Rx of CIDP beyond IVIg and Corticosteroids – What Does the Future Hold?

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Objectives

- Review the pathophysiology of CIDP – potential novel targets
- Address opportunities to target cell mediated autoimmunity
- Discuss the approach to CIDP as an antibody-mediated disease:
  - B cell depletion therapy
  - FcRN blockers
- Examine the role of complement blockade
- Explore other potential novel therapies
Pathophysiology of CIDP

- CIDP is a complex autoimmune disorder with unknown pathogenesis
- Attack causes cellular damages to the myelin sheath, Schwann cells and ultimately axons
- Contribution to this attack mediated by:
  - Cellular response: aberrant T cells
  - Humoral mechanisms: circulating Ab
  - Complement cascade: activation

*Immunotherapy* (2016) 8(2), 165–178
Pathophysiology of CIDP
Cellular Autoimmunity

- Chemokines and proinflammatory cytokines allow for egress of CD4+ & CD8+ T cells & macrophages into peripheral nerves
- Clonal expansion of CD8+ T cells in blood & peripheral nerve
- CD4+ T cells (Tregs) variations in their number and function
- Fas-mediated T-cell apoptosis impairment
- Macrophages - the key final effectors forming small clusters around endoneurial vessels to disrupt and absorb myelin

Immunotherapy (2016) 8(2), 165–178
Alemtuzumab in CIPD

- Alemtuzumab is a monoclonal antibody directed against CD52 on circulating T lymphocytes and monocytes
- Following infusion rapid depletion of CD8+ T cells for 30 months and CD4+ T cells for 60 months on average
- 7 severe IVIG-dependent CIDP cases refractory to conventional immunosuppression
- Mean monthly IVIG use fell by 26%
- 2 prolonged remission, 2 partial response & and 3 no clear benefit
- 3 developed autoimmune disease following alemtuzumab treatment:
  - 2 TPO Ab at 21 and 37 months; 1 thyroiditis
  - 1 autoimmune hemolytic anemia at 18 months - died

J Neurol. 2010 Jun;257(6):913-9
Humoral Autoimmunity in CIDP

- Evidence for a major role of humoral factors:
  - passive transfer experiments using sera or purified IgG from CIDP patients
  - benefits of plasma exchange (PLEX)
  - therapeutic effects of rituximab (RTX)
- Elevated IgG ab to GM1 in serum of 10% of CIDP patients & more frequently elevated in CSF
- Ab to nodal and paranodal adhesion molecules in up to 15% of CIDP cases: neurofascin, contactin, & contactin-associated protein autoantibodies
- Molecular mimicry suggested

J Neurol Sci 1993;114:49-55
Humoral Autoimmunity in CIDP

- Nodal, paranodal & juxtaparanodal regions of axons:
  - saltatory conduction classically
  - maintaining structural integrity of myelin-axolemmal interactions, bidirectional signaling & regulation of ion channels
  - Ab targeting these molecules suggest humoral component
- Neurofascin 155 (NF155):
  - part of L1 family immunoglobulin cell adhesion molecule
  - located on paranodal Schwann cell membranes
- NF 140/186: located on axons at nodes of Ranvier & initial segments
- Contactin-1 and Caspr 1 complex:
  - in the paranodal regions of axons
  - axoglial maintenance

Immunotherapy (2016) 8(2), 165–178
Neuroimmunol Neuroinflammation 2019;6:6
CIDP: Nodal / Paranodal Abs

- Abs against nodal / paranodal proteins in up to 15% of CIDP

- Chronic demyelinating neuropathy with acute/subacute onset of weakness & sensory ataxia with high CSF protein

- In 65 CIDP, IgG Abs were detectable against: Neurofascin 155 (NF155) in 3 (4.6%); Contactin-1 (CNTN1): in 4 (6.2%) & Contactin-associated protein-1 (CASPR 1) in 1 (1.5%)

- 25% had IgG reactivity to DRG neurons, 12% against Schwann cells & 5% to motor neurons

http://www.nature.com/articles/s41598-017-14853-4
Neuropathy with Anti–Neurofascin Antibodies: NF–155 Ab

- **NF-155 Ab** are IgG4
- IgG4 ab do not activate complement
- Acute onset or chronic progressive
- Distal weakness & disabling tremor; sensory ataxia
- CNS involvement: myelopathy, papilledema or ataxia
- CNS demyelination in 25%
- NCS: prolonged distal latencies and reduced CMAP amplitude
- Refractory to IVIg, limited response to corticosteroids
- Good response to PLEX or RTX

Querol et al. Neurology 2014;82:879-86
Neurol Neuroimmunol Neurolinflamm 2015; 2:e149; doi: 10.1212/NXI.0000000000000149
• **NF-140/186 Ab** are IgG4 (4) > IgG3 (1); 5/246 (2%)
• Severe subacute onset
• *Proximal or diffuse* weakness, sensory ataxia *w/o tremor*
• **Focal segmental glomerulosclerosis in 2 cases**
• NCS: demyelination with *conduction block* in 60%; axon loss in 80% (1 reversible CB)
• Nerve biopsy in 1: *axonal* loss
• **Response to:**
  o IVIg (3/4) ? complement-independent pathway for IVIg effect; IgG3 did not respond to IVIg !
  o Corticosteroids (3/5)
  o RTX (1/1)

*Brain. 2017 Jul 1;140(7):1851-1858*
Ab

- **CNTN1 Abs** are IgG3 (GBS-like) or IgG4 (rapid CIDP)
- Subacute onset over 8 to 12 weeks, initial GBS dx
- Progression after initial improvement; tremor in 75%
- Severe **distal or diffuse weakness** with **sensory ataxia; nephrotic Sd**
- NCS: demyelination with early axonal degeneration
- **Paranodal architecture disruption** of dermal myelinated fibers
- **Axonal** damage but no classical signs of demyelination
- Response to prednisone, RTX or PLEX; **less to IVIg if IgG4**
“NODE-OPATHY” in CIDP: Neuropathy with Anti-CASPR 1 Ab

- **CASPR Abs** are IgG3 in GBS or IgG4 in CIDP
- **Distal > proximal weakness**
- Sensory loss *with prominent pain*; IgG binding to TRPV1-immunoreactive DRG neurons
- NCS demyelination
- Nerve bx in CIDP case:
  - axonal loss / degeneration
  - severe paranodal/nodal architecture disruption on teasing
  - dispersion of CASPR & NF
  - elongated nodes of Ranvier
- CIDP case: IVIg ineffective; steroids temporarily effective; stabilization after PLEX; very good response to RTX

*Brain. 2016 Oct;139(Pt 10):2617-2630*
# Pathogenic Antibodies

**Table 1. Summary of the chronic inflammatory demyelinating polyradiculoneuropathy-associated autoantibodies**

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Antibody isotype</th>
<th>Clinical phenotype</th>
<th>Frequency</th>
<th>Gold standard test$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>NF155</td>
<td>IgG4</td>
<td>distal motor involvement, tremor and ataxia</td>
<td>5–10%</td>
<td>CBA</td>
</tr>
<tr>
<td>NF140/186</td>
<td>IgG4</td>
<td>acute aggressive onset, conduction blocks may associate nephrotic syndrome</td>
<td>2%</td>
<td>CBA</td>
</tr>
<tr>
<td>CNTN1</td>
<td>IgG4</td>
<td>acute aggressive onset, axonal involvement may associate nephrotic syndrome</td>
<td>5%</td>
<td>CBA</td>
</tr>
<tr>
<td>Caspr1</td>
<td>IgG4</td>
<td>painful neuropathy</td>
<td>&lt;1%</td>
<td>CBA</td>
</tr>
</tbody>
</table>

*Curr Opin Neurol 2019, 32:651–657*
CIDP: Role of B cells

- B cells differentiate into ab-producing plasma cells
- RTX rapidly depletes B cells from peripheral blood & lymph nodes by binding to CD20 on pre-B cells to mature B cells
- Recovery of naïve B cells is by 9 - 12 months
- There is longer depletion of memory B cells → B-cell repertoire modification
- B cells play a role in ab-independent pathways:
  - Ag presentation
  - T cell & dendritic cell regulation
  - Cytokine and chemokine production
- It is unknown how much if any RTX also targets these pathways

9/13 (69%) had sustained remission of neurological symptoms; 6/9 responders were refractory cases

6/7 refractory cases responded vs. 3/6 sparing IVIg or CS

RTX response started after median of 2 months (1-6)

Response lasted for median of 1 year (1-5)
RTX in CIDP: Review of the Literature

Table 2  Results of published studies on rituximab therapy in patients with CIDP

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>No. of patients</th>
<th>Neuropathy duration (months)</th>
<th>Pre-rituximab therapy</th>
<th>Comorbidity</th>
<th>Clinical response</th>
<th>Months before improvement</th>
<th>Duration of improvement (years)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gorson et al⁷⁸</td>
<td>2</td>
<td>60 (mean)</td>
<td>IVlg, AZA, MM, Ster, PE, Cyclopho</td>
<td>No</td>
<td>No</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Kildireas et al⁷⁸</td>
<td>1</td>
<td>10</td>
<td>No</td>
<td>Gastric lymphoma</td>
<td>Yes</td>
<td>2</td>
<td>&gt;5</td>
</tr>
<tr>
<td>Knecht et al⁶</td>
<td>1</td>
<td>17</td>
<td>Ster, PE, AZA, Cyclopho</td>
<td>Evans Syndrome</td>
<td>Yes</td>
<td>6</td>
<td>1.5</td>
</tr>
<tr>
<td>Kasamon et al⁷⁸</td>
<td>1</td>
<td>&lt;12</td>
<td>Ster</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>Yes</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td>Münch et al⁷⁸</td>
<td>1</td>
<td>20</td>
<td>IVlg</td>
<td>DM</td>
<td>Yes</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Which corresponded to duration of follow-up.
AZA, azathioprine; Cyclopho, Cyclophosphamide; DM, diabetes mellitus; IVlg, intravenous immunoglobulin; MM, mycophenolate mofetil; NA, not available; PE, plasma exchange; Ster, steroids.

- 4 cases refractory CIDP or CIDP needing drug-sparing effect
- All cases responded
- INCAT score improvement started at 2-4 months
RTX in CIDP With Associated Disease

- 21/28 CIDP (75%) patients responded to rituximab:
  - associated autoimmune disease (5/8)
  - with a hematological disease (16/20) (P = 0.63)
- Median time to response was 6 months (1-10 months)
- 2 patients needed RTX again at median follow-up 2.0 years (0.75-9)
- Shorter disease duration: better clinical response (OR 0.81, P = 0.025)
- Response rate was better in common forms (83.3%) than in sensory forms (42.9%) (P = 0.05); intermediate response in Lewis Sumner Sd
- 9/13 treated for insufficient response to CIDP 1st line Rx improved
- 6/8 due to treatment dependence & 6/7 due to malignancy responded

J Peripher Nerv Syst. 2018 Dec;23(4):235-240
FcRn & Its Blockade

- Neonatal Fc Receptor (FcRn) binds IgG Fc fragment intracellularly and allows for recycling of IgG back to the blood
- Binding FcRn blocks IgG recycling (including disease causing autoantibodies) and increases IgG clearance
- “Chemical plasma exchange”
- Rozanolixizumab MyCIDPchoice
  Phase 2 NCT03861481
- ArgenX in CIDP

https://clinicaltrials.gov/ct2/show/NCT03861481
CIDP Pathophysiology: Complement activation

Immunoglobulin and Complement Deposits in Nerves of Patients With Chronic Relapsing Polyneuropathy

Marinos C. Dalakas, MD, W. King Engel, MD


- Immunofluoresence of small intraneural vessels & Schwann cells in 7 CRP nerve bx: IgM: 7 & 6; IgG: 3 & 3 and C3: 6 & 0
- Increased levels of serum C5b-9 in 5/6 CRP cases
- C3d products on peripheral myelin sheaths in 4/6 CIDP; support macrophage-mediated phagocytosis of myelin
- Complement activation likely supports activated macrophages

J Clin Invest. 1987 Nov;80(5):1492-7

Complement Blockade In Other Autoimmune NM Disorders

- Myasthenia Gravis is another antibody-mediated autoimmune disease with evidence for complement engagement.
- Eculizumab binds to the terminal complement C5, which acts at a late stage in the complement cascade.
- Eculizumab is FDA-approved in AChR Ab + MG - requires both meningococcal vaccines 2 weeks pretreatment.
- Other complement blockers are being tested in MG clinical trials.
- There is a case to be made for investigating the role of complement blockade in CIDP.

Figure 3. Complement cascade. The complement cascade can be activated via the classical, lectin, and alternative pathways. The proximal components of complement (proteins upstream of C3) are essential for microbial opsonization and immune complex clearance. All pathways of complement activation converge at the cleavage of the complement protein C3, leading to the generation of molecules with proinflammatory and cell lytic properties. MAC, membrane attack complex; MBL, mannose-binding lectin; M/O, microorganism. Adapted by permission from Ref. 72.

Complement Blockade: Eculizumab in GBS

• GBS is associated with Abs targeting gangliosides with evidence for complement activation
• Eculizumab for GBS: 24 week Phase 2 RCT in Japan NCT02493725
• Eculizumab (n=23) or placebo (n=11)
• Primary outcomes: efficacy (proportion of patients with restored ability to walk independently [functional grade ≤2] at week 4) in eculizumab group and safety in the full analysis set
• At week 4, functional grade ≤2 in 61% (90% CI 42–78; n=14) of eculizumab vs. 45% (20–73; n=5) in PBO group
• Serious adverse events: 2 in eculizumab (anaphylaxis in 1 and intracranial hemorrhage & abscess in another); 1 in PBO (depression)
• 74% of eculizumab group were able to run or healthy vs 18% of PBO
• Lends further support for investigating the role of complement blockade in GBS & CIDP
Conclusions

• CIDP trials are very hard to do, especially due to:
  o Recruitment in a rare disease
  o Placebo effect in a variable disease
  o Variation in disease activity addressed in part by withdrawal designs
  o Most pts respond to Ig, prednisone or PLEX
  o Ab status contributing to heterogeneity in rx response
  o Patient selection: refractory disease vs. dose-dependence/reduction
  o Outcome measure INCAT vs. I-RODS

• Growing number of well powered & well designed studies
• Novel and promising therapies are at various stages of development
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