Immunoglobulin therapy in autoimmune diseases

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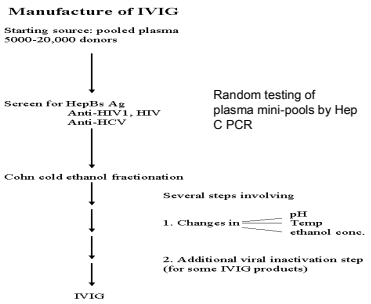
Scope of talk

- Preparation and components of IVIg
- Evidence for the use of IVIg in:
  - ITP
  - Kawasaki disease
  - GBS
  - CIDP
  - MMN
  - Pemphigus
- Mechanisms of action
- Adverse effects

Manufacture of IVIg



Evolution of the route of Ig administration

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IV

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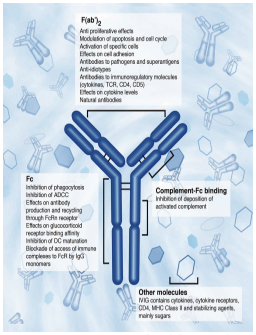
SC

IVIg is a potent immunological soup

- Diverse spectrum of IgG antibodies reflecting donor pool – specificities ~ 10^{15}
- Range of immunologically active molecules – soluble CD4,CD8,HLA-class II,gamma interferon,TGF-β
- Antibodies to IL1-α,CD5,HLA class I,II,CD4,TCR-β

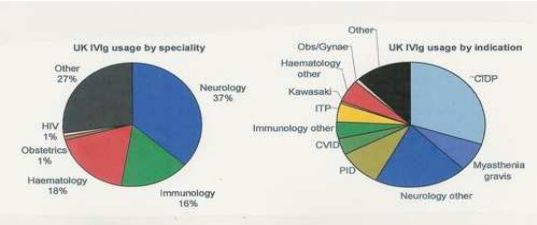


Jolles et al Clin Exp Immunol 2005

IVIg – broad indications

- As replacement therapy in antibody deficiency – standard dose 0.4 g/kg every 2-4 weeks
- As an immunomodulator – much higher dose required 2 g/kg over 2 – 5 days
- NB – 5 fold difference in dose between indications
- ? *Evidence base for these doses*

IVIg usage in the UK – data from pharmacy returns collected for DOH Demand Management Plan (2009)



IVIg as an immunomodulator – another example of serendipity in Immunology

(*Imbach et al.High dose IVIg for ITP in childhood.Lancet 1981)*

- Imbach observes dramatic increase in platelet ct following IVIg in a 12 yr old boy with intractable chronic ITP and hypo-γ secondary to long-term steroids.
- And the flood gates open ……

IVIg in ITP II

- Imbach's observations confirmed thereafter in open studies in both adults and children *(Imbach et al Lancet 1981;1:1228-31)*
- Evidence from randomised studies show that IVIg is equally efficacious as steroids in increasing the platelet count in both adult and childhood ITP *(Blanchette et al Randomised trial of IVIg, IV anti-D and oral prednisolone in childhood acute ITP.Lancet 1994;344:7.3-07)*
- *But, majority of patients with ITP do not require any rx – overall mortality in adult ITP estimated at 1.3% compared to normal population (Portielje et al Morbidity and mortality in adults with ITP. Blood 2001;97:2549-54); in adult ITP,more patients died of infection than of bleeding.*
- *Natural history of ITP in majority of cases is benign – risk of severe,fatal bleed is overstated*

IVIg in ITP III

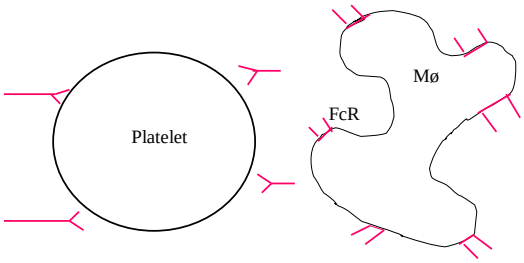
- Although effective in raising platelet count in >75% of patients,the response is not durable
- Therefore,not useful for long-term therapy
- Indications for IVIg in ITP – limited to those instances when a rapid rise in platelet ct is required or if steroids are contra-indicated (pre-operatively,pregnancy,labour)

IVIg in childhood ITP – a transatlantic divide

- Interestingly, UK and US guidelines differ on the need to rx ITP in childhood American Society for Haematology recommends that all children with ITP and plt cts <20 ,000 should be treated with IVIg or steroids irrespective of the clinical manifestations of thrombocytopenia to prevent intracranial haemorrhage
- Risk of ICH estimated at 1:1000 *(Lilleyman J.Intracranial haemorrhage in ITP.Arch Dis Child 1994;71:251-53).*
- BSH guidelines advise expectant approach to children with plt cts < 10,000 and mild symptoms.

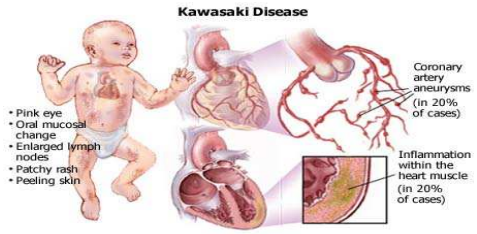
  (Bolton-Maggs P et al The child with ITP;is pharmacotherapy or watchful waiting the best initial management ; a panel discussion from the 2002 meeting of the American Society of Pediatric Haematology/Oncology. J Ped Hem/Oncol 2004;26:146-51)
- Latest international consensus guidelines advocate expectant 'watch and wait' policy for the majority of children with ITP *(Provan et al.Blood 2010;115:168-186)*

How does IVIg effect a rise in the platelet count in ITP ? – Evidence for Fc receptor blockade



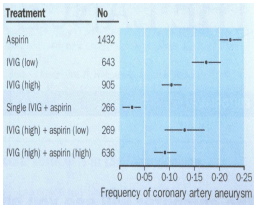
- Dramatic increase in platelet ct in patients treated with anti-CD16 *(Clarkson et al NEJM 1986;314:1236-9)*
- Infusion of Fcγ fragments leads to an increase in plt count in childhood ITP *(Debre et al Lancet 1993;342:945-49)*
- Intravenous anti-D is effective in ITP

IVIg as an immunomodulator -Kawasaki disease – an acute febrile childhood vasculitis characterised by conjunctivitis,lymphadenopathy and coronary arteritis *(Kawasaki et al A new infantile acute febrile mucocutaneous lymph node syndrome prevailing in Japan.Pediatrics 1974;54:271-6)*



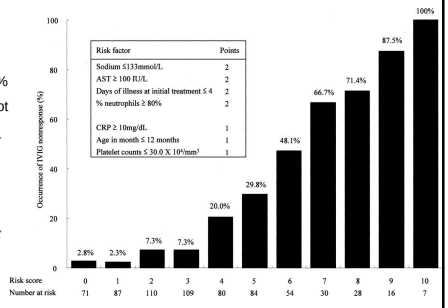
Evidence for use of IVIg in Kawasaki disease

- Sound evidence base supporting the use of high dose IVIg + Aspirin as the rx of choice
- ~ 300 publications,incl RCTs *(Newburger et al The treatment of Kawasaki syn with intravenous gammaglobulin. NEJM 1986;315:341-7; Newburger et al A single intravenous infusion of gammaglobulin as compared with four infusions in the treatment of acute Kawasaki syn.NEJM 1991;324:1633-9)* and a Cochrane review
- *Oates-Whitehead et al IVIg for the treatment of Kawasaki disease in children.Cochrane Database Syst Rev 2003;CD 004000*



IVIg resistance in Kawasaki disease

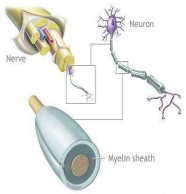
- IVIg resistance occurs in ~ 10-25%
- IVIg resistance not associated with a particular brand or lot of IVIg
- Proportion of patients requiring repeat course of IVIg ~ 14% *(Son et al.Pediatrics 2009)*



Kobayashi et al Circulation 2006

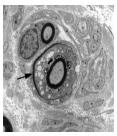
IVIg in autoimmune neurological disease

- Guillain-Barre syndrome
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
- Multifocal motor neuropathy with conduction block (MMN)



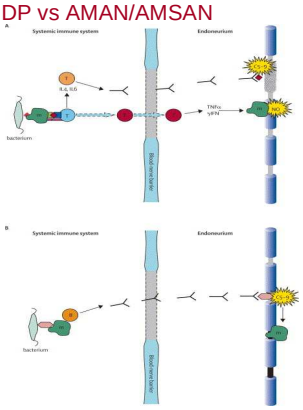
Guillain-Barre syndrome

- Symmetrical ,rapidly evolving flaccid areflexic paralysis often associated with bulbar or respiratory muscle failure
- Onset of paralysis preceded by infection in ~60-70% of patients – *Campylobacter jejuni*, Mycoplasma , CMV,EBV
- Self-limiting disease but ~ 16% left with serious neurological deficits.
- Despite best treatment and intensive care – immediate mortality ~ 5%.
- 3 main pathological forms:
  - Acute inflammatory demyelinating polyneuropathy (AIDP)
  - Acute motor axonal neuropathy (AMAN)
  - Acute motor and sensory axonal neuropathy (AMSAN)
- Anti-ganglioside abs present in acute phase of GBS in a proportion of patients
- 1978 – first report of success of plasma exchange *(Brettle et al Treatment of acute polyneuropathy by plasma exchange. Lancet 1978;ii:1100)*
- 1988 – first report of successful use of IVIg *(Kleyweg et al.Treatment of Guillain-Barre syndrome with high dose gammaglobulin.Neurology 1988;38:1639-42)*

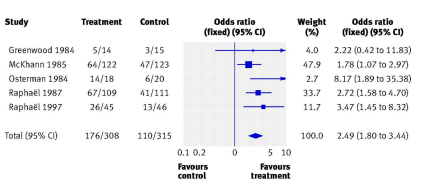


Pathology of AIDP vs AMAN/AMSAN

- AIDP
  - Closely resembles experimental autoimmune neuritis in animals induced by immunisation with myelin
  - Multifocal mononuclear cell infiltration throughout peripheral NS
  - Macrophage invasion of myelin sheaths and denuding of axons
- AMAN/AMSAN
  - Macrophage invasion at nodes of Ranvier leaving myelin sheath intact
  - Paucity of lymphocytic inflammation consistent with antibody-mediated pathogenesis



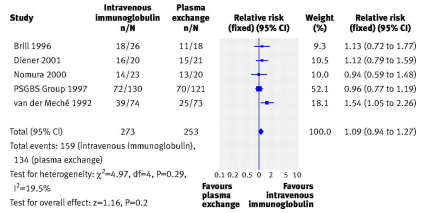
Forest plot of plasma exchange compared with supportive treatment in Guillain-Barre syndrome. Proportion of patients who improved one grade at 4 weeks. Adapted, with permission, from a Cochrane review34



Winer, J. B BMJ 2008;337:a671

BMJ

Forest plot of intravenous immunoglobulin compared with plasma exchange in Guillain-Barre syndrome. Change in disability grade at 4 weeks. Adapted, with permission, from a Cochrane review35



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BMJ

Randomised trials of IVIg in childhood GBS

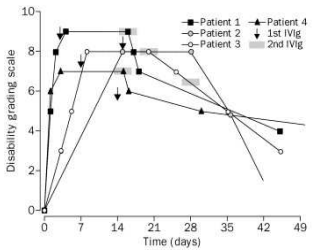
	No of pts	IVIg arm	Placebo/Supportive rx
Gurses et al Scand J Infect Dis 1995	18	*IVIg 1g/kg daily x 2* 7/9 pts recovered full strength	2/9 recovered full strength
Wang et al J Appl Clin Pediatr 2001	54	*Dexamethasone + IVIg* 0.2/0.3 g/kg for 5-6 d Time to partial/ complete recovery 17.1 days	*Dexamethasone* 5-10 mgs daily for 2/52 Time to recovery = 24.8 days
Korinthenberg et al Pediatrics 2005	50	*IVIg 1g/kg x 2 days* Median time to walk unaided 19 days	*IVIg 0.4 g/kg daily x 5* Median time to walk unaided = 13 days

IVIg in Guillain-Barre syndrome – summary

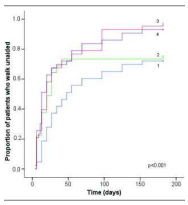
- IVIg as efficacious as plasmapheresis
- In practice, because of its ease of administration high- dose IVIg is now regarded as the treatment of choice in patients with acute paralytic GBS presenting within 2 weeks of onset of symptoms

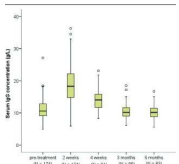
Rx options for patients who deteriorate despite PE or IVIg

- 5 – 10% of patients with GBS deteriorate after initial improvement with IVIg
- Best course of action in this gp is unknown
- PE followed by IVIg no better than PE or IVIg alone
- PE after IVIg – illogical
- In practice, a 2nd course of IVIg may be beneficial *(Farcas et al.Efficacy of repeated IVIg in severe unresponsive GBS Lancet 1997;350:1747)*



Does the pharmacokinetics of IVIg affect outcome in GBS?



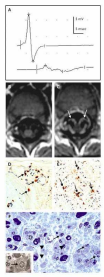


- Significant variation in the increase in serum IgG (ΔIgG) following IVIg
- Patients with a low ΔIgG recovered significantly more slowly
- Low ΔIgG was independently associated with poor outcome

Kuitwaard et al Ann Neurol 2009

IVIg in Chronic Inflammatory Demyelinating Polyneuropathy - I

- CIDP – progressive areflexic symmetrical neuropathy characterised by proximal and distal weakness and sensory loss
- Immunopathogenesis – macrophage mediated segmental demyelination and remyelination accompanied by upregulation of MHC class I and II antigens and variable T lymphocyte infiltrate
- Traditional rx – steroids and /or plasmapheresis
- Patients with pure motor CIDP may deteriorate with steroids *(Donaghy et al.Pure motor demyelinating neuropathy:deterioration after steroid treatment and improvement with intravenous immunoglobulin. J Neurol Neurosurg Psychiat 1994;57:778-83)*



IVIg in CIDP – evidence for short-term efficacy

- Cochrane review of 5 RCTs involving >100 patients with CIDP confirmed significantly more improvement in short-term disability with IVIg compared with placebo/steroids
- However,cost per quality adjusted life year (QALY) is high *(McCrone et al Cost utility assessment of intravenous immunoglobulin and prednisolone for chronic inflammatory demyelinating polyneuropathy.European J Neurology 2003;10:687-94)*
- Association of British Neurology guidelines 2005 (www.abn.org): *"While IVIg is recommended for the treatment of CIDP, for reasons of cost and convenience ,steroids may be preferred as first-line treatment and IVIg reserved for treatment failures or where steroid side effects are troublesome or anticipated"*

IVIg in CIDP – evidence for long-term efficacy

(Hughes et al.IVIg (10% caprylate-chromatography purified) for the treatment of CIDP: a randomised placebo-controlled trial.Lancet Neurol 2008;7:136-144)

- 117 CIDP patients randomised

IVIg 1g/kg Placebo - 24 wks

IVIg Placebo - 24 wks

- Results : Improvement in INCAT disability score seen in 32/59 (54%) treated with IVIg vs 12/58 (21%) treated with placebo
- Results suggest maintenance treatment with IVIg might prevent relapse
- FDA licence for IVIg in CIDP obtained

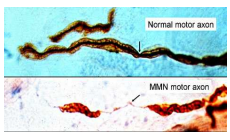
Plasmapheresis Vs IVIg in CIDP

(Dyck et al.A plasma exchange versus immune globulin infusion trial in CIDP.Annals of Neurol 1994;36:838-845)

- Only one randomised,single-blinded,cross-over study
- No of patients = 20
- PE twice a week for 3 wks foll by once a week for 3 weeks.
- IVIg 0.4 g/kg weekly for 3 wks followed by 0.2 g/kg once a week for 3 wks
- Conclusion: PE as efficacious as IVIg in CIDP

IVIg in Multifocal Motor Neuropathy (MMN)

- MMN – distal focal motor neuropathy characterised by segmental demyelination, conduction block and assymetric weakness with relatively preserved muscle bulk.
- Associated with anti-GM1 antibodies in ~ 50-80% of cases.
- Occasionally mistaken for Motor Neurone Disease but can be distinguished electrophysiologically



IVIg in Multifocal Motor Neuropathy – evidence for efficacy

- Systematic review of 4 RCTs of IVIg versus placebo involving >300 patients show a significant short-term improvement in strength *(Van Schaik et al Cochrane database of systematic reviews 2005; CD 004429)*
- Long-term follow up studies show continued response to IVIg although some progression may occur *(Vucic et al Multifocal motor neuropathy –decrease in conduction blocks and reinnervation with long-term IVIg.Neurology 2004;63:1264-69)*
- Other treatment option: Cyclophosphamide but long-term use limited by adverse effects
- ABN guidelines : " IVIg is the only safe treatment which has been shown to work in patients with MMN and is recommended in those with significant disability"

Other autoimmune neurological disorders where IVIg has been shown to be beneficial on the basis of RCTs

- Dermatomyositis *(Dalakas et al A controlled trial of high-dose intravenous immunoglobulin infusions as treatment for dermatomyositis.NEJM 1993;329:1993-2000)*
- Myasthenia gravis – acute exacerbations *(Gajdos et al Intravenous immunoglobulin for myasthenia gravis.Cochrane Database of Systematic Reviews 2003;CD 002277)*
- Lambert-Eaton syndrome *(Maddison et al Treatment for Lambert-Eaton myasthenic syndrome. Cochrane Database of Systematic Reviews 2005)*
- Stiff-person syndrome *(Dalakas et al High dose intravenous gammaglobulin for stiff-person syndrome.NEJM 2001;345:1870-1876)*

IVIg in autoimmune neurological disease - summary

Disease	IVIg as rx of choice	IVIg as adjunctive rx
GBS	Yes	
MMN	Yes	
CIDP	Yes	
Dermatomyositis		Yes
Myasthenia gravis	Only for myasthenic crises	
Stiff-person syn	Yes	Yes
Lambert-Eaton syn		Yes

IVIg offers neurologists a major treatment option in many disabling conditions : *Hughes RAC.Treating nerves:from anecdote to systematic review.J Royal Soc Med 2003;96:432-35*

IVIg in Dermatology

- Diseases in which RCT evidence supports the use of IVIg – pemphigus vulgaris
- Diseases in which observational studies or case series suggest benefit:
  - Autoimmune bullous skin disease –pemphigoid,epidermolysis bullosa acquisita,cicatricial pemphigoid,linear IgA disease and gestational pemphigoid
  - Toxic epidermal necrolysis
- Diseases in which case reports suggest benefit:
  - chronic autoimmune urticaria
  - scleromyxoedema
  - atopic dermatitis
  - pyoderma gangrenosum

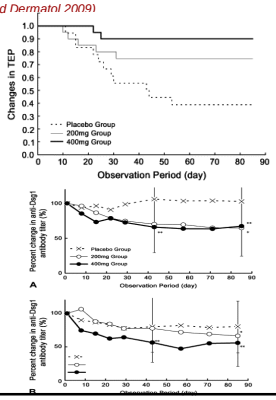
IVIg in pemphigus – RCT evidence *(Amagai et al J Am Acad Dermatol 2009)*

- 61 patients with steroid-resistant pemphigus vulgaris/foliaceus

2g/kg n = 20 | 1g/kg n = 20 | 0 g/kg n = 21

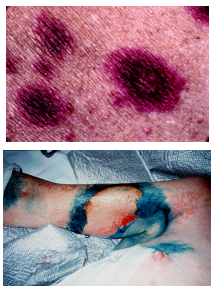
•Primary end-point : time to escape from protocol

•Secondary end-points:pemphigus activity score,anti-dsg antibodies



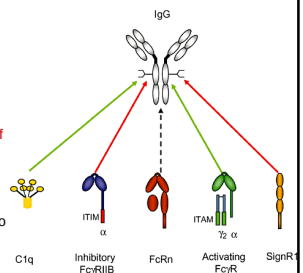
IVIg in Toxic epidermal necrolysis(TEN) – Stevens-Johnson syndrome

- SJS and TEN are two ends of the same spectrum of severe drug-induced exfoliative dermatoses – sulphonamides, anticonvulsants,barbiturates
- No specific treatment available to date – average mortality ~30% in TEN
- Several studies involving >100 patients suggest that IVIG arrests skin and mucosal detachment in the majority of patients with consequent reduction in mortality.
- Despite lack of RCT evidence high-dose IVIg is now used as first-line treatment in many centres
- Endorsed as a high priority (red) indication by UK and European guidelines



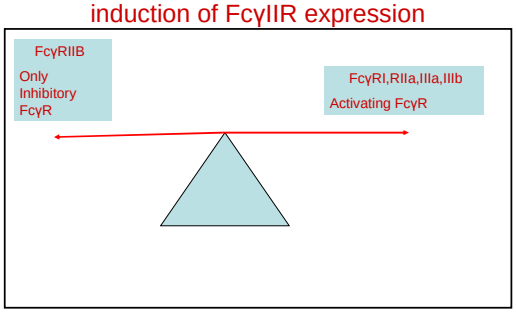
Mechanisms of immunomodulation-focus on the Fc fragment of IgG and sialylation

- Key facts on sialylation:
- All antibodies are glycoproteins – comprising a core heptasaccharide with variable addition of fucose, galactose, sialic acid and N-acetylglucosamine
- Fully processed sialylated N-linked glycan with α2,6 link to galactose – constitutes :~ 1-3% of IgG in IVIg
- Absolute requirement of IgG glycosylation for FcγR binding – deglycosylated IgG unable to mediate inflammatory responses
- Deglycosylated IgG able to bind to FcRn



Aschermann et al Clin Exp Immunol 2009

Importance of sialylation for immunomodulatory action of IVIg – via induction of FcγIIR expression



How does sialylated IgG induce FcγRIIB expression?

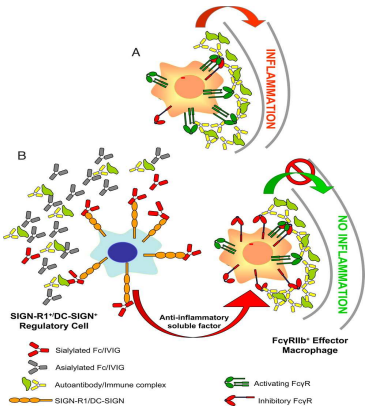
By binding to specific receptors: SIGN-R1

Evidence for SIGN-R1/DC-SIGN as receptors for sialylated Fc/IVIg – murine studies *(Anthony et al PNAS 2008)*

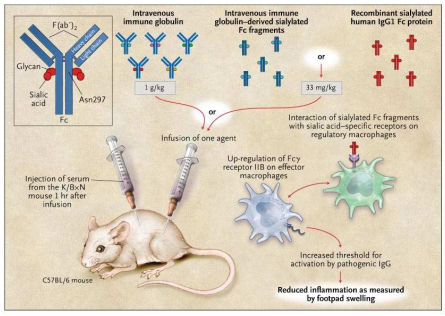
- SIGN-R1: Specific ICAM-3 grabbing non-integrin related-1 receptor –expressed on splenic marginal zone macrophages
- DC-SIGN: human orthologue of SIGN-R1 – tissue distribution differs from SIGN-R1, expressed specifically on dendritic cells
- Anti-SIGN-R1 abrogates protective effect of IVIg in murine models
- Splenectomy abrogates anti-inflammatory activity of sialylated Fc or IVIg
- Sialylated IVIg ineffective in SIGN-R1 deficient mice
- Transfected macrophage cell line expressing SIGN-R1 selectively binds sialylated Fc

Model for anti-inflammatory activity of sialylated Fc IVIg

Anthony et al PNAS 2009

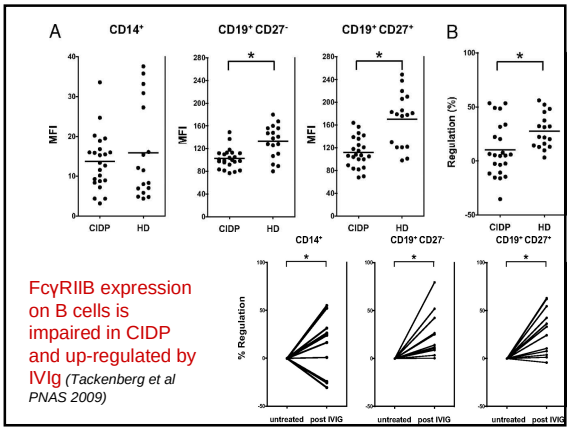


Sialylation – a possible explanation for the anti-inflammatory effect of IVIg *(Kaneko et al Science 2006,Kaveri NEJM 2008)*



Evidence in humans ?

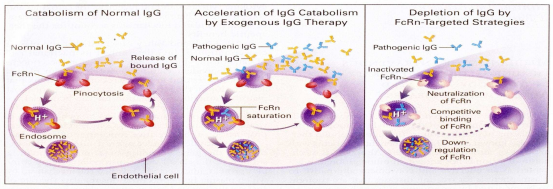
- both intact IVIg and F(ab)2 fragments inhibit TLR-mediated activation of DC as assessed by phosphorylation of ERK ½ *(Bayry et al PNAS 2009)*
- interaction between DC-SIGN and sialylated IgG Fc not essential for the anti-inflammatory activity of IVIg on human DC



FcγRIIB expression on B cells is impaired in CIDP and up-regulated by IVIg *(Tackenberg et al PNAS 2009)*

IVIg as an immunomodulator – focus on blockade of the FcRn receptor as a mechanism to accelerate clearance of endogenous autoantibodies *(Yu et al NEJM 1999;340:227-28))*

- FcRn(Fc receptor of the neonate)- a protective receptor found on endothelial cells and other tissues that prevents catabolism of IgG.
- Saturation of FcRn by exogenous IgG rx allows endogenous pathogenic IgG autoantibodies to be catabolised – possible mechanism of action of high dose IVIg in autoimmune disease



Adverse effects of IVIg - classification

- Immediate infusion-related : may occur with either low or high-dose IVIg
- Complications of increasing serum IgG – dose related,largely confined to use of high dose IVIg (2g/kg) used for immunomodulation
- Transmission of infective agents – hepatitis C,? prions ? parvovirus

Therapeutic Immunoglobulin – looking to the future

- Increasing use of subcutaneous route for Ig delivery
- Proportion of market share of IVIg will be taken up by Rituximab and related biologics
- ? Use of recombinant sialylated Ig for immunomodulation