

Immunoglobulin Replacements Therapy in PID

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Key points:

- Load IV or SC, otherwise it takes 4-6 months to reach a stable IgG trough level + significant reduction of infection
- Trough levels of 5 g/l or below do not prevent progressive structural damage or pneumonia
- IgG levels for infection prevention vary widely between patients
- Higher trough levels reduce infections significantly but there is no ideal IgG levels for all patients
- Several systematic reviews show good evidence for efficacy of Ig therapy in PIDs

Ig substitution therapy for whom?

- Anyone who cannot make protective antibodies:
- Known single gene antibody defects e.g. XLA, HyperIgM syndromes, WAS, XLP, SCID
- Polygenic antibody defects eg CVIDs,
- Partial antibody deficiencies with infections e.g. IgG subclass defects with IgA deficiency
- Not Selective IgA deficiency,
- Maybe not specific antibody deficiency unless significant and appropriate infections

Immunoglobulin Substitution - Report of a WHO Scientific Group (1994):

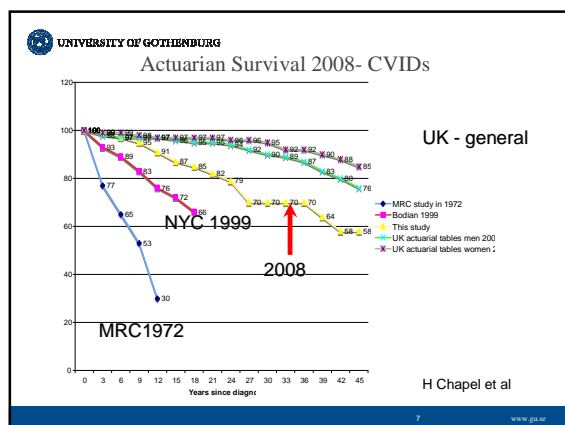
- Replacement therapy with IvIg is life saving
- If replacement therapy is started early, and if sufficient amounts are given with sufficient frequency, the cycle of recurrent infections and progressive lung damage can be arrested
- If large doses of IgG are given, abnormal pulmonary function may improve even if bronchiectasis is present

BUT .. Ig Is Not The Whole Answer Even In Antibody Deficiencies

- Other treatments are needed for particular complications
- Immune suppression - corticosteroids / Rituximab for ITP/AHA
- Non-absorbed steroids for enteropathy +/- Campath
- TNF modifiers for granuloma - etanercept or infliximab
- Ciclosporin/tacrolimus for lymphoid interstitial pneumonitis
- And so on

We know

- IMIg gives low serum levels and poor survival
 - MRC 1972
- IVIg vs IMIg gives less severe infections and less days in hospital
 - Roifman et al
- High dose (500 mg/kg/4weeks) vs. low dose (150 mg/kg) gives fewer days with fever, infections and antibiotics
 - Bernatowska et al

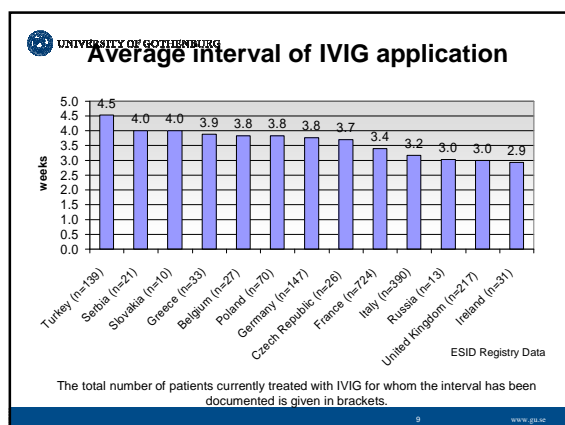


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Reasons for increased survival....

- Greater awareness though *no* improvement in diagnostic delay
- Improved care of children and adults –range of antibiotics, physiotherapy, prompt treatment of infections, specialist teams
- Higher doses of immunoglobulin g/Kg/month – though few outcome studies as yet
- Better compliance – home therapy, self-infusion, IV and SC routes

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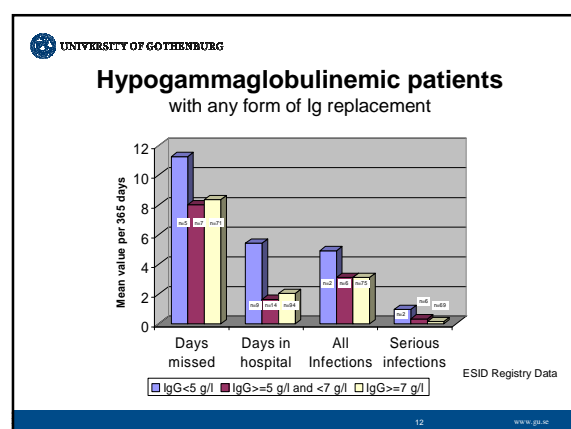
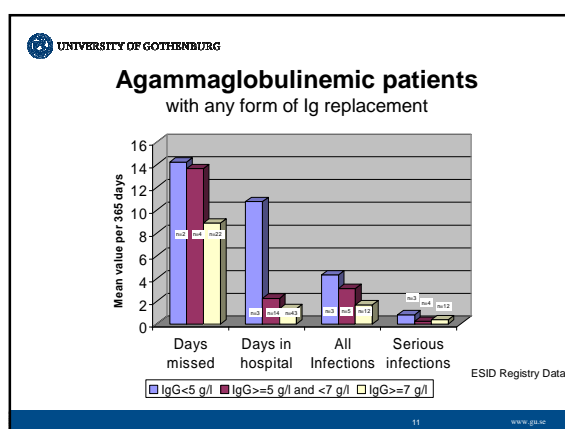
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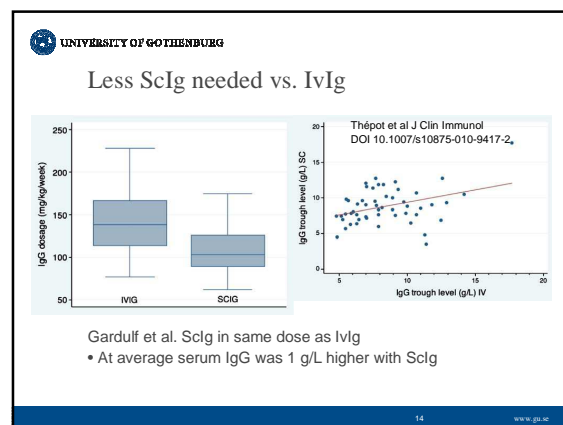
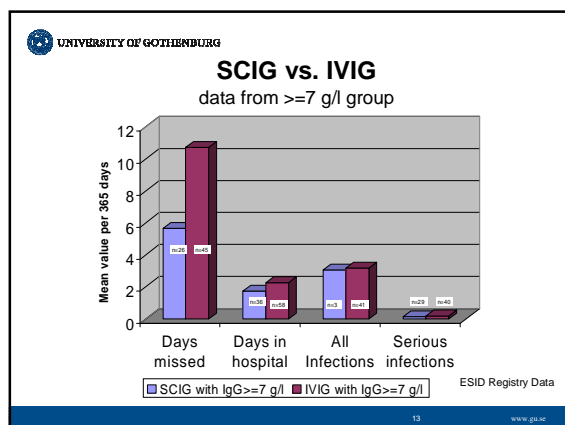
Ig replacement and health outcomes

- Evaluation of data on health-related outcomes from patients receiving Ig replacement
- Patients divided into three groups according to average trough level
(< 5 g/L; between 5 and 7 g/L; ≥ 7 g/L)
- Indicators applied (n patients evaluated)
 - Days missed at school or work (n=133)
 - Days spent in hospital due to antibody deficiency (not including visits to out-patient clinics) (n=203)
 - Number of infectious episodes (n=122)
 - Number of serious bacterial infections (all per 365 days) (n=115)

ESID Registry Data

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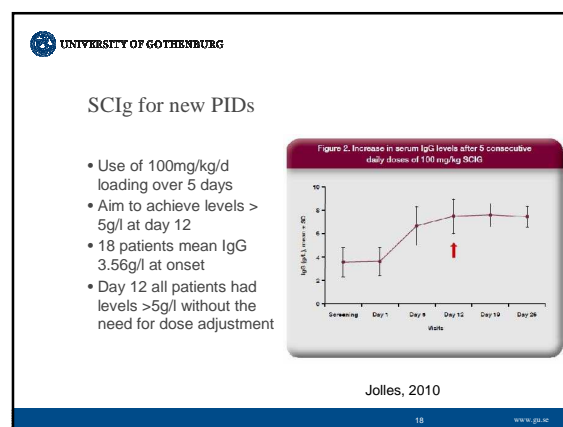
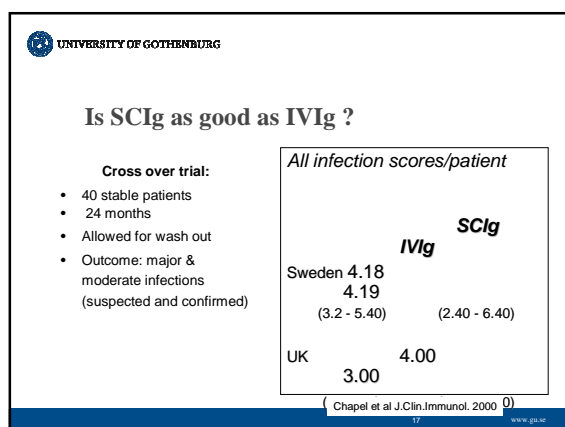
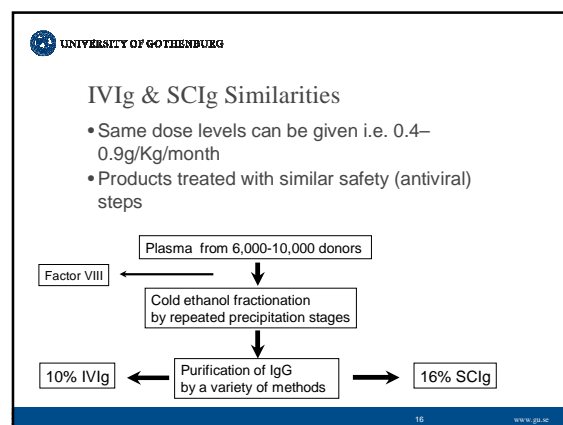
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FDA requirement

- SCiG should be given at a dose 137% higher than the IvIg dose
- Based on theoretical calculation of AUC, not on clinical research

When will FDA change its requirement?

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What Do The Patients Want?

- Both Ivlg and ScIg can be safely self-administered at home
 - Both substitution doses and immunomodulatory doses given at home
- Patients generally prefer home treatment
- Studies on quality of life are scarce
- Do not allow to separate between home treatment per se and mode of administration

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Patients' Preferences

- 15 children investigated during switch over from Ivlg to ScIg
- Followed with CHQ
- Result
 - ScIg provided better health
 - Improved school functioning
 - Reduced emotional stress
 - Fewer limitations on family activities
- BUT no conclusion can be drawn whether it is ScIg or the home treatment that gives improvement of HRQOL

Gardulf et al, 2004

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Advantages of SCIG treatment

- Treatment of patients with poor venous access¹
- Better tolerability in patients not tolerating IVlg
- More even, more physiological, IgG levels²
- SCIG home therapy gives independence from hospital-based treatment¹
- Improves HRQOL for many patients³
- Useful in children in particular
- Fewer 'wear off' effects compared with IVlg
- Reduced costs of home SCIG over hospital IVlg

1. Berger M. *Clin Immunol*. 2004;112:1
2. Ochs H et al. *J Clin Immunol*2006;26:265
3. Gardulf A et al. *J Allergy Clin Immunol*2004;114:936.

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Patient Characteristics

- Keen to take on responsibility for condition and home therapy
- Frequent traveler
- Busy/active lifestyle
- No problems with needles
- Poor veins
- Previous problems on IVlg
- Distance to treatment centre

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How do we do?

- Intravenous therapy given at the hospital or at home
 - In case of antibody deficiency rapid normalization of serum IgG
- Subcutaneous substitution given at home or at hospital
 - Two models for s.c. teaching
 - According to Gardulf – At least 6 – 8 sessions before patient is allowed home treatment
 - According to Abrahamsen – Intense learning during 2-3 days and then fit to do it at home

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This is Our Way for ScIg

- Three (two) days at day care unit
- Both parents involved and responsible
- Day 1
 - Information – oral and written
 - Education
 - Practical hands-on with the equipment
 - Parents and children (dependent upon age) injects themselves and the nurse
- Day 2
 - First s.c. infusion given by the patient or a parent
- Day 3
 - Feed-back and questions

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This is Our Way

- The second infusion - given at home
- The third infusion - given at day care unit
 - Control of infusion technique
 - Questions and answers
 - Control of the infusion site
- Visits at 3 and 6 months; later, about every 6th months
- NO adrenalin, corticosteroids etc. at home

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Other pumps



Graseby MS16A

Freedom 60



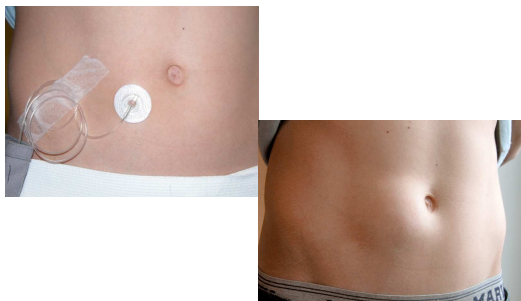
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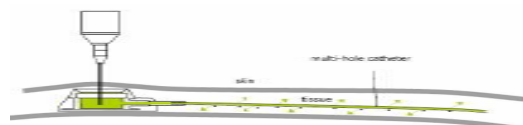


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Miniport (A. Bansal)

- Rapid sc infusion via implanted device
- Laser drilled holes allow diffusion over a larger space
- Pumps not required
- Potential concern over foreign body



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IV Home therapy training time

- IVIg 6 visits lasting approx 3 hours if using newer generation products with higher infusion speeds
- Additional time is mainly to do with training for venous access
- IVIg home therapy training requires approx 50% more nursing time

Stephen Jolles, Cardiff

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Rapid Push R. Shapiro

- 104 patients studied (43%M, 57%F, Av age 21.1 yrs)
- Syringe and 25-35 gauge butterfly
- Rate 1-2ml/minute
- Infusion volume 3-20ml
- Infusion time 5-20 mins
- 1-2 infusion sites
- Infusions may be given daily or 3x/wk
- Local reactions in 1/3

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Rapid Push

- Trough levels equivalent to SCIg via pump
- Levels were higher than previous IVIg at 100% of IV dose
- Chosen less often in children aged 2-10 and more often in teenagers and adults
- Simple, avoids the cost of pumps and is well tolerated
- More frequent administration used

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Hyaluronidase

- Aims to address the volume limitations of administration into the subcutaneous space
- Hyaluronidase cleaves hyaluronan and facilitates fluid dispersion and access to the circulation
- Ovine and bovine hyaluronidase used for decades in the acute setting (LA, opiates, antibiotics, insulin, fluids)

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Hyaluronidase

- Hyaluronidase has been used to facilitate 10% IVIg infusions into sc sites using rHuPH20
- rHuPH20 at 50U/g
- Infusion rates of 300ml/hr
- Infusion volumes of 600ml/site
- Mean AUC bioavailability was 92% of IV dose
- Peaks lower than IVIg and trough levels similar
- Longer term data is needed

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In summary – modern Ig therapies...

- Subcutaneous Ig for those with poor veins, mobile children, elderly patients -gives choice of route
- Choice of interval between infusions to fit with life style – IVIg longer; SCIg more frequent
- Higher concentrations IVIg may be advantageous in terms of time and ease of use
- Easy to use both at home by self-infusion & proven to be safe (Brennan et al; Gardulf et al.)
- IVIg and SCIg are both efficacious in preventing infections (Chapel et al; Gardulf et al.)
- Interchangeable route with same products must be available to fit with life style changes

Thanks to

- Helen Chapel
- Bodo Grimbacher
- Stephen Joller