Future of Immunoglobulin Use?
Focus: Alzheimer’s Disease

DISCLAIMER
Any opinions/recommendations presented are my own and do not necessarily reflect those of any official body.

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Background to AD

- History
- The Disease

Epidemiology

- Some numbers
- Costs

Requirements of regulators

- Guidelines on AD

Studies

- „Therapies“
- Which way forward?
Alois Alzheimer  
* 14 June 1864, † 19 December 1915

Auguste Deter, age 51, † 56

“Ich habe mich sozusagen selbst verloren“
The Disease (1)

brainmind.com/BasalGanglia.html
The Disease (2)

a) ACh
b) Amyloid β
c) Tau tangles
a) Acetylcholine

- ACh (up to 90%)
- nACh receptors
- ACh alters normal neural communication
b) Amyloid β

Amyloid precursor protein
- function not known
- ? synapse formation
- ? neural plasticity

β-amyloid oligomers
- inflammation,
- microglial activation
- loss of synapses
→ neuron death
The Disease (3)

Types
- AD sporadic
- AD familial:
  - mutations in genes:
    - presenilin 1
    - presenilin 2
    - APP

Risk factor
- Carrier of ApoE 4

Features
- Amyloid plaques and TAU tangles

Measurement
- MRI: brain volume, PET: brain activity
- Biomarkers (CSF: TAU, Aβ, pregnancy zone protein)
- Mini Mental State Examination (MMSE)
- Alzheimer’s Disease Assessment Scale – cognitive subscale (ADAS-cog)
AD Progression

from AD neuroimaging initiative (ADNI)
Oldies (but goldies?)

1/3 of EU population will be >60 in 2040
7th leading cause of death (CDC)
1st cause of death in 30 years (WHO)

2010 – 36 million people worldwide
2030 – 66 million people worldwide
2050 – 115 million people worldwide

Number of AD patients doubles every 5-years for > 65 y
Costs of AD

in 2005  $315 billion (medical + informal care)
         $210 billion direct costs of health care (Wimo 2007)

in 2009  $144 billion (medical + informal care)
         $20,000 /patient/y nursing home costs (Zhu 2006)

70% of AD patients live at home → time costs of informal care (Langa 2001):
Mild dementia: 8.5 h/week
Moderate dementia: 17.4 h/week
Severe dementia: 41.5 h/week

Treatment with cholinesterase inhibitors saves 2 months/y in AD progression
(Trinh 2003)
Costs of IVIG

IVIG is priced at $50 - 70/g

BMC Health Serv Res. 2011; 11: 101; Jeffrey L Winters;
Cost-minimization analysis of the direct costs of PE and IVIg in GBS
5 IVIg infusions totaling 2.0 g/kg = $10,329.85
5 PE procedures = $4,638.16

What is the pharmacodynamic (PD) effect?

Cost Effectiveness and Resource Allocation 2010, 8:14; Gord Blackhouse;
Cost-utility of IVIG compared with corticosteroids in CIDP in Canada
5 years IVIG = $124,065
5 years corticosteroids = $2,196

What is the PD effect?
IVIG demand for Alzheimer

IPPC 2009: Patrick Robert, Marketing Research Bureau
in 2012 ➔ 30 million liters of plasma (= 120 million g)

In the case of approval of IVIG (USA + DE)
Lowest estimate: ➔ additional 11 million litres
- Subtracting 70% mild - moderate
- Subtracting 50% undiagnosed
- Subtracting 66% unqualified
- Assuming 50% treatment efficacy
- Assuming 0.2 g/kg/2weeks (low dose)

Highest estimate: ➔ additional 118 million litres
Aims:
- Symptomatic improvement
- Disease modifying effects (so far no medication)
- Primary prevention (so far no medication)

Control group:
- Placebo or add-on to cholinesterase-inhibitors

Tools:
- ADAS-cog, biomarkers, ADL (activities of daily living), AD-CGIC (AD Clinician’s Global Impression of Change), QOL-AD

**J Neurol Neurosurg Psychiatry** doi:10.1136/jnnp-2011-300881, ADNI
3 points decline on the ADAS-Cog appropriate for minimal clinically relevant change (MCRC) for trials of patients with early AD
approved therapies do NOT target underlying cause of AD

- cholinesterase antagonists: donepezil (Aricept®), galantamine (Razadyne®) and rivastigmine (Exelon®) for mild to moderate AD.

- anti-glutamatergics: memantine Namenda® for moderate to severe AD.

experimental amyloid-based strategies

- secretase modulation
- inhibition of Aβ aggregation
- immunization against Aβ

experimental tau-based strategies

experimental IVIG
Vaccine AN1792 with Aβ 1-42 (+ QS-21 adjuvant), \(\Rightarrow\) reductions of Aβ and phospho-tau, most patients did not improve clinically, 6% had encephalitis \(\Rightarrow\) study stopped

Semagacestat (Eli Lilly), an inhibitor of the \(\gamma\)–secretase \(\Rightarrow\) no benefit in 2600 pts.

R-Flurbiprofen (Myriad), a \(\gamma\)-secretase-modulator (a NSAID) \(\Rightarrow\) no benefit on cognition in Phase III

Tramiprosat (Neurochem), inhibitor of Aβ-deposition \(\Rightarrow\) no benefit in cognition in Phase-III-study

**Ongoing**

**Bapineuzumab** (Pfizer), mAb to Aβ 1-42  
**Gantenerumab** (Roche), mAb to Aβ 1-40 + 1-42  
**Solanezumab** (Eli Lilly) mAb to Aβ 16-25  
**GSK 933776** (GSK) mAb to Aβ without effector function  
**MABT5102A** (Genetech) mAb to Aβ 1-40 + 1-42
IVIG Studies: *in vitro* and *in vivo*

IVIG contains natural auto-Abs against Aβ which block synthetic Aβ fibrillisation

IVIG can dissolve preformed synthetic Aβ fibrils

IVIG promotes Aβ uptake via microglia

IVIG penetrates leaky BBB of „AD“ mice

Active immunisation with Aβ 1-42 reduces plaques + memory deficits

Passive immunisation with mAb against Aβ reduces plaques + memory deficits
IVIG-AD studies in humans

Natural Aβ Abs are lower in AD patients than in age matched controls

Polyclonal IgG contains 0.2% Abs against Aβ

- 1 retrospective, case-controlled study from US claims data base, (Fillit, 2009) incidence of AD in pts. with IVIG (847) vs. untreated controls (84700) → 2% vs 4% (50% risk reduction)

- 1 comparative study of Aβ Abs-content in different IVIGs (Klaver, 2009)

- 2 short-term, open-label studies with promising results (Relkin 2009, Dodel 2010)
ClinicalTrials.gov: Alzheimer

- **958 trials**
- **295/958 recruiting**
- **4/958 IVIG**

<table>
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<th>Study status</th>
<th>Type</th>
<th>Design</th>
<th>Endpoints</th>
<th>Company</th>
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<tr>
<td>Completed</td>
<td>Phase II Study of IVIG for AD</td>
<td>db, pc, 6 m</td>
<td>Efficacy + safety</td>
<td>Baxter</td>
<td>4/2010</td>
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<td>Recruiting</td>
<td>Study of IVIG in Amnestic Mild Cognitive Impairment</td>
<td>db, pc, 24 m</td>
<td>MRI: ventricular volume</td>
<td>Sutter Health Newgam 10%</td>
<td>1/2013</td>
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<td>Phase II Study of IVIG 10% on the Treatment of Mild to Moderate AD</td>
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<td>Surrogate parameters</td>
<td>Octapharma Octagam</td>
<td>1/2011</td>
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<td>Active, not recruiting</td>
<td>Phase III Study Evaluating Safety and Effectiveness of IVIG for the Treatment of Mild to Moderate AD</td>
<td>db, pc, 18 m</td>
<td>Efficacy + safety</td>
<td>Baxter</td>
<td>1/2013</td>
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What if only 0.2% of plasma were necessary? (Abs against Aβ)

11 000 000 L → 22 000 L
118 000 000 L → 236 000 L
The AD avalanche is upon us
The costs of the aging population are increasing
If IVIG studies are efficacious and safe, the given product will be authorised
Industry has to perform PD studies to radically cut consumption and cost
For further info…
**IVIG Studies**

IV immunoglobulin is associated with a reduced risk of Alzheimer disease and related disorders.

**Fillit H, Hess G, Hill J, Bonnet P, Toso C.**
Alzheimer's Drug Discovery Foundation, New York, NY, USA.

Abstract

**OBJECTIVE:**
To compare the incidence of Alzheimer disease and related disorders (ADRD) in patients treated with IV immunoglobulin (IVlg) for non-Alzheimer disease (AD) indications vs untreated controls.

**METHODS:**
This retrospective case-control analysis used medical claims for patients > or =65 years old from a national database of 20 million age-qualified patients. Cases received > or =1 IVlg administration during April 1, 2001-August 31, 2004, had claims 1 year prior to first (index) IVlg administration to confirm absence of pre-index ADRD, and had > or =3 years of continuous claims post-index. Untreated controls had their first medical claim during April 1, 2000-August 31, 2004, and otherwise met the same requirements as cases. Controls were matched 100:1 to cases on age, gender, and risk factors for ADRD. The relative incidence of ADRD post-index for the IVlg-treated cases vs untreated controls was estimated using Kaplan-Meier survival curves and a Cox proportional hazards model.

**RESULTS:**
Treated patients in the Kaplan-Meier analysis had lower ADRD incidence (p = 0.02) with an estimated 2.6% of the 847 IVlg-treated vs 4.6% of 84,700 controls diagnosed with ADRD at 60 months after index date. Treated patients in the Cox proportional hazard model had a 42% lower risk of being diagnosed with ADRD (hazard ratio, 0.577; 95% confidence interval, 0.359 to 0.930; p = 0.024) with an estimated 2.8% of treated vs 4.8% of controls diagnosed with ADRD at 60 months after index date.

**CONCLUSIONS:**
Previous treatment with IV immunoglobulin was associated with a reduced risk of developing Alzheimer disease and related disorders (ADRD) in this study. Evidence from additional studies is needed to evaluate the relationship between IVlg exposure and ADRD diagnosis.

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Abstract

Intravenous immunoglobulin (IVIg) has been proposed as a potential agent for Alzheimer's disease (AD) immunotherapy because it contains antibodies against beta-amyloid (Abeta). We carried out an open label dose-ranging study in 8 mild AD patients in which IVIg was added to approved AD therapies for 6 months, discontinued, and then resumed for another 9 months. Infusions were generally well-tolerated. Anti-Abeta antibodies in the serum from AD patients increased in proportion to IVIg dose and had a shorter half-life than anti-hepatitis antibodies and total IgG. Plasma Abeta levels increased transiently after each infusion. Cerebrospinal fluid Abeta decreased significantly at 6 months, returned to baseline after washout and decreased again after IVIg was re-administered for an additional 9 months. Mini-mental state scores increased an average of 2.5 points after 6 months, returned to baseline during washout and remained stable during subsequent IVIg treatment. Our findings confirm and extend those obtained by Dodel et al. [Dodel, R.C et al 2004. Intravenous immunoglobulins containing antibodies against beta-amyloid for the treatment of Alzheimer's disease. J. Neurol. Neurosurg. Psychiatry 75, 1472-1474] from a 6-month trial of IVIg in 5 AD patients and justify further studies of IVIg for treatment of AD.
Antibody concentrations to Abeta1-42 monomer and soluble oligomers in untreated and antibody-antigen-dissociated intravenous immunoglobulin preparations.

Klaver AC, Finke JM, Digambaranath J, Balasubramaniam M, Loeffler DA. Division of Neurology, Beaumont Research Institute, William Beaumont Hospital, Suite 507, Royal Oak, MI 48073, USA. Andrea.Klaver@beaumont.edu

Abstract
Cognitive improvement in Alzheimer’s disease (AD) patients treated with intravenous immunoglobulin (IvIg) has been attributed to its antibodies to amyloid beta (Abeta). We compared the concentrations of specific antibodies to soluble Abeta1-42 conformations, namely Abeta1-42 monomer and Abeta1-42 soluble oligomers, between three IvIg preparations, Gamunex, Gammagard, and Flebogamma. To determine specific antibody concentrations to these Abeta1-42 conformations, nonspecific binding of the IvIg preparations to the Abeta reverse sequence, Abeta42-1, was subtracted. These antibodies were measured in untreated IvIg preparations and also after they were treated to dissociate antibody-antigen complexes, because this procedure has been reported to increase the detectable levels of serum anti-Abeta antibodies. Antibody levels to Abeta1-42 monomer were significantly higher in untreated Gamunex than in the other two IvIg preparations, and antibody-antigen dissociation increased the measured anti-Abeta monomer concentrations in Gamunex and Gammagard. Dissociated Gamunex and Gammagard had higher anti-Abeta monomer levels than Flebogamma. Generally similar results were found for antibodies to soluble Abeta1-42 oligomers, with the exception that after antibody-antigen dissociation, only Gammagard had significantly higher antibody levels than Flebogamma. These differences in antibody concentrations to Abeta1-42 conformations (particularly to Abeta1-42 soluble oligomers, thought to be the most neurotoxic conformation of soluble Abeta) and the increased availability of these antibodies after antibody-antigen complex dissociation have important implications for IvIg treatment of AD patients.
Intravenous immunoglobulins as a treatment for Alzheimer's disease: rationale and current evidence

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Abstract
Current treatment options for Alzheimer's disease (AD) exert only a short-lived effect on disease symptoms. Active and passive immunotherapy have both been shown to be effective in clearing plaques, removing beta-amyloid (Abeta) and improving behaviour in animal models of AD. Although the first active immunization trial in humans was discontinued because of severe adverse effects, several new approaches are currently being investigated in clinical trials. Recently, commercially available intravenous immunoglobulins (IVIG) have been used in small pilot trials for the treatment of patients with AD, based on the hypothesis that IVIG contains naturally occurring autoantibodies (nAbs-Abeta) that specifically recognize and block the toxic effects of Abeta. Furthermore, these nAbs-Abeta are reduced in AD patients compared with healthy controls, supporting the notion of replacement with IVIG. Beyond the occurrence of nAbs-Abeta, evidence for several other mechanisms associated with IVIG in AD has been reported in preclinical experiments and clinical studies. In 2009, a phase III clinical trial involving more than 360 AD patients was initiated and may provide conclusive evidence for the effect of IVIG as a treatment option for AD in 2011. In this article, we review the current knowledge and scientific rationale for using IVIG in patients with AD and other neurodegenerative disorders.