Intravenous immunoglobulin: uses other than for immune replacement

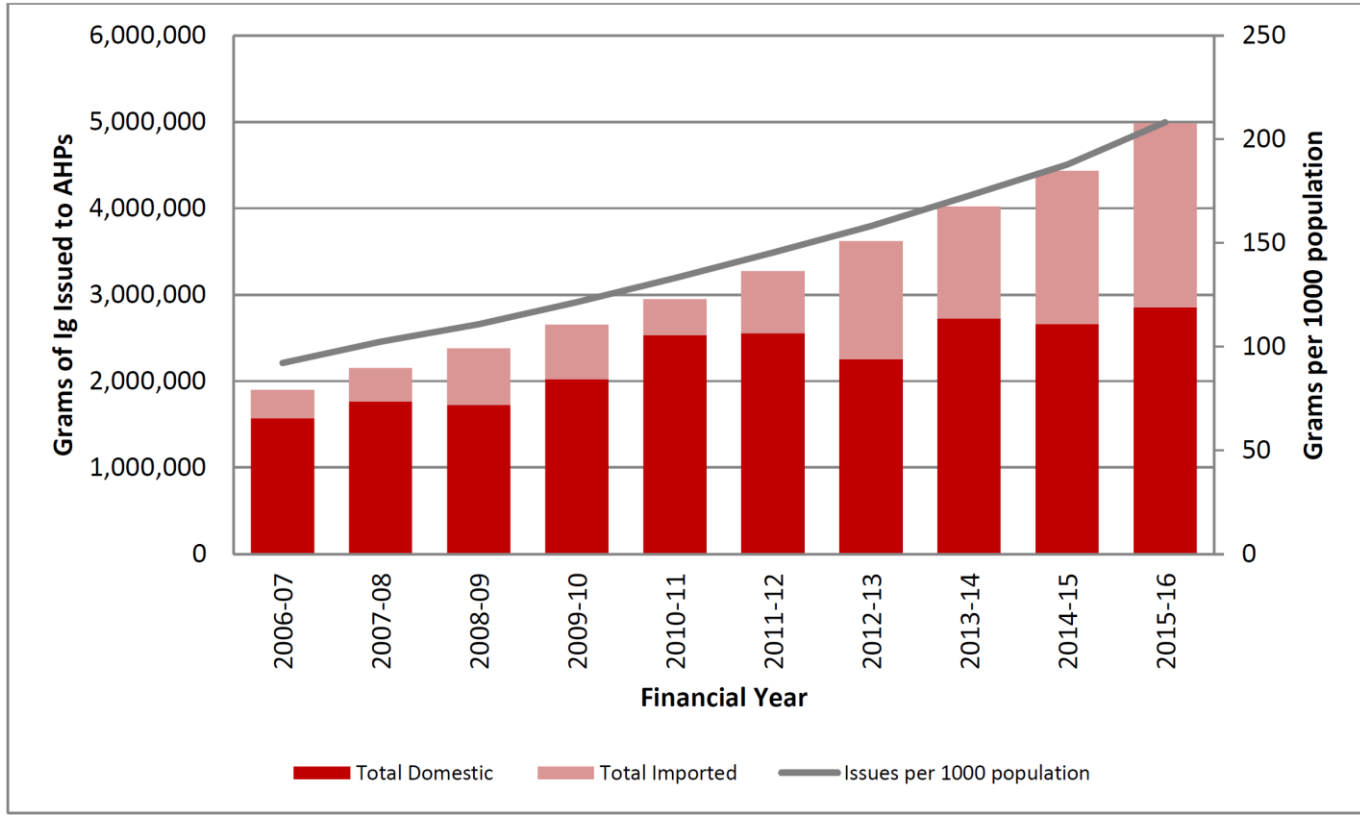
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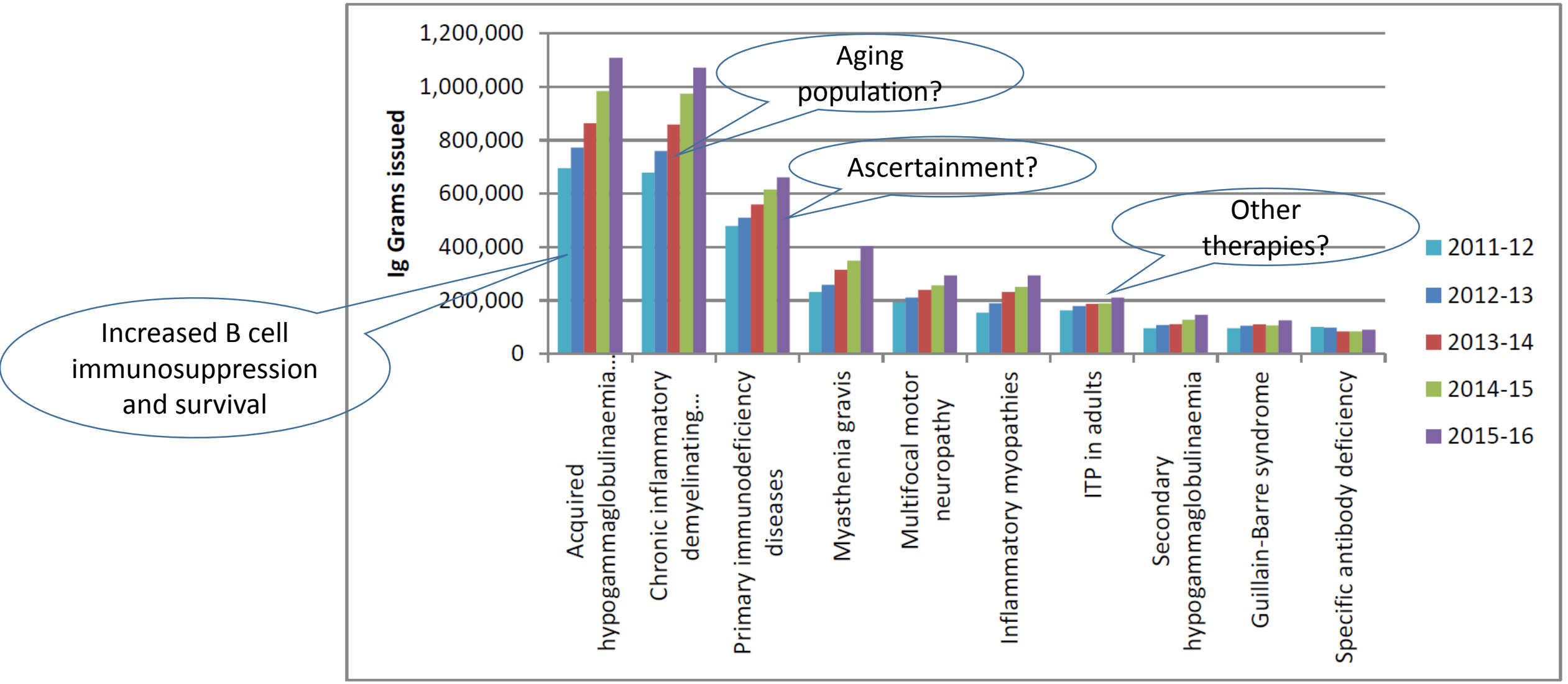
Immunoglobulin

- Replacement of immunoglobulins lacking due to B cell immunodeficiency (primary, secondary to B cell malignancy)
- Passive immunisation
- Modulate the immune system to control inflammation



Australian IVIg use 10 year trend

Source: NBA. Report on the issues and use of intravenous immunoglobulin 2015-16



Australian IVIg use 10 year trend

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Australia's National Blood Authority (2012) "Established Role"

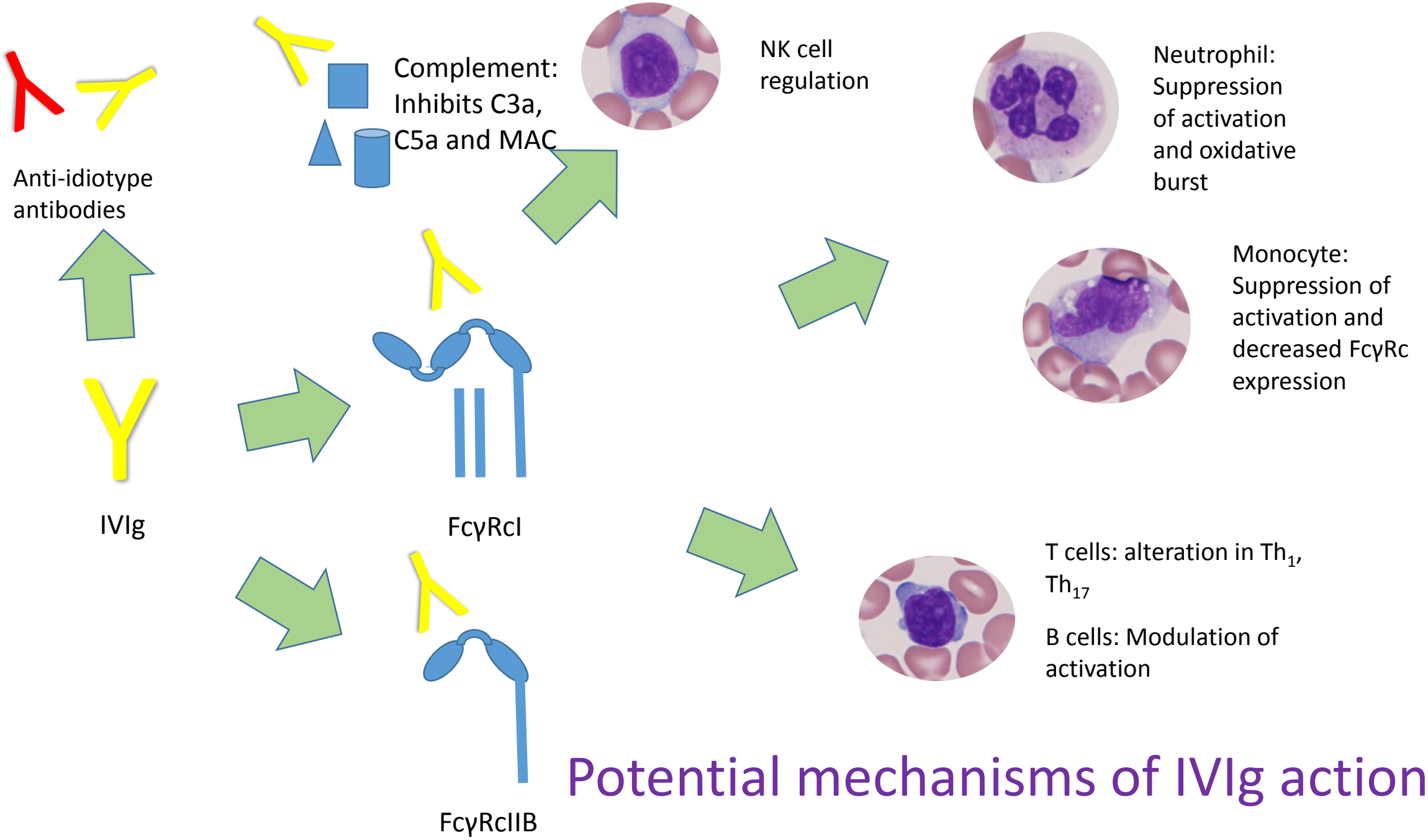
- Acquired hypogammaglobulinaemia secondary to haematological malignancies
- Chronic inflammatory demyelinating polyneuropathy
- Guillain–Barré syndrome
- Idiopathic (autoimmune) thrombocytopenia purpura(ITP) - Adult
- Inflammatory myopathies
- Kawasaki disease
- Lambert–Eaton myasthenic syndrome
- Multifocal motor neuropathy
- Myasthenia gravis
- Neonatal haemochromatosis
- Primary immunodeficiency diseases
- Stiff person syndrome

Australia's National Blood Authority (2012) "Emerging Role"

- Acute disseminated encephalomyelitis
- Anca -positive systemic necrotising vasculitis
- Autoimmune haemolytic anaemia
- Bullous pemphigoid
- Cicatricial pemphigoid
- Evans syndrome - autoimmune haemolytic anaemia with immune thrombocytopenia
- Foeto-maternal/neonatal alloimmune thrombocytopenia
- Haemophagocytic syndrome
- Idiopathic (autoimmune) thrombocytopenia purpura – Children 15 years and younger
- IgM paraproteinaemic neuropathy
- Kidney transplantation
- Multiple sclerosis
- Opsoclonus-Myoclonus ataxia
- Pemphigus foliaceus
- Pemphigus vulgaris
- Post-transfusion purpura
- Secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency)
- Specific antibody deficiency (including IgG subclasses)
- Toxic epidermal necrolysis/Stevens–Johnson syndrome
- Toxic shock syndrome

Australia's National Blood Authority (2012) "Exceptional Circumstances"

- Acute leukaemia in children
- Autoimmune congenital heart block
- Autoimmune neutropenia
- Autoimmune uveitis
- Catastrophic antiphospholipid syndrome
- Coagulation factor inhibitors
- Devic disease
- Diabetic amyotrophy
- Epidermolysis bullosa acquisita
- Epilepsy
- Graves ophthalmopathy
- Haemolytic disease of the newborn
- Haemolytic transfusion reaction
- Hashimoto encephalopathy
- HIV in children
- Limbic encephalitis - nonparaneoplastic
- Limbic encephalitis - paraneoplastic
- Myocarditis in children
- Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections
- Paraneoplastic cerebellar degeneration
- Paraneoplastic subacute sensory neuropathy
- Potassium channel antibody-associated encephalopathy
- Pure red cell aplasia
- Pure white cell aplasia
- Pyoderma gangrenosum
- Rasmussen syndrome
- Scleromyxedema
- Sjogren's syndrome
- Solid organ transplantation (other than kidney)
- Susac syndrome
- Systemic capillary leak syndrome



Potential mechanisms of IVIg action

Immune modulation by IVIg

- Functional blockade of Fc receptors, probably by saturating receptors
  - Important in ITP
- Anti-idiotypic antibodies
  - Neutralisation of autoantibodies
  - Prevention of auto-antibody production
- Complement inhibition
- Modulation of cytokine production by monocytes and lymphocytes
- Activation or blockade of Fas (CD95)
  - Fas is pro-apoptotic. IVIg contains activating and inhibiting Abs
- Inhibition of dendritic cells
- Signalling through the Fc gamma RIIB inhibitory receptor

Immune thrombocytopenic purpura (ITP)

- Immune mediated destruction of platelets
  - Associated reduction in platelet production due to effects on megakaryocytes
- Primary or secondary
- Risk of bleeding, although serious haemorrhage is uncommon
- Antibodies identified targeting GPIb/IX complex or GPIIb/IIIa

- Seasonal variation / association with viral infection in adults with acute ITP resolve by 12 months

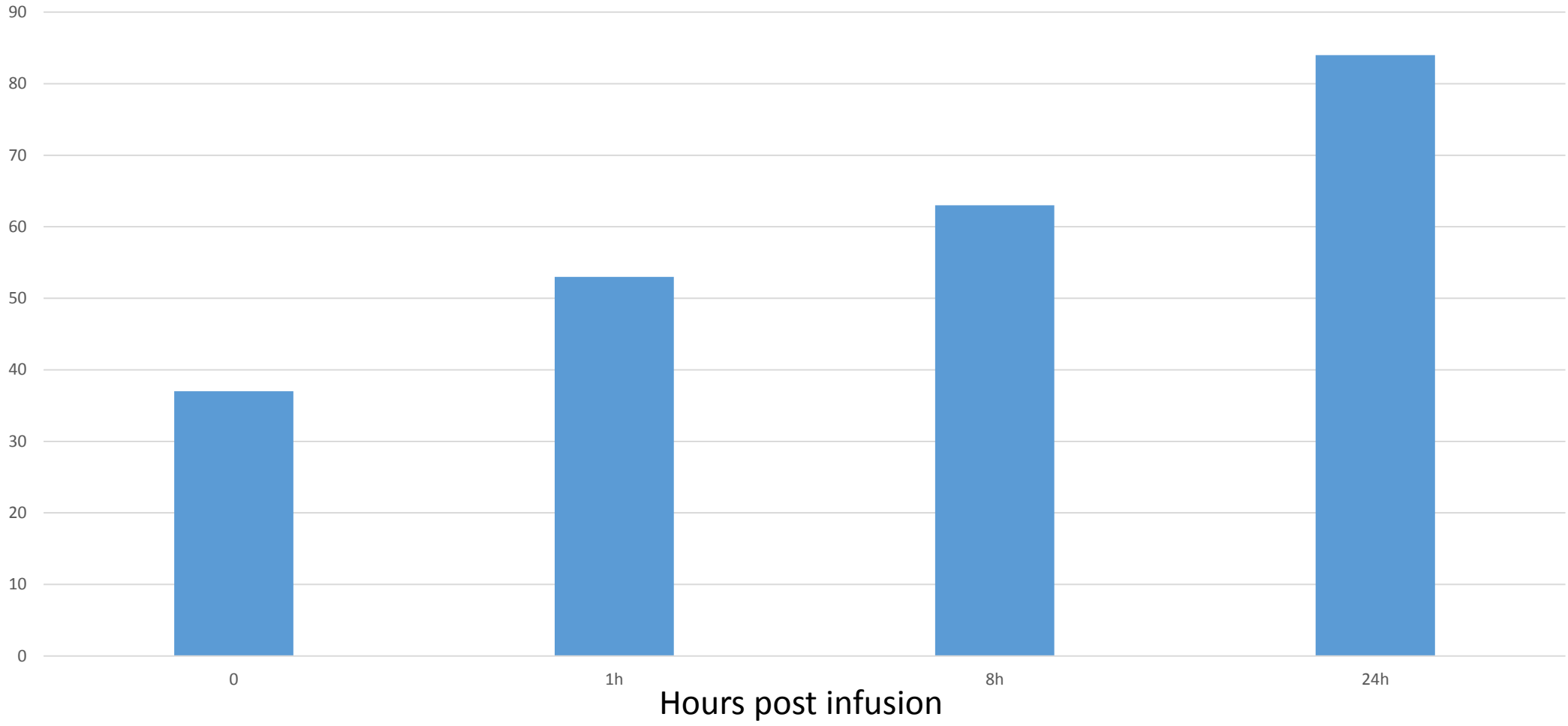
ITP Therapies

- First line
  - Steroids
  - Intravenous immunoglobulin
  - Anti-D
- Subsequent
  - Thrombopoietin receptor agonists
  - Rituximab
  - Splenectomy
  - Azathioprine
  - Danazol
  - Dapsone
  - Mycophenolate
  - Ciclosporin
  - Vincristine
  - Cyclophosphamide

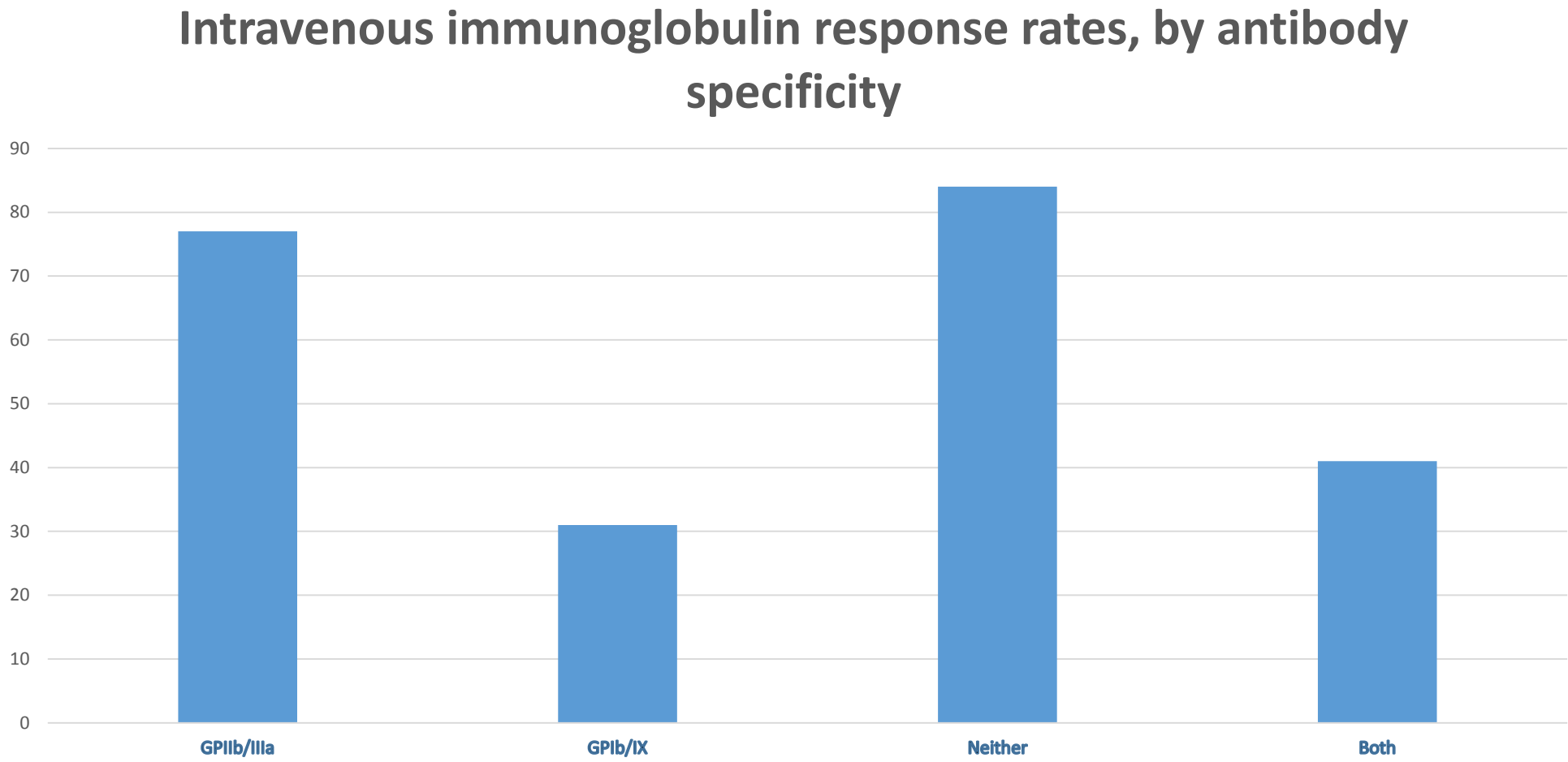
Intravenous immunoglobulin in ITP

- Proven
- Rapid onset in terms of reduction in bleeding, followed by improvements in platelet count
- Responses aren’t universal – non-responders less likely to respond to splenectomy

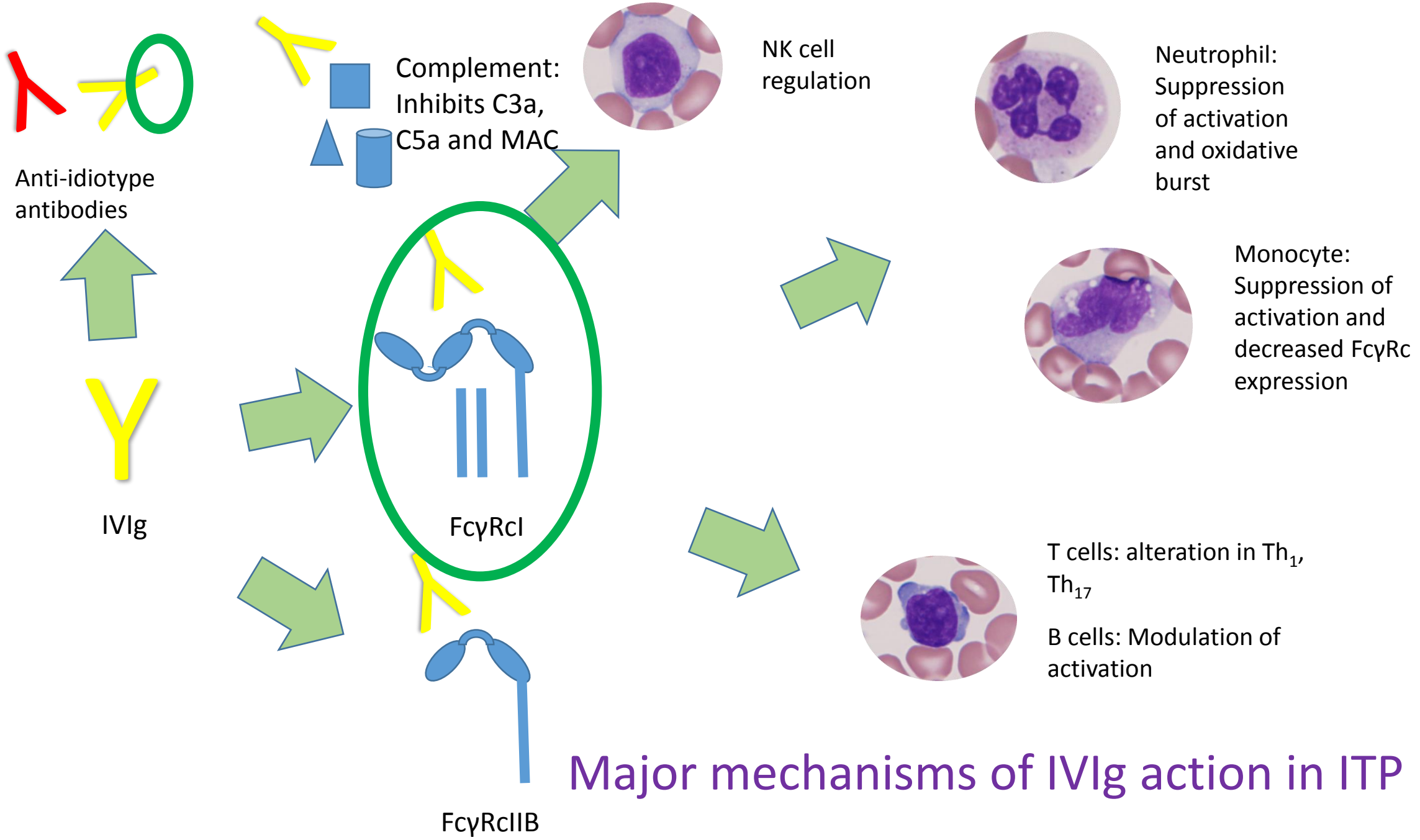
Cumulative increases in platelet count (%) following IVIg 0.8-1.2g/kg for ITP



Derived from Mayer et al Vox Sang 2011



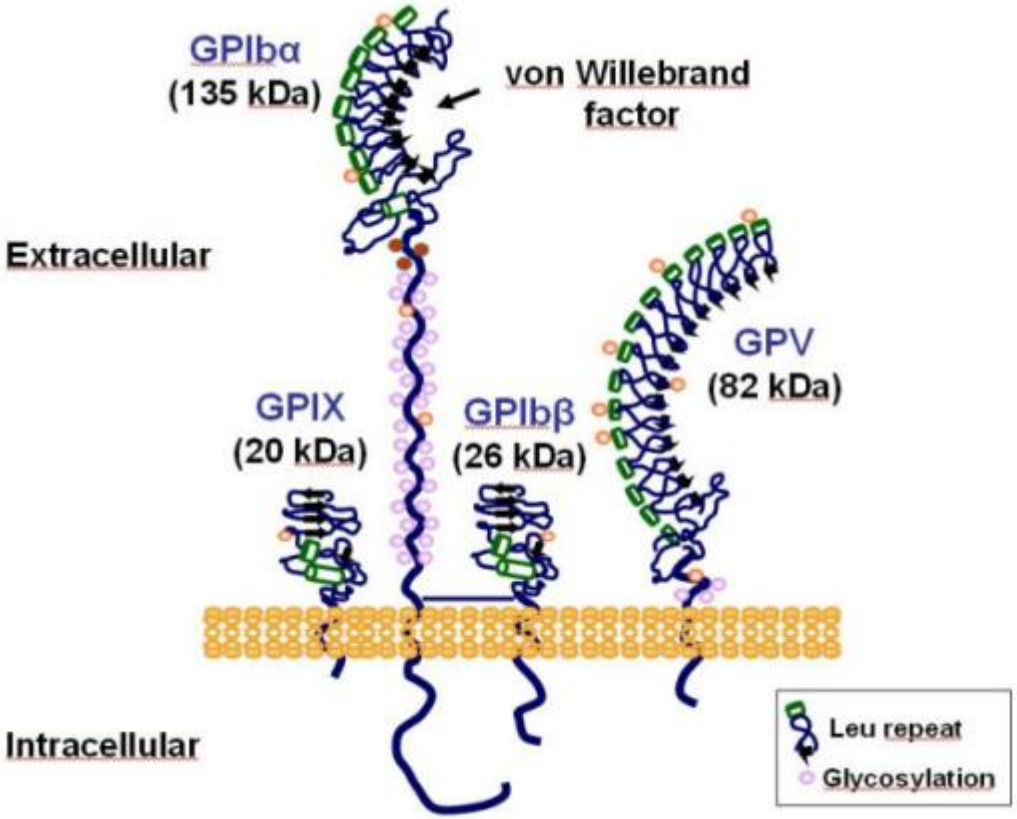
The presence of GPIb/IX antibodies confers a risk of lower response rates to intravenous immunoglobulin. Derived from Peng J, et al Blood 2014.



Major mechanisms of IVIg action in ITP

Fc-FcR independent platelet clearance in ITP

- Antibodies to GPIb-α associated with platelet activation, desialylation and removal of platelets via hepatic Ashwell-Morell (asialoglyprotein) receptors.
- Potential to respond to neuraminidase inhibitors (eg oseltamivir) (Li et al Nature Comm. 2015)

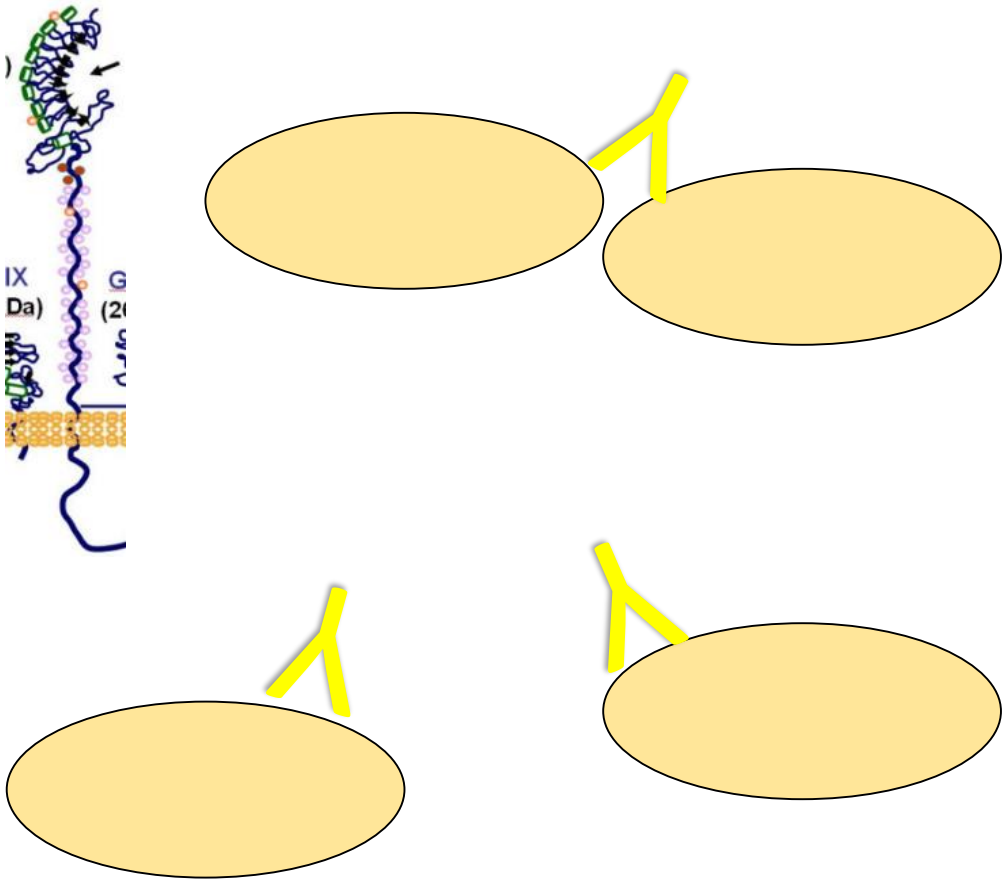


Lanza F, Orphanet J rare Dis 2006 (Creative Commons)

Fc-FcR independent platelet clearance in ITP

- To cause thrombocytopenia, Ligand Binding Domain antibodies to GPIb-α require:
- Dimeric antibodies to cross-link platelets
- Strong enough to maintain bonds under shear to open the mechanosensory domain leading to internal signalling, activation and clearance

Quach Blood 2018



ITP: Summary

- Intravenous immunoglobulin is highly effective in a proportion of patients with Fc-FcR dependent mechanisms of platelet clearance

- Identification of mechanisms of antibody action may help to define patients likely or unlikely to respond to immunoglobulin therapy

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

- Inflammatory condition leading to peripheral neuropathy
- Mild to debilitating
- No diagnostic antibody tests

- Steroids, plasma exchange and intravenous immunoglobulin have proven efficacy
- Little evidence for other agents, although mycophenolate, etanercept have been used.
- Rituximab limited benefit; azathioprine, interferon-β or methotrexate

Correct diagnosis of CIDP

- Diagnostic precision may assist therapeutic decisions
- Anti-MAG (myelin associated glycoprotein) in IgM paraproteinaemia associated polyneuropathy
  - B cell depletion to reduce IgM paraprotein
- POEMS (osteosclerotic myeloma with neuropathy and usually IgA lambda paraproteins)
  - Radiation, systemic myeloma therapy
- Axonal neuropathies don’t respond to IVIg

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

- Used due to limited other options?
- Reconsider IVIg role when there is failure to achieve a significant functional improvement, relapse

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

- Dose uncertain:
- Initial studies used 2g/kg dose (split over 2-5 days).
- One study (Hughes Lancet Neurol 2008) used 2g/kg followed by 1g/kg maintenance 3 weekly

- Recent RCT showed no difference with 0.2g/kg/week v 0.4g/kg/week *subcutaneous* immunoglobulin as maintenance therapy (van Schaik et al Lancet Neurol 2018)
- In this study about one third of patients relapsed or progressed during the 24 week therapy.

- The majority of patients at our centre are on 0.4g/kg 4 weekly maintenance

Intravenous immunoglobulin: negatives for patients

- Adverse events
- Venous access
- Time – patient
  - Weeks J et al found no improvement in quality adjusted life when the burden of hospital visits taken into account for immune replacement in CLL
- Subcutaneous immunoglobulin may reduce these, with emerging evidence in immune modulation

Adverse event	Number of events occurring during infusions	Number of events occurring after infusions
Headache	6	8
Nausea	7	4
Generalised aches and pains	2	7
Fatigue	-	8
Chills	1	3
Fever	1	2
Light-headed		1
Unpleasant taste		1
Flushing		1
Renal angle pain		1
Burning in fingers	1	

Adverse events with Intragam 10 fast infusions (n=104). Crispin and Burgess Transfus Apher Sci. 2018

Immunoglobulin: more negatives

- Cost of production
  - Including donor recruitment
- Time and costs for infusion in hospitals
- Donor inconvenience and safety

Common themes

- Accurate diagnosis may improve targeting of therapy
- Alternative agents often not available:
  - Single agent rituximab for IgM associated polyneuropathy
  - Rituximab for ITP (compare the cost of low dose – 100mg flat dose, weekly x 4) with IVIg, but rituximab is not approved
  - Infliximab for Kawasaki disease (better responses than repeat IVIg in refractory patients)
- Very limited studies – lower doses may be effective, but few comparative data
- Persistence in the face of therapeutic failure, perhaps due to a lack of alternative treatment options

Updates on potential indications

IVIg in Alzheimer disease: Premise

- Accumulation of β-amyloid (Aβ) is an early, ubiquitous event in Alzheimer disease
- Thought to be integral to pathogenesis, monoclonals under investigation
- Pooled human immunoglobulin contains anti-Aβ as naturally occurring antibodies
- These have a broader range of epitopes, but lower avidity

- Mouse models suggested immunoglobulin may prevent Alzheimer disease progression, although this may be via a non-specific anti-inflammatory effect (eg. Puli et al J Neuroinflammation 2012)

- Fillit et al (Neurology 2009) showed a lower rate of Alzheimer disease in people given IVIg compared with controls (based on insurance claim data)

Table 2 Results of cognitive testing 12 and 24 months following baseline

	IVIG n=24		Placebo n=25	
	12 Months Mean±SD	24 Months Mean±SD	12 Months Mean±SD	24 Months Mean±SD
MMSE	26.04±3.76	24.00±4.91	25.38±4.28	24.46±4.79
ADAS-Cog	11.03±6.66	15.39±10.55	11.00±9.14	13.25±11.77
CDR-SB	2.70±1.63	4.33±3.48	2.65±2.13	3.37±2.73

ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale; CDR-SB, Clinical Dementia Rating-Sum of Boxes; IVIG, intravenous immunoglobulin; MMSE, Mini-Mental State Examination.

Figure 3 Kaplan–Meier survival analysis of conversion to Alzheimer's disease dementia following intravenous immunoglobulin (IVIG) or placebo.

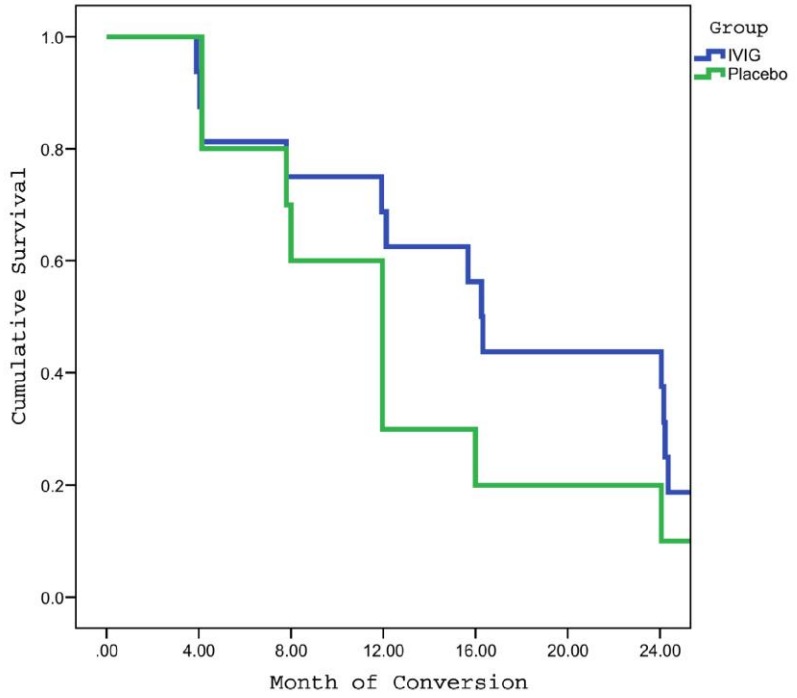
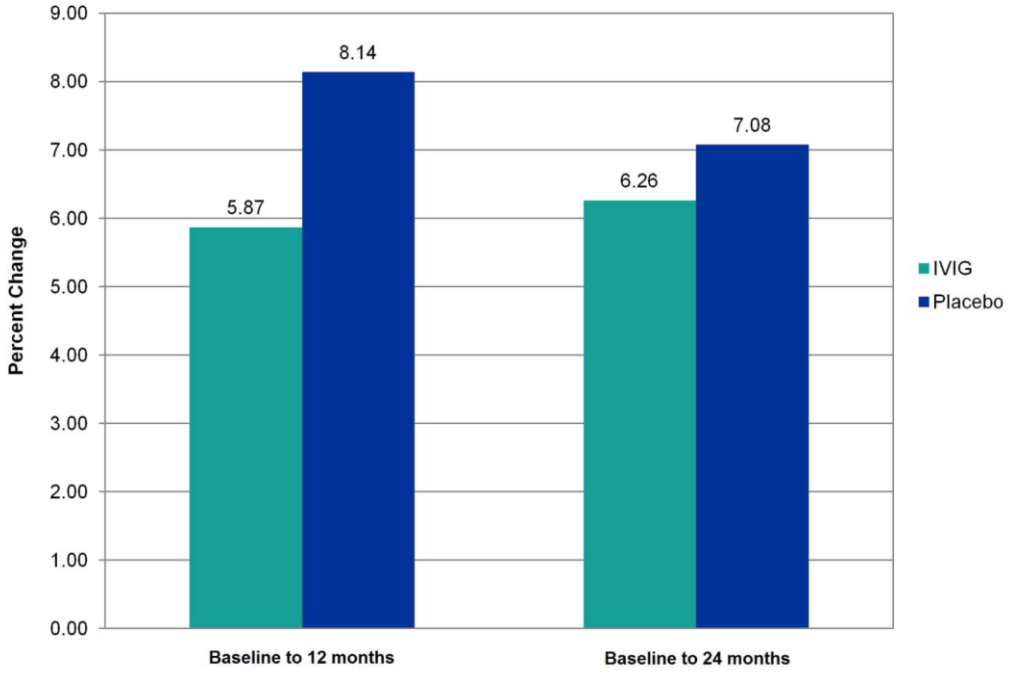


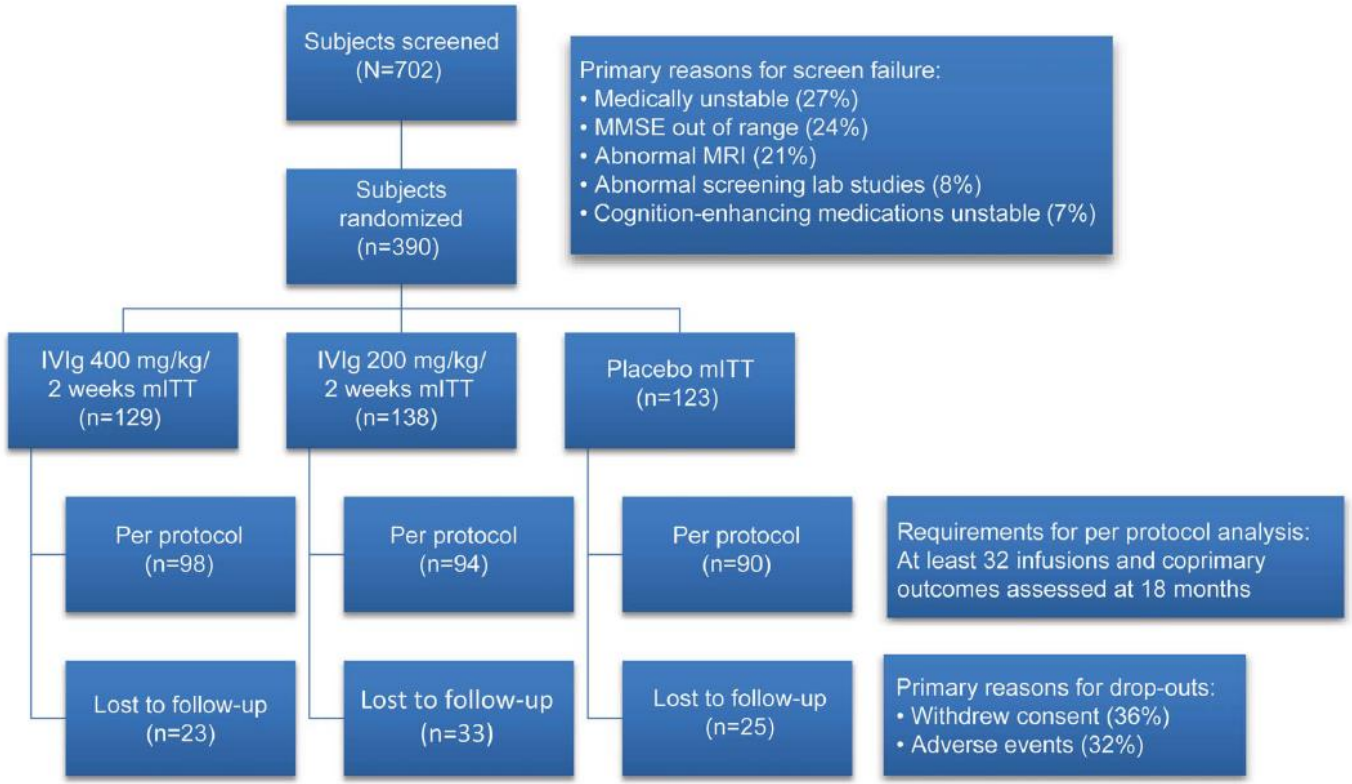
Figure 1 Brain atrophy: annualised per cent change in ventricular volume (cm^3) at 12 and 24 months following intravenous immunoglobulin (IVIG) or placebo.



- Kile S et al J Neurol Neurosurg Psychiatry 2017
- Single centre randomised saline controlled study of 2g/kg IVIg over 5 days of mild cognitive impairment to prevent progression
- Benefits at one year, not 2, in the late mild cognitive impairment group

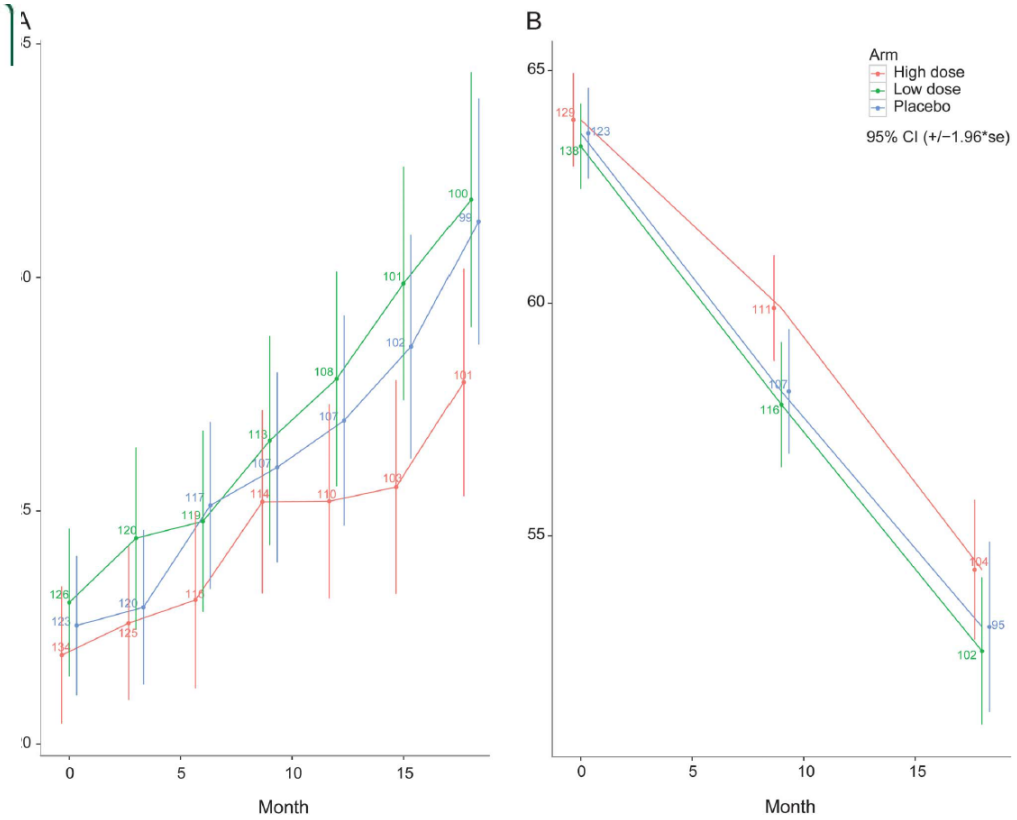
- Relkin et al Neurology 2017
- Community dwelling (with partner) AD patients with MMSE 16-26
- Concurrent NMDA or cholinesterase inhibitors allowed as long as stable for 12 weeks
- MRI consistent with AD
- Primary outcome was change in Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory

Figure 1 Participant flow



IVIg = IV immunoglobulin; mITT = modified intent to treat; MMSE = Mini-Mental State Examination.

Figure 2 Primary outcomes

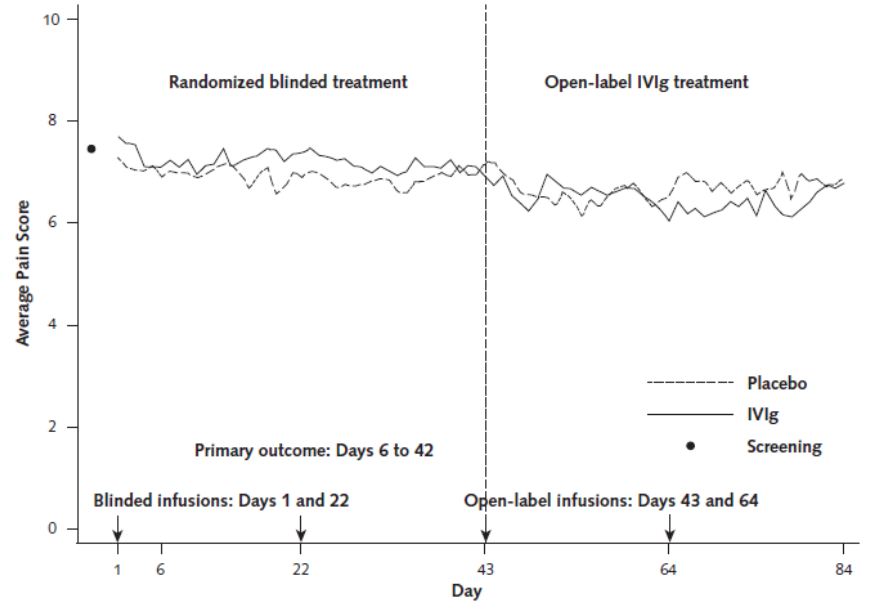


nated mean change from baseline to 18 months on the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS) (scores ranging from and higher scores indicating impairment) for the modified intent-to-treat population based on analysis of covariance analysis. No significant ces were observed. (B) Estimated mean change from baseline on the Alzheimer's Disease Cooperative Study Activities of Daily Living Scale (scores from 0 to 78 and higher scores indicate less functional impairment). Error bars indicate estimated standard errors. No significant differences were d. Numbers indicate participants contributing to the analysis at each timepoint. CI = confidence interval.

Complex regional pain syndrome

- Sensory
- Motor / trophic changes
- Swelling or sweating
- Temperature or colour changes

Figure 2. Average pain score for each day, by trial group (days 1 to 84).



- Chance finding led to a small study suggesting benefit of IVIg
- Larger RCT published Oct 2017 (Goebel et al. Ann Int Med)
- 0.5g/kg D 1 and 22 with pain measured by numeric rating scale from day 6 after each infusion

Conclusions

- Immunoglobulin has a proven therapeutic role as immune modulation therapy
- Not all conditions respond – there is a need for more studies to clarify and for potentially common indications early phase studies should be confirmed prior to adopting as standard of care.
- Not all patients respond. A better understanding of pathogenesis and attention to patient responses may lead to better targeting of scarce resource
- Emerging therapeutic options need to be considered as alternatives. Difficulty in establishing efficacy with rare diseases.

Acknowledgements

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