GRIFOLS
- Takeda
- HORIZON
- accredo
- octapharma
- ADMA BILOGICS
- AstraZeneca
- Pharming
- X4 PHARMACEUTICALS
- KEDRION BIOPHARMA
- ENZYVANT
- Chiesi

global rare diseases
A WORD FROM OUR SPONSOR

CSL Behring
U.S. Plasma Center Network
Focused on Growth, as Demand for Plasma Increases

• Continued urgent need for plasma donations is growing as many therapies for those affected by serious, rare and life-threatening diseases require plasma as a raw material.

• CSL Plasma is focused on growth, expanding our center network and investing in our business and employees to meet this demand in a safe and compliant manner.

• Employee growth and development opportunities help advance our workforce in care of our donors as we look to the future.
Partnerships Help Us Advocate for Patients

- CSL Behring and CSL Plasma actively work with organizations to develop programs and activities for patients.
- We partner with these groups to improve and expand educational and outreach efforts about these diseases and the importance of plasma donation.

<table>
<thead>
<tr>
<th>Medical/Pharma</th>
<th>Hemophilia Organizations</th>
<th>Immune Deficiency Organizations</th>
<th>Rare Disease Organizations</th>
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<tbody>
<tr>
<td>Plasma Protein Therapeutics Association (PPTA)</td>
<td>National Hemophilia Foundation and locally based chapters</td>
<td>Immune Deficiency Foundation</td>
<td>National Organization for Rare Diseases</td>
</tr>
<tr>
<td>Biotechnology Innovation Organization (BIO)</td>
<td>Hemophilia Federation of America and locally based member</td>
<td>International Patient Organization For Primary Immunodeficiencies</td>
<td>Alpha-1 Foundation</td>
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<tr>
<td>Pharmaceutical Research and Manufacturers of Biotechnology Innovation Organization (BIO)</td>
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<td>GBS</td>
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<td>U.S. Hereditary Angioedema Association</td>
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<td>Jeffrey Modell Foundation</td>
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A WORD FROM OUR SPONSOR
X4 Mission

X4’s mission is to develop treatments that have a clear and profound impact for people with rare diseases, including primary immunodeficiencies and cancer.

We incorporate the patient perspective into our work in pursuit of our mission.

The patient perspective is not the only data point, but it is a data point in every decision we make.

WHIM Syndrome

Chronic Neutropenia
To Achieve our Mission:

X4 Aspires To Be a For-Profit, Stand-Alone, Research, Development and Commercialization Business

(“FIPCO” Fully Integrated Pharma-Patient-focused Company)

Because We Put Patients First

WHIM Syndrome            Chronic Neutropenia
HOW DOES IT WORK?
You can order the test through your doctor or through PATH4WARD.

ORDER THROUGH PATH4WARD

1. Visit www.Invitae.com/PATH4WARD. Click “Patient” and schedule time to speak with a genetic counselor to see if you are eligible for the no-cost genetic test.

2. Once you receive the test kit, complete the test kit instructions and provide a saliva sample.

3. Mail the test kit back.

4. The PATH4WARD team will share results with you in about 20 days.

5. Schedule a no-cost genetic counseling appointment to discuss your results. Call Genome Medical at 877-688-0992 or email clinical@genomemedical.com.

ORDER THROUGH YOUR DOCTOR

1. Ask your doctor to request a saliva test kit from Invitae.com/PATH4WARD.

2. Provide a saliva sample at your doctor’s office or at home.

3. Your doctor will mail the test kit back if you provided a sample at the office. If you do the test at home, mail the test kit back with the completed requisition form from your doctor.

4. Results are emailed to your doctor. Check with your doctor in about 20 days for results.

5. Schedule a genetic counseling appointment to discuss your results. Call GeneMatters at 1-866-741-5331 or schedule online at www.gene-matters.com code: PATH.
Primary Immunodeficiency with Presence of Autoimmunity: *Treatment Considerations*

Terry O Harville, MD, PhD, D(ABMLI), F(ACHI)

University of Arkansas for Medical Sciences
Department of Pathology and Laboratory Medicine
Department of Internal Medicine, Hematology/Oncology
Laboratories of Histocompatibility, Immunogenetics, and Transplantation
Little Rock, Arkansas
Disclaimers!

- I will be discussing my interpretations of the information.
- It may *not* be different from what others say or what you have read, *but may seem to be different because of the way I state it*.
- Please ask me if I say something that appears to be in contradiction.
- Due to time limitations, things may be omitted from discussion…*but, hopefully have not been overlooked*. 
**“Pre”-Conclusions**

In general, similar processes and immune mechanisms which result in “autoimmunity” in a person with otherwise “normal” immunity …result in “autoimmunity” in a person with immunodeficiency …treatment must be geared towards maximizing the therapy for the immunodeficiency…then adding what is needed to control the autoimmunity…*individualized for each patient!*

…Auto-inflammatory diseases are due to issues with “innate” immunity …Autoimmunity diseases are due to issues with “adaptive” immunity …*but…*
…Things are Always More Complicated Than What You Would Want

- Numerous genes have been identified where...
- Immunodeficiency…
- And/Or…
- Autoimmunity may be present…
# Genes Associated with Immunodeficiency and Autoimmunity

<table>
<thead>
<tr>
<th>Gene Affected</th>
<th>Primary Immunodeficiency</th>
<th>Autoimmunity</th>
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<tbody>
<tr>
<td>AIRE</td>
<td>APECED</td>
<td>Polyendocrinopathy</td>
</tr>
<tr>
<td>BAFF-R</td>
<td>CVID</td>
<td>Hematologic, Other</td>
</tr>
<tr>
<td>BCL10</td>
<td>Antibody Deficiency</td>
<td>Gastrointestinal Disease</td>
</tr>
<tr>
<td>CD19</td>
<td>CVID</td>
<td>Hematologic, Glomerulonephritis, Other</td>
</tr>
<tr>
<td>CD81</td>
<td>Antibody Deficiency</td>
<td>Glomerulonephritis, Other</td>
</tr>
<tr>
<td>CTLA4</td>
<td>Antibody Deficiency</td>
<td>Lymphoproliferation, Other</td>
</tr>
<tr>
<td>FOXP3</td>
<td>IPEX</td>
<td>Immunodysregulation, Polyendocrinopathy, and Enteropathy, X-linked</td>
</tr>
<tr>
<td>ICOS</td>
<td>CVID</td>
<td>Hematologic, Other</td>
</tr>
<tr>
<td>IL21</td>
<td>Antibody Deficiency</td>
<td>Colitis, Other</td>
</tr>
<tr>
<td>LRBA</td>
<td>Antibody Deficiency (IgG and IgA)</td>
<td>Inflammatory Bowel Disease</td>
</tr>
<tr>
<td>MSH-5</td>
<td>CVID</td>
<td>Hematologic, Other</td>
</tr>
<tr>
<td>NFKB2</td>
<td>Antibody Deficiency</td>
<td>Alopecia, Endocrine Adrenal</td>
</tr>
<tr>
<td>PIK3CD (p110δ)</td>
<td>Antibody Deficiency</td>
<td>Lymphoproliferation, Inflammatory Bowel Disease</td>
</tr>
<tr>
<td>TNFRSF5</td>
<td>Decreased IgG, IgA (IgM normal or increased)</td>
<td>Gastrointestinal Disease</td>
</tr>
<tr>
<td>TNFRSF7</td>
<td>Antibody Deficiency</td>
<td>Aplastic Anemia</td>
</tr>
<tr>
<td>TNFSF12</td>
<td>Decreased IgA and IgM</td>
<td>Glomerulonephritis, Other</td>
</tr>
<tr>
<td>TACI (TNFRSF13B)</td>
<td>CVID, IGAD2</td>
<td>Hematologic, Other</td>
</tr>
<tr>
<td>WASP</td>
<td>WAS</td>
<td>ITP, Vasculitis</td>
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</table>
Further...Genome-Wide Disease Association Studies for Autoimmunity Demonstrate the HLA Gene Locus has the Overwhelming Greatest Number of Associations
Who Develops Autoimmunity?

Those unfortunate persons who have inherited susceptibility...

...and undergo the promoting environmental factors
So...Is Autoimmunity Different in Patients with Primary Immunodeficiency?

Even though...there are now numerous genes identified where immunodeficiency and autoimmunity may both exist...

...and...in some cases, these may be responsible for autoimmune manifestations when no evidence of immunodeficiency can be found...

The ultimate features of autoimmunity may not be much different between the immunodeficient and non-immunodeficient
Autoimmunity may be more difficult to fully define and diagnose (that is provide a specific “named diagnosis”) in patients with immunodeficiency...

...and...frequently can be more difficult to treat and control in the immunodeficient
Objectives of this Presentation

After completion of this presentation, the attendee should better:

- Understand to some extent the processes required for the development of “normal immunity”
- Understand how “normal immunity” works to maintain a homeostatic balance to prevent disease manifestations
- Understand that when the “balance” goes awry…that inflammation and autoimmune symptoms may arise
Objectives of this Presentation (cont)

- Understand that treatment of the immunodeficiency with Immunoglobulin replacement (especially higher doses*) may be a good way to treat autoimmunity
- Understand that removal of B lymphocytes with rituximab may be one of the better approaches for treatment
- Understand that individualized therapy based on the genes involved may provide the best therapeutic intervention

Basic Question:

Why is there Immunity?
The First Question: Why does Immunity exist?

We Think the Primary Reason...

...Self versus Non-Self Recognition...

...which allows discrimination of self-tissues from infectious organisms
Why does Immunity exist?

But the “Real Reason”…

“Reproduction”

(...but that’s a different story, for another day)
Next Question… *Why*…Autoimmunity?

We normally produce millions of individual T lymphocytes and B lymphocytes. Each should have the capability to recognize specific foreign proteins:

1. Some can recognize foreign proteins appropriately, and are *USEFUL*.
2. Some fail to interact appropriately and are *USELESS*.
3. Some interact *TOO STRONGLY* with self tissue and could cause autoimmune disease.
“Goldilocks’ Rule”

Therefore, we can think of the formation of our antigen recognition repertoire as following a…

“Goldilocks’ Rule”…

…discard the “useless” and the “too tight binding” T and B lymphocytes

…and keep the ones that are “just right”
Normal “Prevention” of Autoimmunity

- More than 95% of the T and B lymphocytes produced may be useless or harmful …careful “Quality Control” needed

- “Central” Tolerization – at the thymus for T lymphocytes and in the bone marrow for B lymphocytes

- Select against the useless and too tight binding cells …keep the just right cells
…but not all of the useless and too tight binding cells can be eliminated

…therefore…

“Peripheral” Tolerization – mechanisms to control the cells which failed to be eliminated by Central Tolerization

- Anergy (under-stimulation)
- Apoptosis (over-stimulation)
- Treg suppression (“active” interaction with the same self-antigen) (*Doppelgänger-like*)
Normal Prevention of Autoimmunity (cont)

Generally, these mechanisms work well…

…but, infections, chemicals, or other factors may alter their abilities to eliminate or control “autoreactive” cells…

…or, gene mutations may reduce specific signaling (**Loss of Function [LOF]**) or increase specific signaling (**Gain of Function [GOF]**), affecting immune cell activity…

…*then, autoimmune disease*
Normal Control of Autoimmunity

Normally, careful *counter-regulation* mechanisms are in place to prevent any one cell type from becoming too active and exerting detrimental effects...

...For Example: *skewing toward Th1/Th17 type T lymphocytes promotes inflammatory autoimmunity*
Th Paradigm
CD4 T Lymphocytes

CD4+ Thymic emigrant

Naive

Th1

Th2

Treg

Th17

(CMI or DTH)
- anti-viral (intracellular pathogens)
- control cellular immunity
(inflammatory)

(Counter-regulate each other)

(B lymphocyte help)
- anti-parasitic
- promote B lymphocyte proliferation
- promote B lymphocyte differentiation
- stimulate antibody production
(anti-inflammatory)

(Autoimmune)
- anti-fungal (extracellular pathogens)
(inflammatory)

(Immunosuppressive)
- down-regulate activated T lymphocytes
(anti-inflammatory)
Th Paradigm

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Treg

(Autoimmune)
- anti-fungal (extracellular pathogens)
*(inflammatory)*

Naïve

CD4+ Thymic emigrant

IL4

TGFβ & IL6

(Down-regulate)

Th17

(Immunosuppressive)
- down-regulate activated T lymphocytes
*(anti-inflammatory)*
Immunologic Principles

- The Immune System is Programmed by Default Toward the *Th2 Response*
  - *Parasite Protection*
  - *Antibody Production*

- *Th2 Response Driven to Extreme May Result in Allergic Disease*

- *Th2 Response Driven to Extreme May Result in Autoantibody Production and “may result in SLE and diseases similar to or related to SLE, eg, dermatomyositis, Sjögren's Syndrome” (SARDs Subgroup 1)*
Immunologic Principles (cont)

Th1 Response Results in Cell-Mediated Immunity (CMI):
- *Regulation of cellular immune responses*
- *Protection against Viruses*
- *Protection against Mycobacteria*
- *Protection against “Intracellular” Pathogens*

Th1 Response Driven to Extreme May Be Involved With (especially in conjunction with Th17 reactivity):
- *Autoimmunity or Rheumatologic Disorders*
- *Acute Graft Rejection*
- *Inflammation Seen in Rashes (eg, Psoriasis)*
Immunologic Principles (cont)

**Th17 Response Produces a Cell-Mediated Type of Immunity:**
- **Protection against Fungal Pathogens**
- **Protection against “Extracellular” Organisms**

**Increased Th17 Responsiveness is Likely Responsible for, or has a role in:**
- **Most Autoimmune or Rheumatologic Disorders**
- **Other Inflammatory Reactions**
- **Acute Graft Rejection**
Immunologic Principles (cont)

Treg Response Produces a Cell-Mediated Type of Immunity:

- *Intracellular Expression of FoxP3*
- *Production of IL10 & TGFβ*
- *Responsible for down-regulating activated immunity*
- *Responsible for “Tolerance Induction”*
The various Th Cells Produce Cytokines which “Counter-Regulate” Each Other…

ie, “create a balance” or homeostasis between excessive inflammation and protection against invading pathogens
Th Paradigm
CD4 T Lymphocytes

Th1
Th2

INFγ

Treg
Th17

Naïve

CD4+ Thymic emigrant

IL12 (& IL18)
IL4
TGFβ
TGFβ & IL6

(Counter-regulation)
Th Paradigm
CD4 T Lymphocytes

CD4+ Thymic emigrant

Naïve

IL4

Th2

TGFB & IL6

Treg

Th1

IL12 (& IL18)

Th17

IL4
IL10

(Counter-regulation)
**Th Paradigm**
CD4 T Lymphocytes

- **Th1**
  - IL-12 (& IL-18)

- **Th2**
  - IL-4
  - TGFβ & IL-6

- **Treg**
  - TGFβ
  - IL-10

- **Tn17**
  - TGFβ
  - IL-10

(Counter-regulation)
CD4+ Thymic emigrant

CD4 T Lymphocytes

Naïve

Th1

Th2

Th17

Treg

IL-12 (& IL-18)

IL-4

TGFβ & IL-6

IL-6

IL-21

(Counter-regulation)
Th1/17 – Th2 Counter-Regulation

Th1/17 Inflammatory

Treg

Th2 “Anti”-Inflammatory
Autoimmunity - Quality Control Failure of Normal Immunity?

If antibodies or T lymphocytes, which *bind too tightly* to self tissues, are not eliminated or controlled, then these may adversely react

...the result, *Autoimmunity*
Quality Control Failure

This is probably one of the major reasons of autoimmune disease in persons with *otherwise* normal immunity

...and likely plays an important role in patients with immunodeficiencies

...may be a consequence of altered signal transduction due to gene mutations
What About Quality Control in the Setting of Immunodeficiency?

We can make >150 million different antibodies and individual T lymphocytes.

If we have an immunodeficiency which impairs this process…
Then we may have fewer antibodies and T lymphocytes to select from...

Our “immune system” wants us to survive, ie, not die from an infection...

...even at the risk of autoimmunity...
Patients with Immunodeficiency:

To compensate for *under*-production of “normal” antibodies and “normal” T lymphocytes … may retain “useless” and “too tightly binding” ones

The useless ones may cause waste of valuable resources…which may help promote unwellness
Patients with Immunodeficiency:

The retained “too tightly binding” antigen receptors may result in autoimmune disease.
Lack of Elimination of Autoreactive T Lymphocytes in Patients with Immunodeficiencies

Unfortunately, patients with immunodeficiency...may not eliminate potentially autoreactive T lymphocytes...attempting to keep any T lymphocyte which may help fight infections...even with the risk of self-reactivity
B lymphocyte Involvement

Since we produce a new B lymphocyte repertoire about every two weeks…

…some have thought it was strictly the T lymphocyte “lack” of control resulting in autoantibodies and disease

It is now clear that B lymphocytes play a more active immuno-stimulatory role as antigen presenters
B lymphocyte (red) – T lymphocyte (green) Interaction

“The B & T Waltz”
Thus B lymphocytes may promote autoimmunity:

1) Autoantibody Production

2) Antigen presentation and stimulation of autoreactive T lymphocytes
Patients may be going to autoimmune subspecialists (Rheumatology, Pulmonology, Gastroenterology, etc)

Several years ago...adolescent girl treated for inflammatory bowel disease...not getting better...began having increased infections...thought to be due to treatment...finally Immunology consulted...antibody deficiency diagnosed...treatment with IVIg resulted in improvement of IBD (other IBD medications eventually discontinued)

We performed a study: “Impact of Immunodeficiency on Multiple Sclerosis Patients Receiving Rituximab. Terry Harville, MD, PhD; M. Chris Runken, PharmD; Joshua M. Noone, PhD”... We found: Evaluation of medical codes in large database, 404 patients with MS were treated with rituximab...53 (13%) were subsequently diagnosed with primary immunodeficiency...we concluded these patients likely were at risk for, or already had, primary immunodeficiency, but not yet diagnosed...MS being the main issue was the focus of treatment...with subsequent “unmasking” of primary immunodeficiency
Maximize Immunoglobulin replacement for the underlying immunodeficiency (especially higher doses more frequently, may be helpful)

IVIg may be better than SCIG, for some
- Higher dosing
- “Bolus” or “spike in concentration” effect

Medications used to treat autoimmunity in patients with normal immunity may be helpful
- Caution, extra caution, with corticosteroids
- Multiple adverse side-effects
- May not control immuno-reactivity, and result in “rebound” effect when tapered
Treatment Concepts (cont)

- Consider using rituximab early, while continuing the immunoglobulin replacement (may, in general, “calm” the process)
  - After symptoms are better controlled, then may taper the dosing

- Consider use of the various immunologic response modifiers – Use “Genetic Studies” to identify “gene responsible” – apply specific therapy (eg, mTor inhibitor for PIK3CA mutation)

- MUST individualize to a particular patient’s needs (one size DOES NOT fit all)
Summary

The development of the “normal” immune repertoire results in the production of “useless” and potentially autoreactive antibodies and T lymphocytes (*Goldilocks' Rule*).

Control mechanisms are present to attempt to prevent these from resulting in autoimmunity…

…but, genes and environmental factors (viruses, infectious organisms, chemicals, irradiation, etc) may allow the autoreactive T lymphocytes to become active.

The risks for certain autoimmune disorders depend on the HLA components that one has inherited.
Summary (cont)

Patients with primary immunodeficiency may be at even higher risk due to “preservation” of otherwise potentially autoreactive cells, attempting to provide for immune protection (ie, Quality Control Failure)...

...further...genes may be present with risks for promoting immunodeficiency, as well as, autoimmunity...

...and...there may be greater difficulty in controlling the balance of the cytokines and cellular reactivities, due to the “deficiencies”, or “gain of function” (GOF)
Summary (cont)

- B lymphocytes may be the “enemy” in many immunodeficiencies…
  - Lack of “good” antibodies
  - Autoantibody production
  - Auto-antigen stimulation of T lymphocytes

Thus…maximizing Immunoglobulin replacement (considering higher and more frequent dosing…IVIg may be better than SCIg)…

…and…use of rituximab may be the useful treatment

…use of targeted therapies for the genes involved

…evolving role for Jak inhibitors
THANK YOU!

Terry Harville, MD, PhD
University of Arkansas for Medical Sciences
College of Medicine
Helpful savings and financial support from a dedicated point of contact
Monday through Friday from 8 AM to 8 PM ET

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(1-844-699-3624)

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1-888-MYGAMUNEX
(1-888-694-2686)

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Our focus is on patients

Immunodeficient care and support — centered on the patient

To reach our Accredo team, call toll-free 866.820.IVIG (866.820.4844)
YOUR QUESTIONS ANSWERED
Concept -- The Cytokine “Soup” Determines the State of Activation of the T Lymphocyte by the Balance of Activating and Inhibiting Cytokines—“Quasi-Vector Addition”
Potential Targets of Biologic Response Modifiers for Treatment of Autoimmunities

Mφ → TNF, IL1 → CD25, CD4 → CTLA4 (CD152), CD11a/CD18 → Th1 or Th17 or Th22 → TNF, INF-γ, IL2, (IL6), IL15, IL17, IL22, IL23

CD4+ Thymic emigrant → Naïve → IL4, IL5, (IL6), IL9, IL10, IL13 → Th2 or Th9 or Th13
THANK YOU!

Terry Harville, MD, PhD
University of Arkansas for Medical Sciences
College of Medicine
From all of us at IDF

Thank You!

You make the IDF community stronger

Immune Deficiency Foundation