Financial Disclosure

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Objectives

• Appraise novel therapies and advances in CIDP therapy

• Review Nodal and paranodal antibodies and their therapy

• Discuss the role of complement inhibition in CIDP and in GBS
What Are Patients Actually Taking?

Treatment of CIDP Patients with Active Progressive Disease in 2010

- IGG: 58%
- Corticosteroids: 18%
- Other: 8%
- Methotrexate: 6%
- Cyclosporin: 4%
- Azathioprine: 3%
- Mycophenylate Mofetil: 3%
- Plasma Exchange: 4%

N=491
Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomised, double-blind, placebo-controlled, phase 3 trial

Ivo N van Schaik, Vara Bril, Non van Geloven, Hans-Peter Hartung, Richard A Lewis, Gjon Sobue, John-Philip Lawo, Michaela Praus, Orel Mielke, Billie L Dun, David R Corinaldesi, Ingemar S J Markies, on behalf of the PATH study group

2019

• Secondary outcomes in either low or high dose were superior to PBO except for I-RODS in low dose group
• FDA-approved March 2018 as maintenance therapy for CIDP

Primary outcome* met in:
63% of placebo subjects (57)
39% of low dose SCIg (57)
33% of high dose SCIg (58)
(p < 0.001)

* % of subjects who relapse or withdraw during the SC treatment period
Poster 96: AANEM Meeting
October 11 2018 – Washington, DC

**Figure 3: Subject preference for SCIG or previous IVIG treatment**

- Prefer SCIG: Placebo (n=57) - 22, 0.2 g/kg IgPro20 (n=57) - 80, 0.4 g/kg IgPro20 (n=58) - 31
- Prefer previous IVIG: Placebo (n=57) - 14, 0.2 g/kg IgPro20 (n=57) - 10, 0.4 g/kg IgPro20 (n=58) - 11
- No preference: Placebo (n=57) - 1, 0.2 g/kg IgPro20 (n=57) - 3, 0.4 g/kg IgPro20 (n=58) - 0

**Figure 4: Ease of subcutaneous administration as rated by subjects at last post-dose observation**

- Extremely difficult: 1%
- Very difficult: 7%
- Difficult: 17%
- Somewhat easy: 22%
- Easy: 37%
- Very easy: 12%
- Extremely easy: 4%
Criteria

• Patients who completed PATH study or successfully rescued from a relapse during PATH study were eligible

• **Original protocol inclusion**: gap between studies ≤8 weeks; exceptions if OLE not yet open to enrollment at site

• **Protocol amendment 1 inclusion** criteria allowed for longer gap:
  o patients completed PATH study (SC week 25) or successfully rescued from a relapse during SCIG or placebo treatment

• **Exclusion** criteria same as PATH but after protocol amendment:
  o gap between studies > 1 day; new medical condition and/or social behavior during PATH study that could be an issue per PI judgment

• Most patients had a time gap between PATH completion and entry into OLE
PATH OLE: Patient Disposition

OLE N = 82 (PATH N = 172)

• 62 enrolled under original protocol:
  o 0.4 g/kg initial weekly dose (high dose)
  o If no relapse for 24 weeks (52/62) → switched to 0.2 g/kg/wk for another 24 weeks

• 20 enrolled under protocol amendment:
  o 0.2 g/kg initial weekly dose for 48 weeks unless relapse (low dose)
  o If relapse on low-dose, subjects given option to switch to high-dose SCIG
  o If relapse on high-dose SCIG → may remain on high dose or be discontinued depending on patient & PI judgment
  o If subject and PI chose to remain on high dose, subject:
    • Could remain in OLE if successfully recover from relapse within 4 wks
    • Would be discontinued from the study if no successful recovery
PATH OLE: Relapse and Recovery Rates

- 16/82 withdrew from the study: relapses 8; patient 3 or doctor 2 decisions; AEs 3

- Lowest relapse rate (1 of 21, 5%) in those with high-dose treatment in PATH & continued high-dose treatment in OLE

- 52/62 switched high to low dose; 26 relapsed & 92% (24/26) recovered after reinitiating high dose

### Table 3 Relapse rates and time to first relapse by treatment and status at end of the PATH study

<table>
<thead>
<tr>
<th>Extension study treatment</th>
<th>0.2 g/kg</th>
<th>0.4 g/kg</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse rates&lt;sup&gt;a&lt;/sup&gt; in the extension study</td>
<td>73</td>
<td>72</td>
<td>82</td>
</tr>
<tr>
<td>Subjects treated in the extension study</td>
<td>73</td>
<td>72</td>
<td>82</td>
</tr>
<tr>
<td>Relapsers in the extension study, subjects (%)</td>
<td>35 (47.9%)</td>
<td>7 (9.7%)</td>
<td>41 (50.0%)</td>
</tr>
<tr>
<td>Nonrelapsers in the extension study, subjects (%)</td>
<td>38 (52.1%)</td>
<td>65 (90.3%)</td>
<td>41 (50.0%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> These relapse rates refer to all subjects in the extension study, irrespective of treatment and status at the end of the PATH study. Status at the end of the PATH study (nonrelapser/relapser) was as defined by the primary end point.
CIDP Candidates for Conversion from IVIg to SCIlg

- Venous access problems
- Logistical issues to & from infusion center
- Patient autonomy
- Improved patient QOL*
- More consistent serum IgG levels / reduced wearing-off effect
- Adverse effects esp. disabling headaches
- Conserving hospital & nursing resources

* In the PATH study, Health-related quality-of-life measures generally showed better outcomes for both SCIlg groups than for placebo
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*
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:
  o 2 TPO Ab at 21 and 37 months; 1 thyroiditis
  o 1 autoimmune hemolytic anemia at 18 months - died

J Neurol. 2010 Jun;257(6):913-9
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

Querol, L et al. Nat Rev Neurol. 2017 Sep;13(9):533-547. doi: 10.1038/nrneurol.2017.84
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 Neuroinflamm 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

*J Neurol Neurosurg Psychiatry* 2015;86:720–728
"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>
<thead>
<tr>
<th>Antigen</th>
<th>Antibody isotype</th>
<th>Clinical phenotype</th>
<th>Frequency</th>
<th>Gold standard test</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>

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

*Curr Opin Neurol 2019, 32:651–657*
RTX in CIDP: Report of 13 Cases

- 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 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
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.

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
Complement Blockade: ANX005 for GBS

• ANX005: human IgG4 monoclonal antibody that binds to human C1q & functionally inhibits the classical complement cascade both in vitro and in vivo
• Phase 1b placebo controlled, dose escalation trial of ANX005 in 31 GBS patients
• Objectives: safety/tolerability, dosing levels, & target engagement; follow up 8 wks
• Well-tolerated at all dose levels; no drug-related SAEs or drug-related exiting
• Full & prolonged C1q engagement and classical cascade inhibition in blood & CSF
• Patients treated with ANX005: significantly reduced neurofilament light chain
• Consistent positive trends across key GBS outcome measures; on muscle strength
• NCT04035135 starting September 2019: A Phase 1b Study to Evaluate the Safety, Tolerability and Drug-Drug Interactions of ANX005 and IVIg in Subjects With GBS

Conclusions

- GBS & CIDP trials are very hard to do, especially due to:
  - Recruitment in rare diseases
  - Placebo effect / natural h/o
  - Variation in disease activity (addressed in part for CIDP by withdrawal designs)
  - Most pts respond to Ig or PLEX (prednisone for CIDP)
  - Ab status contributing to heterogeneity in rx response?
  - Patient selection: severe disease in GBS; in CIDP refractory disease vs. dose-dependence/reduction
  - Clinically relevant and sensitive outcome measures
- Growing number of well powered & well designed studies
- Novel and promising therapies are in various stages of development for both CIDP and GBS
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