# OUNIVERSITY OF GOTHENBURG

# THE GOTHENBURG EXPERIENCE **OF IV IMMUNOGLOBULIN TREATMENT FOR PANDAS/PANS**

### Disclosure

- PI phase IV study Takeda
- Head Oversight Committee Jansen

Y OF GOTHENBURG | SAHLGRENSKA ACADENY | Depar

Expert advice Lipum

# Why treat with IVIG?

- The idea is as you know that PANS is a disease of an immune system gone wrong
- Immunoglobulins are not only antibodies against germs • But Immunoglobulins have immunomodulatory properties if

Y OF GOTHENBURG | SAHLGRENSKA ACADEMY | De

- given in high dose First proven for immune thrombocytopenia Later extended to many disorder including proven neurologic disorders
- There are other ways to modulate/suppress an immune response that we will hear about during the afternoon (rituximab, plasmapheresis and others)

### How does immunoglobulins modulate the immune system?

- Functional Blockade of Fc Receptor
- Autoantibody Neutralization and Inhibition of Autoantibody Production
- Complement Inhibition
- Modulation of Cytokine and Cytokine Antagonist Production
- Activation or Functional Blockade of the Death Receptor Fas (CD95)
- Modulation of Dendritic Cell Properties
- Signaling through the Inhibitory Fc Receptor, Fc- $\!\gamma$  RIIB
- Enhanced Steroid Sensitivity Expand Lymphocyte Repertoire Diversity



### The immunomodulatory effect depends on disease and dose

For most disorders we do not know how IVIG works
 Kawasaki disease – cytokine release is modulated

Or what dose to use
 \_ 0.8, 1 or 2 grams/Kg

- For immune neurological disorders? Only a few with proven effect in controlled studies (JDM, Guillain Barré)
  Case studies
  A few with proven no effect

RSITY OF GOTHENBURG | SAHLGRENSKA ACADEMY



### Swedo et al, NIH Randomized Study - PANDAS

- 29 children randomized to plasma exchange (10), IVIG (9) or placebo (10) at one occasion
- Blinded to IVIG or placebo, but not plasma exchange - But IVIG gives headache & nausea, not saline = placebo
- Evaluated at 1 month and 12 month
- Physical examination, anti-Strep ab, CY-BOC scale and CGIl scale

### Results

Change in OCD and tics



 Significant change in OCD score at 1 and 12 months for the plasma exchange and IVIG groups compared to base line
 No change for placebo group

 Children with exacerbations were offered re-treatment (3/19)

# NIH /Yale Randomized Study

- 35 children with PANDAS randomized to IVIG or placebo
- Blinded phase only 6 weeks = 1 infusion
- Non-responders got a 2<sup>nd</sup> infusion at 6 weeks
- All evaluated at 6, 12 weeks and 24 weeks

TY OF GOTHENBURG | SAHLGRENSKA AC

Physical examination, Spinal tap, MRI at 12 w, CY-BOC scale and CGI-I scale

### Results



No difference found at 6 weeks

No conclusion can be drawn
 Only one treatment dose

 Open phase follow-up at best an indication that longer treatment needed to possibly find a difference between IVIG and placebo

# **Retrospective Survey**

- Retrospective on-line survey of treatment response
- Close to 700 patients
- Both children and adults
- 656 given IVIG at some time, varying dose and schedule
   plus other therapies given at the same time

J CHILD ADOLESCENT PSYCHOPHARMACOL COLOG

• Results reported for 265 (191)

Y OF GOTHENBURG | SAHLGRENSKA A

## **Retrospective survey - Results**

SITY OF GOTHENBURG | SAHLGRENSKA ACADEMY

8

- · 49% responded that IVIG was very effective
- 59% had IVG because of some kind of antibody deficiency (not defined)
- IVIG was more effective in the antibody deficiency group
- The data can only by used to tell that IVIG is used to treat PANS/PANDAS, not to tell if it is an effective treatment

#### **Open Label Study of 21 Patients** 3 clinical sites Mean age: 10.9 yrs; males (13 [62%]); females (8 [38%]). Mean follow-up time from Visit 0 to Visit 8 was Male and Female Children Ages 4 – 16 Years with a Diagnosis of PANS 186 days Late follow-up (Visit 9) occurred 29-46+ weeks after last IVIG infusion to gather data on durability of response. 0 STUDY D f washe 18 weeks A Multi-site, Open-Label, Pilo Study



24 media

# Efficacy Endpoints

- Changes in Psychological Evaluation Scores from Baseline to Visits 7/8/9
- Parent-Rated Symptom Survey
   Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS)
- Yale Global Tic Severity Scale (YGTSS)
- Anxiety Disorders Interview Schedule for DSM-IV (ADIS)
  Clinical Global Impression (CGI)
- Pediatric Acute Neuropsychiatric Symptom Scale Phone Interview Scores
- Parent and Patient Artifacts (various)



# The Gothenburg Experience – The First 12 months

- 23 patients diagnosed with PANS
- 8 patients (2 treated outside Gothenburg) with PANS
- IVIG (Privigen®) 2 g/Kg every 4<sup>th</sup> week for 6 months
- Some patients repeated treatment owing to relapse
- Results given for first 12 months

Unpublished data



			_

## Schooling

# Before IVIG - Not participating or only sporadic in school After IVIG

<ul> <li>Not in school</li> </ul>		
<ul> <li>Partially</li> </ul>		
– Fully		
	Unpublished data	

### Was the IVIG sustained?

NEURG | SANLGRE

- 2 had full remission after just one IVIG infusion and did get only that single infusion,

   their remission was sustained for >1 year
- then remission was sustained tof >1 year
   2 children were treated for 6 months and 7 months, respectively and have since had remission for several months
   The other 4 were treated for much longer periods as symptoms recurred at varying time points after each infusion
   For 1 patient the effect vanished after 1.5 years and treatment was stopped
   For 1 patient intervals between infusions could periodically be prolonged for several month and were eventually stopped
   For 2 patients relapse has occurred within 1 3 months and further treatment is pending

Unpublished data

# Summary of Our Experience

- Few patients given IVIG
- Should be so 3rd line tx after COX-inhibitors and antibiotics
- Some patients obviously dramatic response, but is it because of of IVIG or natural course of disease?- too few patients to draw a firm conclusion
- But at least our results are in line with the extended case reports and the results from the recent open study

## **General Conclusions**

- From strict science point,, the question of the benefit of IVIG is still unsolved
   The two randomized studies have several flaws and points at different directions
- The new open study, case reports and our and others
   experience points to IVIG being efficacious for some but not all
- New study(ies) needed

RSITY OF GOTHENBURG | SAHLGRENSKA ACADEMY

 We need new therapies as there is a global shortage of IVIG and IVIG is a very expensive treatment (6 months ≈350 000 SEK or 35 000 € if the person weights 50 kg)

# Outstanding Questions: How should the new studies needed be done?

- · Who to include and when in the disease
- Dose: 0.8, 1.0 or 2.0 grams/kg?
- Given over 1 ? or 2 days?
- Interval: 3 weeks (as is T1/2 of Ig), 4 weeks or other?
- Duration of treatment: 1 dose, 6 months?
- Duration of follow-up: 6 mo, 1yr, 2 yr
- Route: IVIG, ScIg, facilitated ScIg?
- Outcome measures?
- RTC or Open study?

UNIVERSITY OF GOTHENBURG | SAHLGRENSKA ACADE

# Acknowledgement

- To the patients and their families
  Our inspiration and our most important teachers
- To the Gillberg Center Team
   Ats Jonsson
   Elisabeth Fernell
   Christopher Gillberg

TY OF GOTHENBURG | SAHLGRENSKA ACADEMY