Immunoglobulines polyvalentes dans le traitement des maladies systémiques/autoimmunes

Luc Mouthon

Service de Médecine Interne, hôpital Cochin,

Centre de Référence Vascularites nécrosantes et sclérodermie systémique

Assistance publique-Hôpitaux de Paris, Paris

Université Paris Descartes, Inserm U1016, Institut Cochin, Paris

Conflits d'intérêt

- **Consultant**: Actelion, CSL Behring, LFB Biotechnologies, Lilly, Pfizer, Octapharma
  - Financial support to ARMIIC
- **Invertigateur**: Actelion, CSL Behring, Pfizer
- **Soutien financier (ARMIIC)**: Actelion, CSL Behring, GSK, LFB Biotechnologies, Pfizer
- **Conférence invitée**: SOBI, Roche, Actelion, CSL Behring, Octapharma, GSK, LFB Biotechnologies, Pfizer, Lilly, UCB pharma

- Depuis janvier 2014: Président du groupe d'experts de l'AP-HP, juste prescription

Intravenous immunoglobulin (IVIg)

- Normal human IgG
- Obtained from a pool of plasma of more than 1000 healthy blood donors

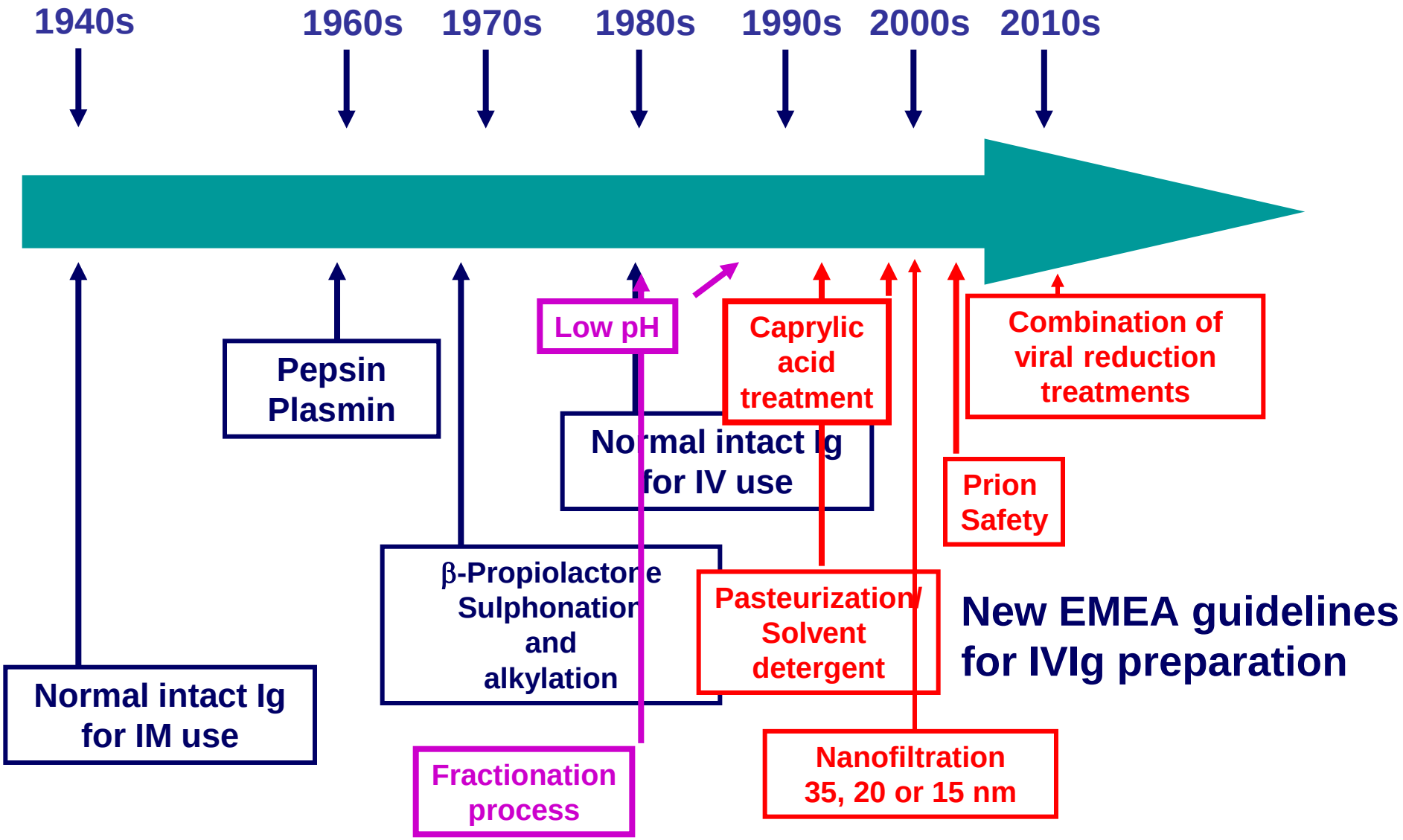
before 1980

- Indications :
  - Substitutive therapy of humoral immune deficiencies
  - Treatment of systemic inflammatory and/or autoimmune diseases

- Drug status (blood derived stable drug):
  - Since 1995

Mouthon L, Hématologie 2005

Pre-existing and purposely introduced viral reduction treatments



EMEA guidelines for the preparation of Intravenous immunoglobulin

4th edition - 2002

Plasma : pool > 1000 donnors

Security of the preparation

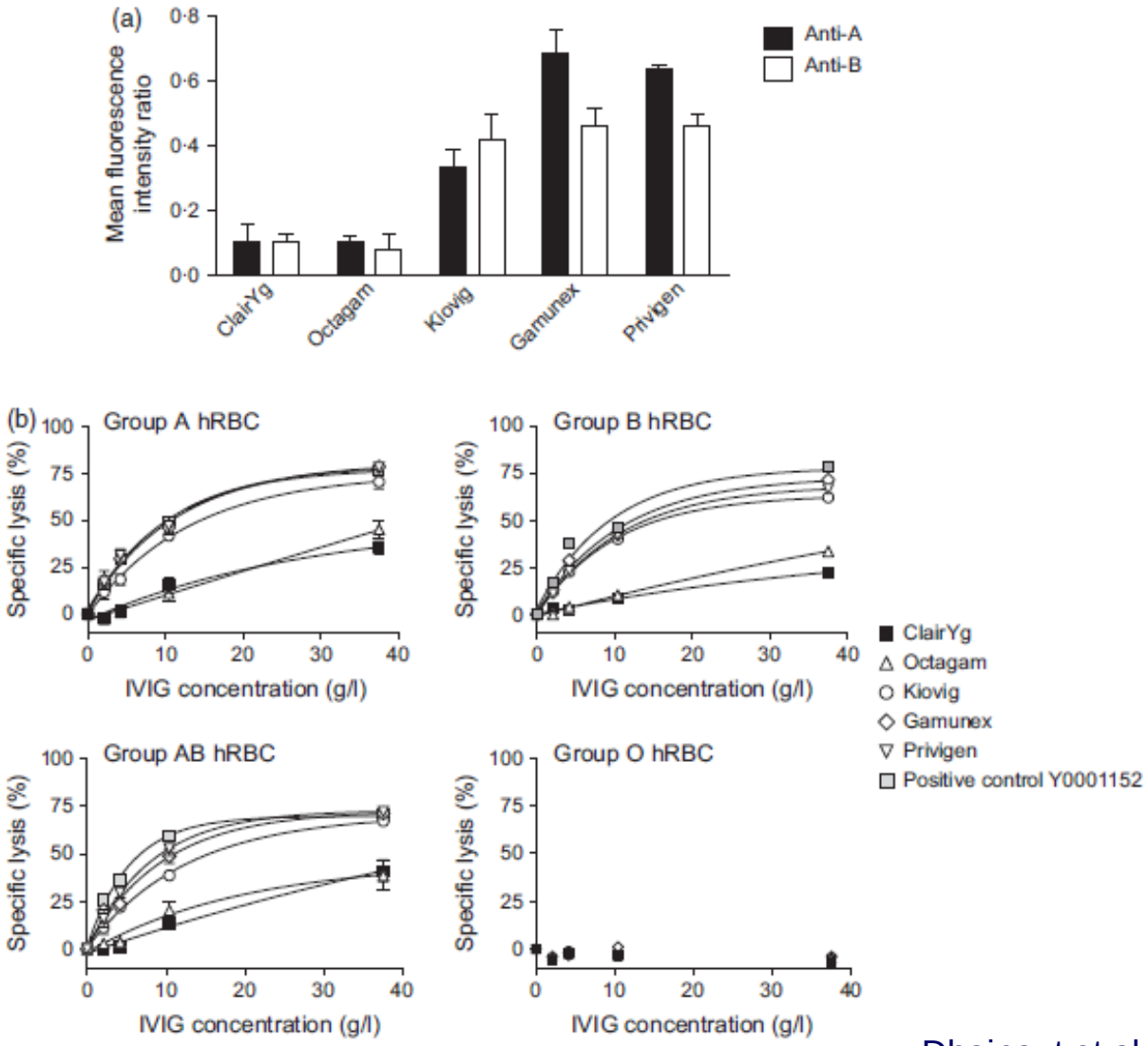
- **One or more steps to inactivate infectious agents**
- **No transmission of infection**
- **Absence of secondary effects related to products used for virus inactivation**
- **Prekallikreine activator <35 UI/ml**
- **anti-A & anti-B hemaglutinins: absence of agglutination at a dilution of 1/64**

–**Thrombin generation test**

Quality control

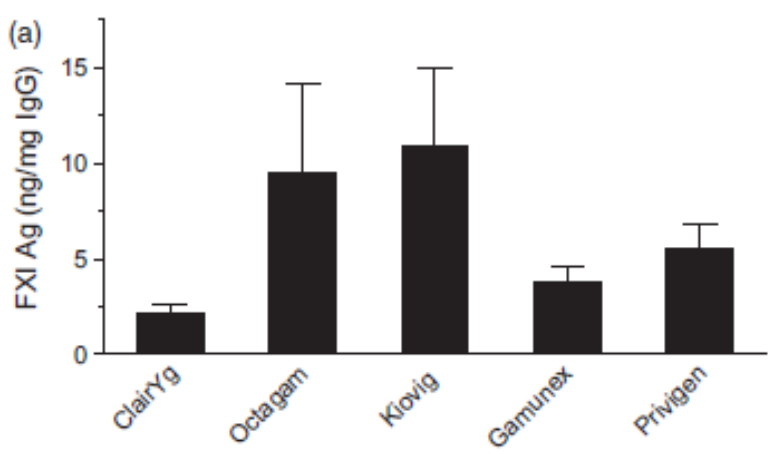
- **Anti-complement activity ≥ 50 %**
- **Total protein content ≥ 90%**
- **monomere/dimere ≥ 90 %**
- **Polymeres/agregates < 3 %**
- **≥ 2 antibodies (viral & bacterial) concentration ≥ 3 times over that of the pool of plasma**
- **distribution of IgG sub-classes identical to that of normal human plasma**
- **functional Fc portion**
- **Anti-HBs Ag Abs : titer > 0,5 UI/g of Ig**

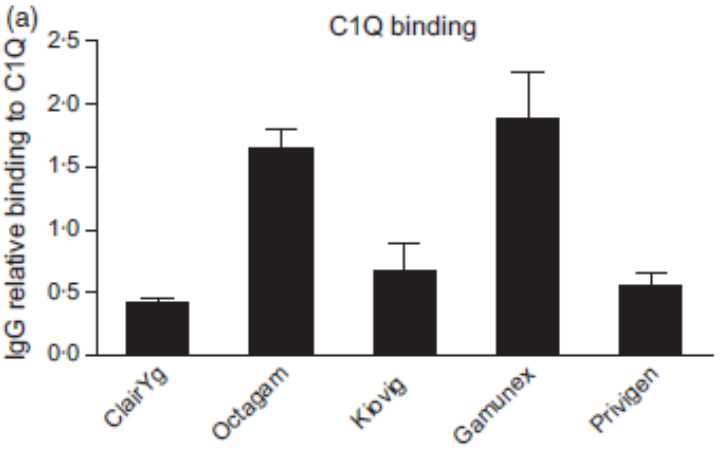
(a) Quantification of anti-A (black box) and anti-B (white box) haemagglutinins in five liquid intravenous immunoglobulin (IVIg) products tested in triplicates using flow cytometry assay

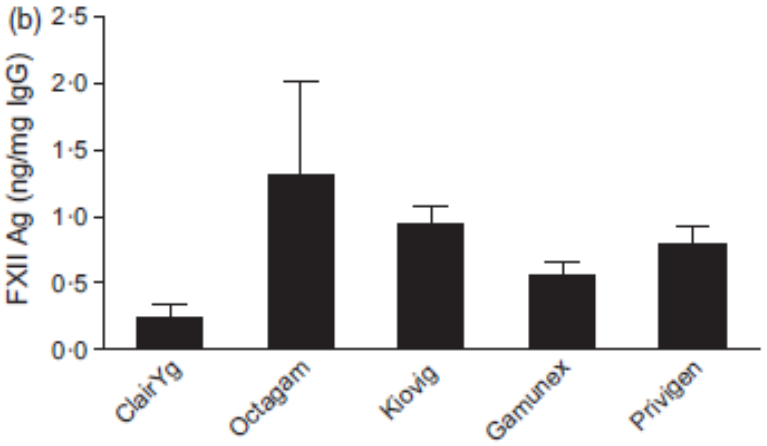


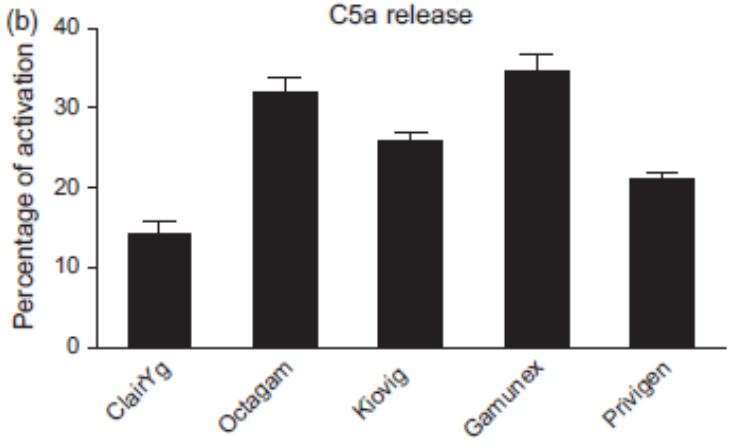
Dhainaut et al. Vox Sang 2012

Quantification of FXI Antigen and FXII Antigen in five liquid intravenous immunoglobulin products using enzyme-linked immunosorbent assay.









Dhainaut et al. Vox Sang 2012

Quel risque infectieux ?

Ig IV : transmission infections

- Virus non impliqués
  - VHA
  - VHB
  - VIH
  - Parvovirus B19

- Virus impliqués
  - VHC

  Période 1977-1994

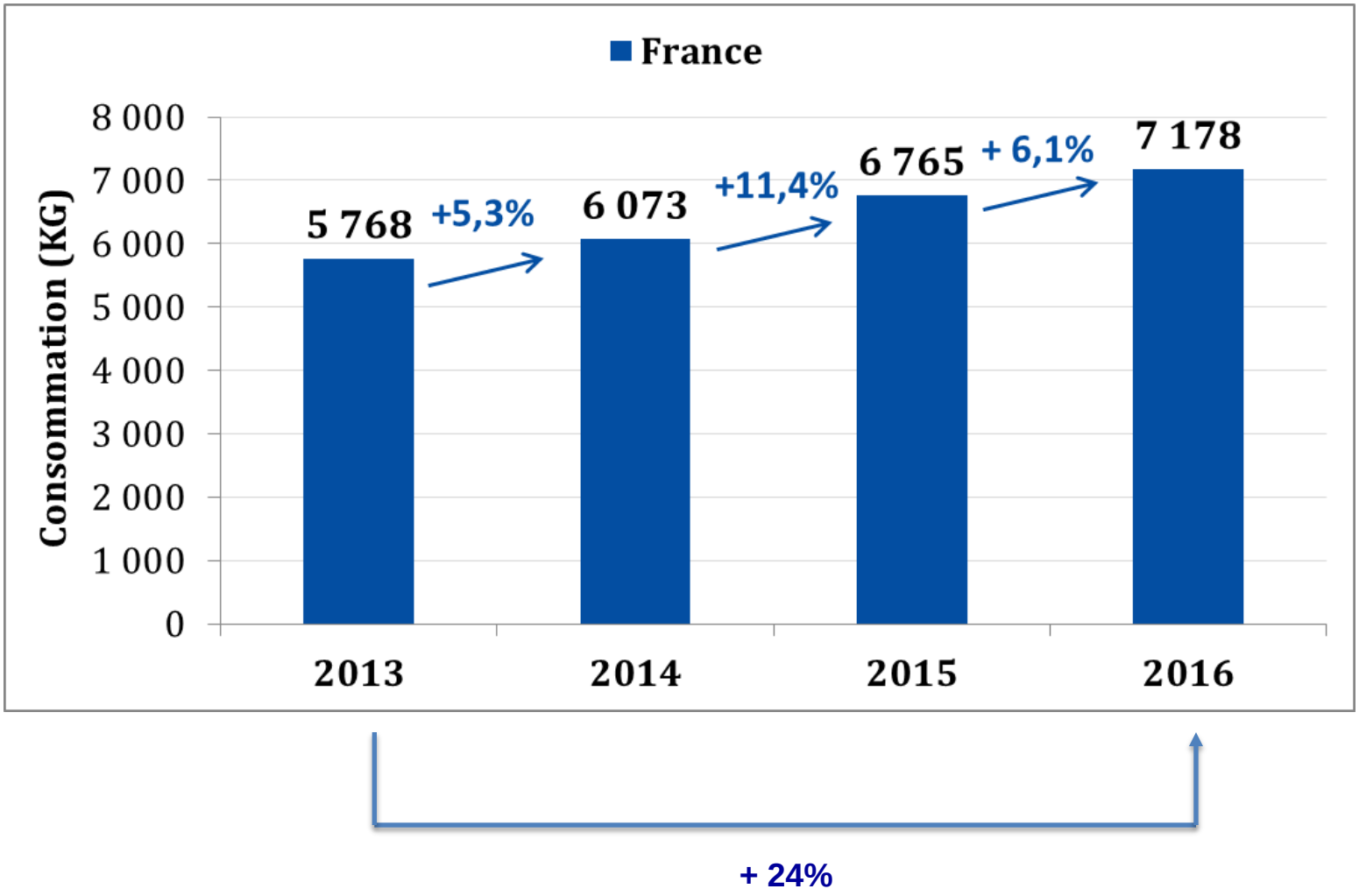
  7 produits impliqués

  450 patients concernés

Aucun cas de Kreutzfeld-Jacob décrit

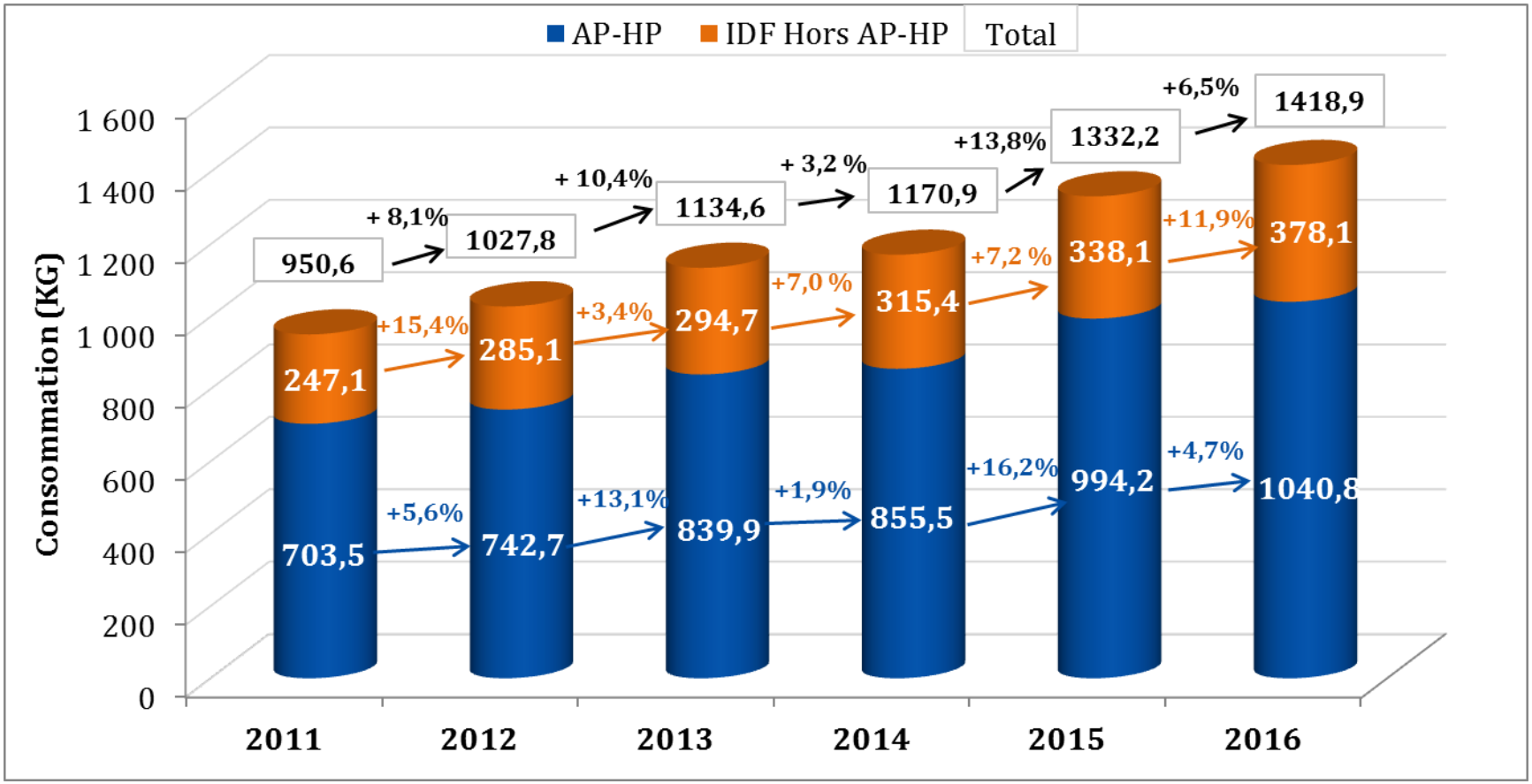
Quelle consommation ?

Evolution de la consommation des IGIV



Données PMSI

Evolution des consommations d'IGIV en IDF

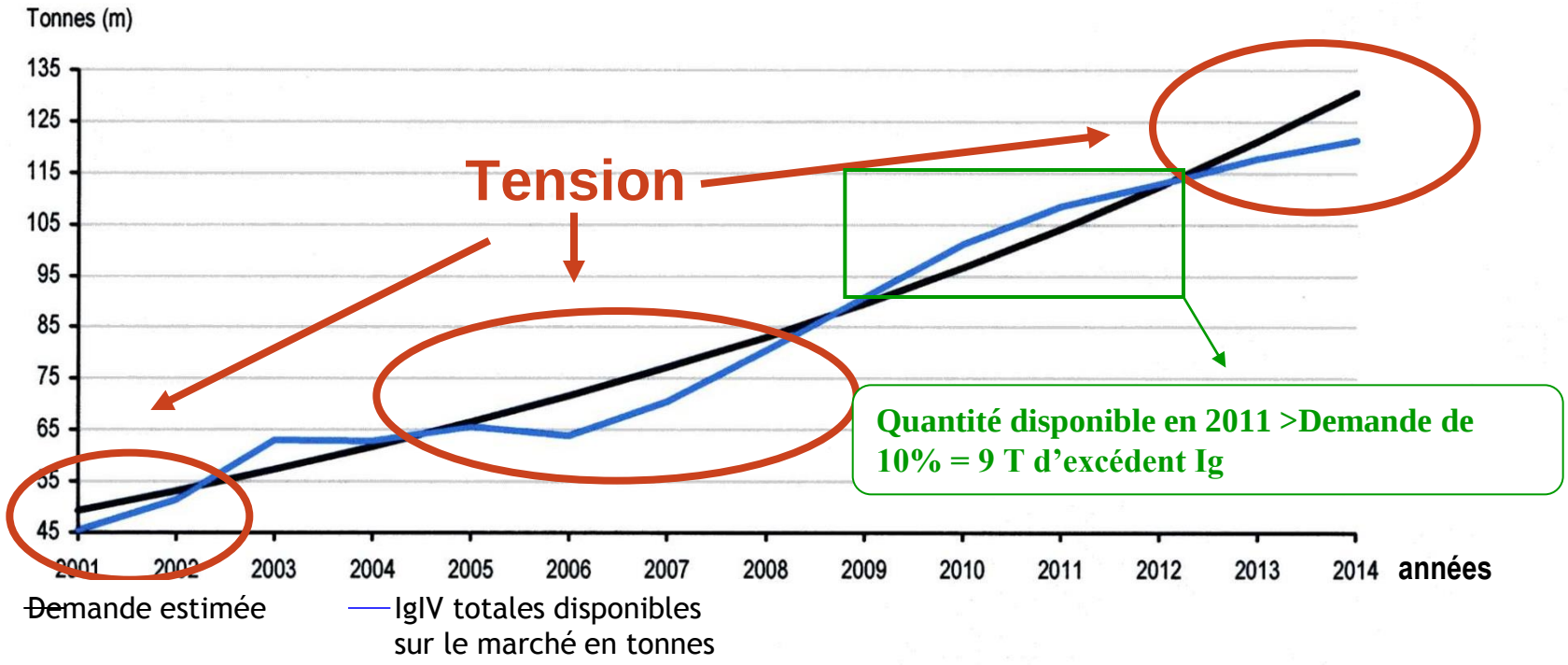


+ 49 %

Données PMSI

Le marché mondial des Ig → alternance de périodes de tension et d'approvisionnement normal

Estimation des demandes (Etats-Unis et autres pays) et des quantités disponibles en IgIV



Source: MRB, UBS estimates // Note: Examines US & EU derived IVIG vs global demand for US & EU IVIG including ROW demand (global tradable market)

Quelles préparations ?

Préparations d'IgIV disponibles sur le marché en 2016

Préparations commerciales	Laboratoire	Voie d'administration	AMM en immunomodulation
Sandoglobuline®	CSL Behring	IV	Oui
Tegeline®	LFB Biotechnologie	IV	Oui
Privigen®	CSL Behring	IV	Oui
Clairyg®	LFB Biotechnologie	IV	Oui
Octagam®	Octapharma	IV	Oui
Gammagard®	Baxalta	IV	Oui
Kiovig®	Baxalta	IV	Oui
Flebogamma	Griffols	IV	Oui
Gammanorm®	Octapharma	SC	Non
Subcuvia®	Baxalta	SC	Non
Vivaglobin®	CSL Behring	SC	Non
Hizentra®	CSL Behring	SC	Non
HyQvia	Baxalta	SC	Non

Quelles indications ?

Note for Guidance on the clinical investigation of IVIg

Substitutive therapy	Immunomodulation
- Primary humoral immune deficiencies with hypogammaglobulinemia or agammaglobulinemia :	- Immune thrombocytopenic purpura in children and adults with high risk of bleeding or before surgery
• X-linked agammaglobulinemia / constitutive hypogammaglobulinemia • Common variable immune deficiency • Severe combined immune deficiency • Wiskott Aldrich syndrome	-Guillain-Barré syndrome -Kawasaki disease
- Multiple myeloma and CLL with severe hypogammaglobulinemia and recurrent infections	
Bone marrow allograft	

Note for Guidance on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg). The European Agency for the Evaluation of Medicinal Products CPMP/BPWG/388/95 rev. 1

Group I (recognized) (I): authorized and/or scientifically validated

- Primary immune deficiencies with defective antibody production, including bone marrow allograft in patients with primary immune deficiencies #
- Secondary immune deficiencies with defective antibody production, including chronic lymphocytic leukemia and multiple myeloma with recurrent infections #
- Children HIV infection associated with recurrent bacterial infections #

Last update : June 2011

 # : Randomized controlled study

The effect of two different dosages of IVIg on the incidence of recurrent infections in patients with primary hypogammaglobulinemia.

A randomized, double-blind, multicenter crossover trial.
Eijkhout HW et al. Ann Intern Med 2001;135:165-74.

- **High dose IVIg (adults, 0.6 g/kg/4 week; children, 0.8 g/kg/4 week) together with reduction of the number and severity of infections in comparison to "standard" dose (adults, 0.3 g/kg/4 week; children, 0.4 g/kg/4 week)**
- **Increased serum IgG from 6.5 g/l (low dose) to 9.4 g/l (high dose).**
- **Objective: 8 g/l residual IgG**

Guidelines for supportive care in multiple myeloma 2011

John A. Snowden,[1] Sam H. Ahmedzai,[2] John Ashcroft,[3] Shirley D'Sa,[4] Timothy Littlewood,[5] Eric Low,[6] Helen Lucraft,[7] Rhona Maclean,[1] Sylvia Feyler,[8] Guy Pratt[9] and Jennifer M. Bird[10] On behalf of the Haemato-oncology Task Force of the British Committee for Standards in Haematology and UK Myeloma Forum

Recommendations

- Vaccination against influenza, *Streptococcus pneumonia* and *Haemophilus influenzae* is recommended but efficacy is not guaranteed (Grade C recommendation; level IV evidence).
- Prophylactic immunoglobulin is not routinely recommended but may be useful in a small sub-set of patients with severe, recurrent bacterial infections and hypogammaglobulinaemia (Grade C recommendation; level IV evidence).
- Prophylactic aciclovir is recommended for patients receiving bortezomib therapy, following autologous stem cell transplantation or patients with recurrent herpetic infections (Grade C recommendation; level IV evidence).

IVIg in prophylaxis of infections in multiple myeloma and CLL

- « Validated » 25 years ago
- Only in multiple myeloma and CLL
- No benefit in patients undergoing autologous SCT for multiple myeloma
- No RCT in the modern area
- No RCT comparing IVIg to antibiotic prophylaxis (cross over)
- Discuss IVIg after failure of antibiotic prophylaxis

A multicenter, randomized, double-blind comparison of different doses of IVIg for prevention of GVHD and infection after allogeneic BMT.

Winston DJ et al. Bone Marrow Transplant 2001;28:187-96.

- **Multicenter, randomized, double-blind trial, comparing doses of 0.1 g/kg, 0.25 g/kg, or 0.5 g/kg of IVIg weekly for 90 days and then monthly until 1 year after grafting.**
- **No significant difference (frequency of acute or chronic GVHD, infection and interstitial pneumonia, types of infection, relapse of hematological malignancy or survival)**
- **More frequent minor secondary effects in the high dose group.**

Recommandations Afssaps (06/05/08) de priorisation des indications des IgIV en situation de tension forte sur les approvisionnements pour le marché français (I)

	Indications AMM
Indications prioritaires (A)	- DIP avec défaut de production d'Ac, y compris allogreffe de cellules souches hématopoïétiques chez DIP - Maladie de Kawasaki - PTI de l'enfant et de l'adulte avec syndrome hémorragique viscéral (nouveau)
Indications à réserver aux urgences vitales et/ou en cas d'échec des alternatives (B)	- DIS avec défaut de production d'Ac, en particulier la LLC ou le myélome associés à des infections à répétition - Infection de l'enfant par le VIH associé à des infections bactériennes - Neuropathies motrices multifocales - PTI de l'enfant et de l'adulte - Syndrome de Guillain-Barré de l'adulte
Indications non prioritaires (pouvant attendre la fin de la pénurie)©	- Rétinochoroïdopathie de Birdshot

Ig sous cutanées

- 2006: AMM obtenue par trois préparations d'IgSC dans le traitement substitutif des déficits immunitaires primitifs et des déficits immunitaires secondaires

Ig sous cutanées DIS
Etude d'efficacité chez 17 malades ayant un déficit immunitaire secondaire (dont 14 LLC).

- **Les taux moyens d'IgG augmentent significativement sous Ig sc et on note une diminution significative du nombre de jours passés à l'hôpital, du nombre d'admissions et du nombre de traitements antibiotiques.**
- **Cependant, aucune efficacité n'est notée chez 6 des 17 patients, alors que les taux résiduels d'IgG moyens sous traitements sont relativement faibles (5.3 g/l).**
- **De façon importante, ces malades étaient neutropéniques et sous cytostatiques.**
- **Il n'est pas fait mention précisément des comorbidités ou du traitement chimiothérapique associé. Il n'est pas même fait mention de l'âge des malades.**

Hammarstrom, Lancet 1995

Revision of the note for Guidance on the clinical investigation of IVIg

European medical agency meeting
5-6 July 2006

- Addition ?
  - Acute myasthenia gravis Yes ?
  - Chronic inflammatory polyradiculoneuritis Yes ?
  - Multifocal motor polyneuropathy with conduction blocks Yes ?
  - Corticoresistant dermatomyositis No

- Modification ?
  - Secondary immune deficiencies Yes (AB) ?
  - Severe sepsis in neonates No

- Removal ?
  - Bone marrow allograft No

European medical agency meeting
5-6 July 2006

- Addition ?
  - Acute myasthenia gravis Yes? XXX
  - Chronic inflammatory polyradiculoneuritis Yes? XXX
  - Multifocal motor polyneuropathy with conduction blocks Yes? XXX
  - Corticoresistant dermatomyositis No

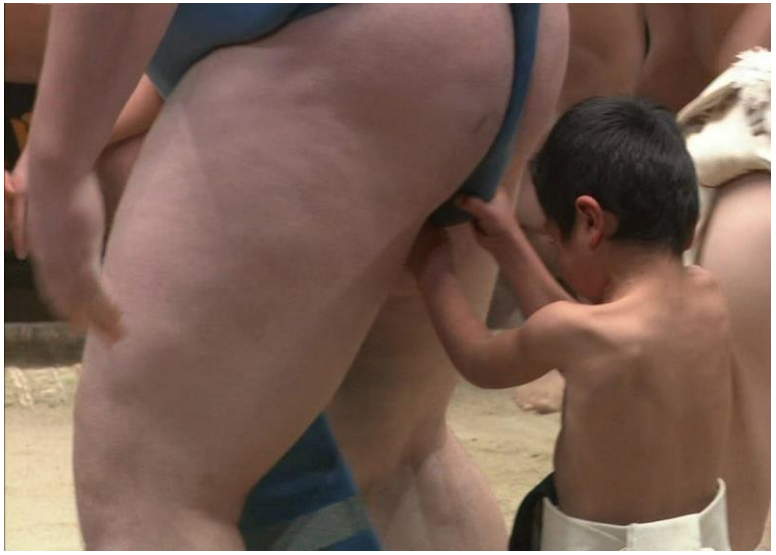
- Modification ?
  - Secondary immune deficiencies Yes? XXX (AB)?
  - Severe sepsis in neonates No

- Removal ?
  - Bone marrow allograft No

Revision of the note for Guidance on the clinical investigation of IVIg: 2006 issue (I)

Revision of the note for Guidance on the clinical investigation of IVIg: 2006 issue (II)

Revision of the note for Guidance on the clinical investigation of IVIg: 2018 issue



Evolution du core SPC

Note for Guidance on the clinical investigation of IVIg: proposition of modification (I)

Replacement therapy:

- Primary immunodeficiency syndromes with impaired antibody production.

- Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent bacterial infections, ineffective antibiotic treatment and either proven specific antibody failure (PSAF)* or serum IgG level of < 4 g/l

* PSAF= failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines

- Children and adolescents with congenital AIDS and recurrent bacterial infections.
- Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation (HSCT).
- **Yes if fulfilling previous recommendations**

Group I (recognized) (II): Authorized and/or scientifically validated)

- ***Immunologic thrombocytopenic purpura (ITP) in adults and children*** #
- ITP associated with HIV infection
- ***Kawasaki disease*** #
- Corticoresistant dermatomyositis #
- Myasthenia gravis #

*** Authorized in France**

 # : Randomized controlled study

Last update : June 2011

IVIg for the treatment of Kawasaki disease in children

- 16/59 randomized controlled studies analyzed
- Significant decrease of the occurrence of new coronary abnormalities at day 30 (RR 0.74 (0.61-0.90)).
- Meta-analysis IVIg 0,4 g/kg/d 5 d vs 2 g/kg 1 d: significant reduction of the number of coronary aneurysms at day 30 (RR4,47 (1.55-12.86))
- Patients with no coronary aneurysm at diagnosis: significant reduction of new aneurysms (RR 0.67 (0.46-1)
- **Conclusion: children fulfiling diagnosis criteria for Kawasaki disease must be treated with IVIg 2 g/kg single dose within 10 days after the first symptom**

Cochrane database Syst Rev 2003; 4 CD004OOO

Myasthenia Gravis exacerbation

- Randomised study comparing plasma exchanges to IVIg
- 87 patients: acute myasthenia gravis
  - 41 received three PE
  - 46 received 0.4 g/kg/d IgIV (50% 3 d, 50% 5 d).
- Similar efficacy as assessed by the myasthenia gravis muscle score
- Better tolerance of IVIg
- IgIV : alternative therapy to plasma exchanges in the treatment of myasthenia gravis

- Another prospective randomized trial in 173 patients found no difference between 1 g/kg and 2 g/kg IVIg infusion

Gajdos P., et al. Ann Neurol 1997; 41: 789-796
Gajdos P et al. Arch Neurol 2005; 62: 1689-93

Group I (recognized) (III): authorized and/or scientifically validated

- ***Guillain-Barré syndrome in adults*** # and children #
- ***Chronic demyelinating polyneuropathy*** # *****,*** including the Lewis & Sumner syndrome
- ***Multifocal motor polyneuropathy with conduction blocks*** # *
- Stiff person syndrome #

*** Authorized in France**

 # : Randomized controlled study

Last update : June 2011

[Intervention Review]

Intravenous immunoglobulin for Guillain-Barré syndrome

Richard AC Hughes[1], Anthony V Swan[2], Pieter A van Doorn[3]

- A previous Cochrane review has shown that plasma exchange (PE) hastens recovery compared with supportive treatment alone.
- There are no adequate comparisons of IVIg with placebo in adults but this review provides moderate quality evidence that, in severe disease, IVIg started within two weeks from onset hastens recovery as much as PE.
- Adverse events were not significantly more frequent with either treatment but IVIg is significantly much more likely to be completed than PE.
- Also according to moderate quality evidence, giving IVIg after PE did not confer significant extra benefit.
- In children, according to low quality evidence, IVIg probably hastens recovery compared with supportive care alone.
- More research is needed in mild disease and in patients whose treatment starts more than two weeks after onset. Dose-ranging studies are also needed

Cochrane Database of Systematic Reviews 2010, Issue 6. Art. No.: CD002063.

Motor multifocal neuropathy with conduction blocks

- Four prospective randomized trials vs placebo evidenced a significant improvement of motor deficiency

- Meta-analysis: muscle strenght improved in 78% of patients who received IVIg vs 4% of patients who received placebo

Azulay, 1994;
Van den Berg, 1995;
van den Berg-Vos, 2002;
Leger, 2001;
Federico, 2000;
van Schaik, 2005

Chronic inflammatory demyelinating polyneuropathy

8 RCTs, including 332 participants
5 (n=235) compared IVIg against placebo
1 (n=20) compared IVIg with PE
1 (n=32) compared IVIg with prednisolone
1 (n=46) compared IVIg with IV methylprednisolone

CONCLUSIONS

IVIg improves disability for at least 2 to 6 weeks compared with placebo, with an NNTB of 3. During this period efficacy was similar to plasma exchange, oral prednisolone and IV methylprednisolone.
In one large trial, the benefit of IVIg persisted for 24 and, possibly, 48 weeks.
Further research is needed to compare the long-term benefits as well as side effects of IVIg with other treatments.

Long term cost benefit studies are needed

Eftomov F et al. Cochrane Database Syst Rev. 2013

Evolution du core SPC

Note for Guidance on the clinical investigation of IVIg: proposition of modification (II)

Immunomodulatory effect in:

- Primary immune thrombocytopenia*(ITP) in patients at high risk of bleeding or prior to surgery to correct the platelet count
- Guillain Barré Syndrome (GBS)
- Kawasaki disease
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Multifocal motor neuropathy (MMN)

Group I (recognized) (IV): authorized and/or scientifically validated

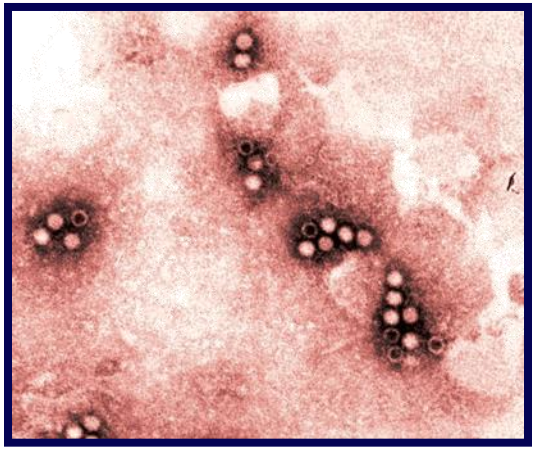
- Acute or chronic severe parvovirus B19 infections in patients with primary or secondary immune deficiencies §
- ***Birdshot rétinochoroïdopathy****

§ : ongoing retrospective study
*** Authorized in France**
 # : Randomized controlled study

Last update : June 2011

Parvovirus B19 infection: IVIg therapy

Mouthon et al. Autoimmun rev, 2006

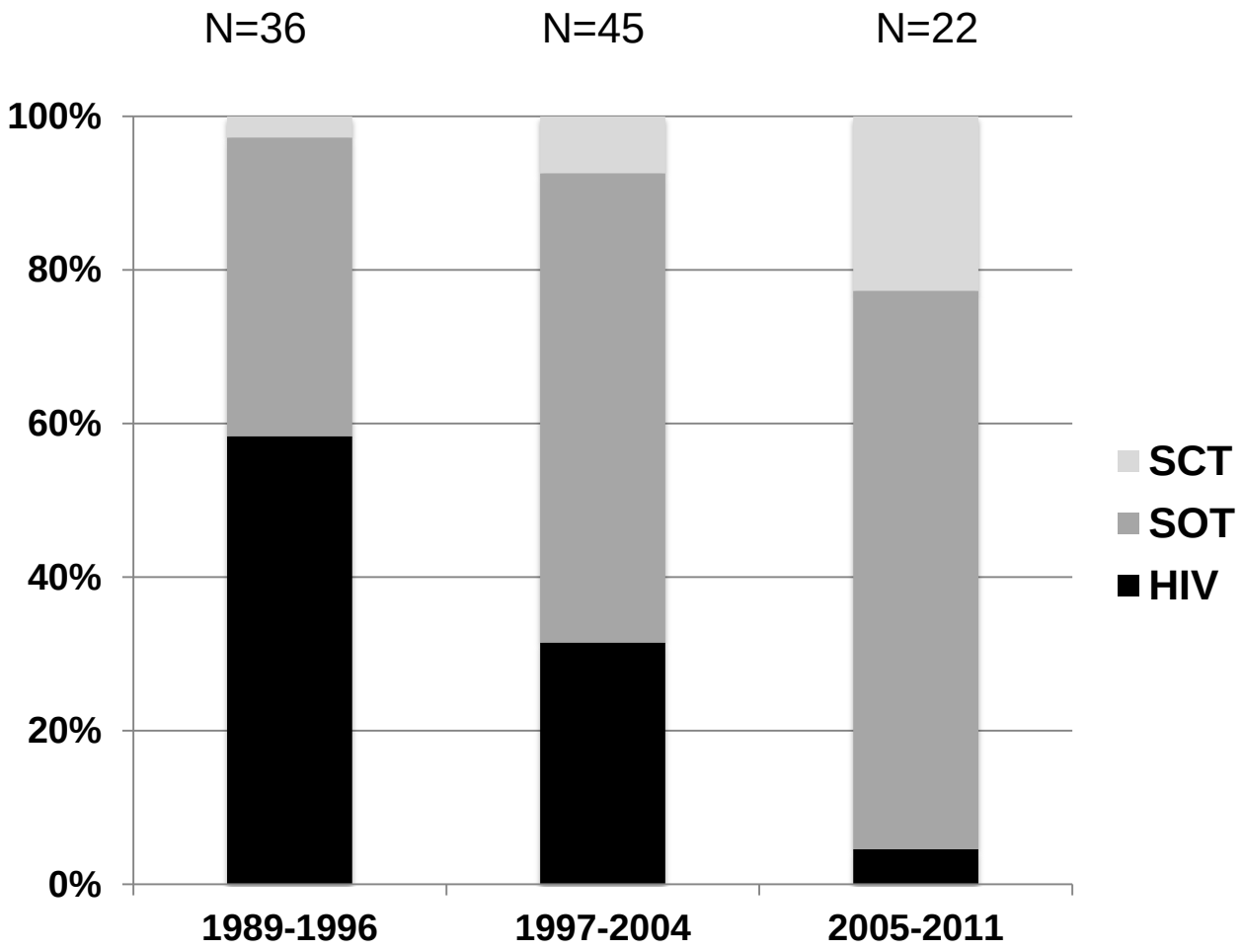


IVIg : privileged source of anti-parvovirus B19 Ab

IVIg treatment:

- Severe anemia secondary to chronic *Parvovirus B19* infection.
  - Solid organ transplantation (kidney, heart/lung)
  - Primary antibody deficiency (hyper-IgM syndrome, CVID)
  - HIV infection (CD4 < 80/mm3 relapse; efficacy of HAART without IVIg)

Distribution from 1989 to 2011 of HIV, solid-organ transplant (SOT) and stem cell transplantation (SCT) among 133 patients with HPV-B19 infection associated with PRCA treated with IVIg.



Crabol et al. Clin Infect Dis 2013.

AFSSAPS Recommandations for IVIg treatment in tension situation on the French market (I)

	Group 1. Licensed indications (AMM)
Prioritary indication (A)	- PID with defective Ab production, including stem cell transplantation in patients with PID - Kawasaki disease - ITP in children and adults with visceral hemorrhage
Indications reserved to vital emergencies and/or in case of failure of alternative treatment (B)	- Secondary ID with defective Ab production, mainly CLL and multiple myeloma associated with recurrent infections - HIV infection in children with recurrent bacterial infections - Motor multifocal neuropathy - ITP in children and adults - Guillain-Barré syndrome in adults
Non prioritary indications (can wait the end of shortage)	- Birdshot Retinochoroïdopathy

AFSSAPS Recommandations for IVIg treatment in « shortage » situation on the French market (II)

	Groupe I non licensed indications (no AMM)
Prioritary indication (A)	- Guillain & Barré in children - Chronic PVB19 infection in patients with immune deficiency
Indications reserved to vital emergencies and/or in case of failure of alternative treatment (B)	- Corticoresistant dermatomyositis - Acute Myasthenia gravis - Chronic inflammatory demyelinating polyradiculoneuropathy - ITP associated with HIV infection - Stiff man syndrome
Non prioritary indications (can wait the end of shortage)	

Group II (under evaluation) (II)

- Inclusion body myositis with esophagus involvement
- Demyelinating central nervous system except multiple sclerosis and Devic syndrome
- Corticoresistant polymyositis
- Autoimmune encephalitis including Rasmussen
- Epilepsia refractory to treatment in children

Last update : June 2011

 # : Randomized controlled study

Group II (under evaluation) (III)

- Acquired hypocoagulability secondary to anti-Factor VIII or anti-von Willebrand factor autoantibodies
- Adult onset Still's disease
- Anti-phospholipid syndrome, in the absence of efficacy of anticoagulants
- ANCA-positive systemic vasculitides #
- Corticoresistant pemphigus vulgaris

§ : ongoing prospective study

 # : Randomized controlled study

Last update : June 2011

Group II (under evaluation) (IV)

- Recurrent abortions of the first trimestre #
- Prophylaxis of kidney graft rejection in hyperimmunized patients
- Acute rejection in patients undergoing kidney transplantation
- Prophylaxis of acute rejection in patients undergoing kidney transplantation
- Perinatal hemochromatosis
- Platelet alloimmunisation

Last update : June 2011

 # : Randomized controlled study

AFSSAPS Recommandations for IVIg treatment in « shortage » situation on the French market (III)

	Groupe II
Prioritary indication (A)	
Indications reserved to vital emergencies and/or in case of failure of alternative treatment (B	-Adult onset Still's disease -ANCA-positive systemic vasculitides -Corticoresistant polymyositis - APLS in the absence of efficacy of anti-coagulation therapy - Epilepsia in childhood: refractory cases in children - Autoimmune encephalitis including Rasmussen - Demyelinating conditions of the CNS except multiple sclerosis and Devic - Renal transplantation : curative treatment of acute humoral rejection - Renal transplantation : prophylactic treatment of acute humoral rejection - Inclusion body myositis with esophagus involvement

Temporary therapeutic protocols

- Acute Myasthenia gravis
- Lambert-Eaton syndrome
- Corticoresistant polymyositis
- Corticoresistant dermatomyositis
- Chronic inflammatory polyradiculoneuropathy
- Miller-Fisher syndrome
- Stiff man syndrome
- Acquired Willebrand disease
- ANCA-associated vasculitis (first relapse)
- Catastrophic anti-pholpholipid syndrome
- Inclusion body myositis with severe dysphagia
- Prophylaxis of kidney graft rejection in hyperimmunized patients
- Acute rejection in patients undergoing kidney transplantation
- Prophylaxis of acute rejection in patients undergoing kidney transplantation

- Acute or chronic severe parvovirus B19 infections (about to start)

Quels critères et facteurs d'efficacité ?

Critères et facteurs d'efficacité des IgIV

- Dépendants de l'hôte: récepteurs Fc
- Dépendants de l'immunodépression du patient
- Dépendant de la pathologie
  - Données de la littérature
  - Alternatives thérapeutiques
  - Traitements combinés
- Dépendant de la dose
- Dépendant des préparations d'IgIV

TDT and pseudosimpling based case-control analysis of activating FcgR gene variants among IVIg responding and IVIg non-responding Kawasaki patients in three racial groups

	IVIG Responders				IVIG non-responders			
	TDT statistics		Pseudosibling case-control†		TDT statistics		Pseudosibling case-control†	
Genes & Polymorphisms	Informative families*	z-statistics (p-value)	OR (95% CI)	p	Informative families*	z-statistics (p-value)	OR (95% CI)	p
FcγRIIA-131H/R								
All	115	**+2.1 (0.04)**	**1.40 (1.01–1.95)**	**0.04**	41	**+1.81 (0.07)**	1.72 (0.96–3.08)	0.07
Caucasians	67	+0.97 (0.33)	1.24 (0.81–1.90)	0.33	21	+0.76 (0.45)	1.33 (0.63–2.82)	0.45
Asians	17	**+2.40 (0.02)**	**4.00 (1.34–11.96)**	**0.01**	-	-	4.00 (0.45–35.79)	0.21
FcγRIIIA-158V/F								
All	108	−0.25 (0.80)	1.00 (0.72–1.39)	1	40	+1.48 (0.14)	1.5 (0.83–2.72)	0.18
Caucasians	67	+0.43 (0.67)	1.10 (0.72–1.68)	0.67	22	+0.82 (0.41)	1.4 (0.62–3.15)	0.42
Asians	19	**−2.04 (0.04)**	**4.00 (1.34–11.96)**	**0.01**	-	-	-	-
FcγRIIIB-NA1								
All	95	+1.51 (0.13)	1.28 (0.89–1.82)	0.18	34	**+3.70 (0.0002)**	**3.67 (1.75–7.66)**	**0.0006**
Caucasians	48	+1.21 (0.23)	1.29 (0.79–2.10)	0.32	20	**+2.71 (0.007)**	**3.6 (1.34–9.70)**	**0.01**
Asians	22	+0.82 (0.41)	2.14 (0.87–5.26)	0.10	-	-	-	-

* TDT statistics was only performed where there were 10 or more informative families;

† OR (additive) based on the genotype of the KD patients and pseudosibling controls derived from the 3 alternate genotypes based on the untransmitted alleles

- FCγRIIIB-NA1 haplotype is excessively transmitted to non-IVIg responding patients
- Phenotyping could predict IVIg response and help to decide whether alternative forms of treatment would be beneficial.

Sheta S et al. Dis Cardiovasc Genet 2012

Intérêt et limites des IgIV?

Intérêt et limites des IgIV dans les MAI: non liés à la pathologie ou a l'individu

Intérêts

- Très bonne tolérance
- Pas de transmission d'agent infectieux
- Efficacité dans un grand nombre de pathologies
- Ne majore pas l'immunodépression
- Restaure l'homéostasie du système immunitaire

Limites

- Coût (30-55 euros/gramme)
- Matière première (plasma) épuisable: difficultés approvisionnement
- Produit stable dérivé du sang: risque infectieux
- Différences entre préparations
- Voie d'administration: nécessité d'un abord veineux
- Nombre limité de pathologies ayant une AMM

Immunomodulation with subcutaneous Ig

Long-term therapy with high doses of subcutaneous immunoglobulin in multifocal motor neuropathy

Thomas Harbo, Henning Andersen and Johannes Jakobsen

Neurology 2010;75;1377
DOI 10.1212/WNL.0b013e3181f735ce

Contents lists available at ScienceDirect

Autoimmunity Reviews **2010**

journal homepage: www.elsevier.com/locate/autrev

Review

Subcutaneous immunoglobulin in polymyositis and dermatomyositis: A novel application

Maria Giovanna Danieli [a,*], Lucia Pettinari [a], Romina Moretti [a], Francesco Logullo [b], Armando Gabrielli [a]

[a] *Clinica Medica, Dipartimento di Scienze Mediche e Chirurgiche, Università Politecnica delle Marche & Ospedali Riuniti, Ancona, Italy*
[b] *Clinica Neurologica, Università Politecnica delle Marche & Ospedali Riuniti, Ancona, Italy*

Quelle tolérance ?

Ig IV: Réactions d'intolérance 1

- Effets indésirables habituels
  - Fréquence: 0,5 à 3 %
  - Manifestations : céphalées, nausées, fièvre, vomissements, frissons
  - Plus rares : fatigue, HTA, tachycardie, douleurs abdominales, oppression thoracique, dyspnée, myalgies
- Conduite à tenir
  - Gravité toujours modérée
  - Réduction ou arrêt temporaire de la perfusion

Ig IV: Réactions d'intolérance 2

- Réactions d'hypersensibilité
  - Réactions anaphylactiques: Ac anti-IgA
  - Fréquence: 0,1 %
  - DICV - déficit en IgG2
  - Rash; choc
  - Prévention si déficit complet en IgA
- Réactions anaphylactoïdes
  - Moins sévères
  - Rôle des agrégats Ig

Ig IV: complications rares

- Insuffisance rénale aigue
- Méningite aseptique
- Thrombose
- Hémolyse

➢ Les préparations d'IgIV sont très bien tolérées

IgIV: risque d'insuffisance rénale

Dose/débit dépendant

- Sujet de plus de 65 ans
- Hyperviscosité
- Hypovolémie
- Antibiotiques néphrotoxiques
- Diurétiques
- Obésité
- Insuffisance rénale
- Diabète
- Hypertension artérielle

IgIV: modifications des tests biologiques

- Hyponatrémies : fausses hyponatrémies (hyperprotidémie au moment de la perfusion).

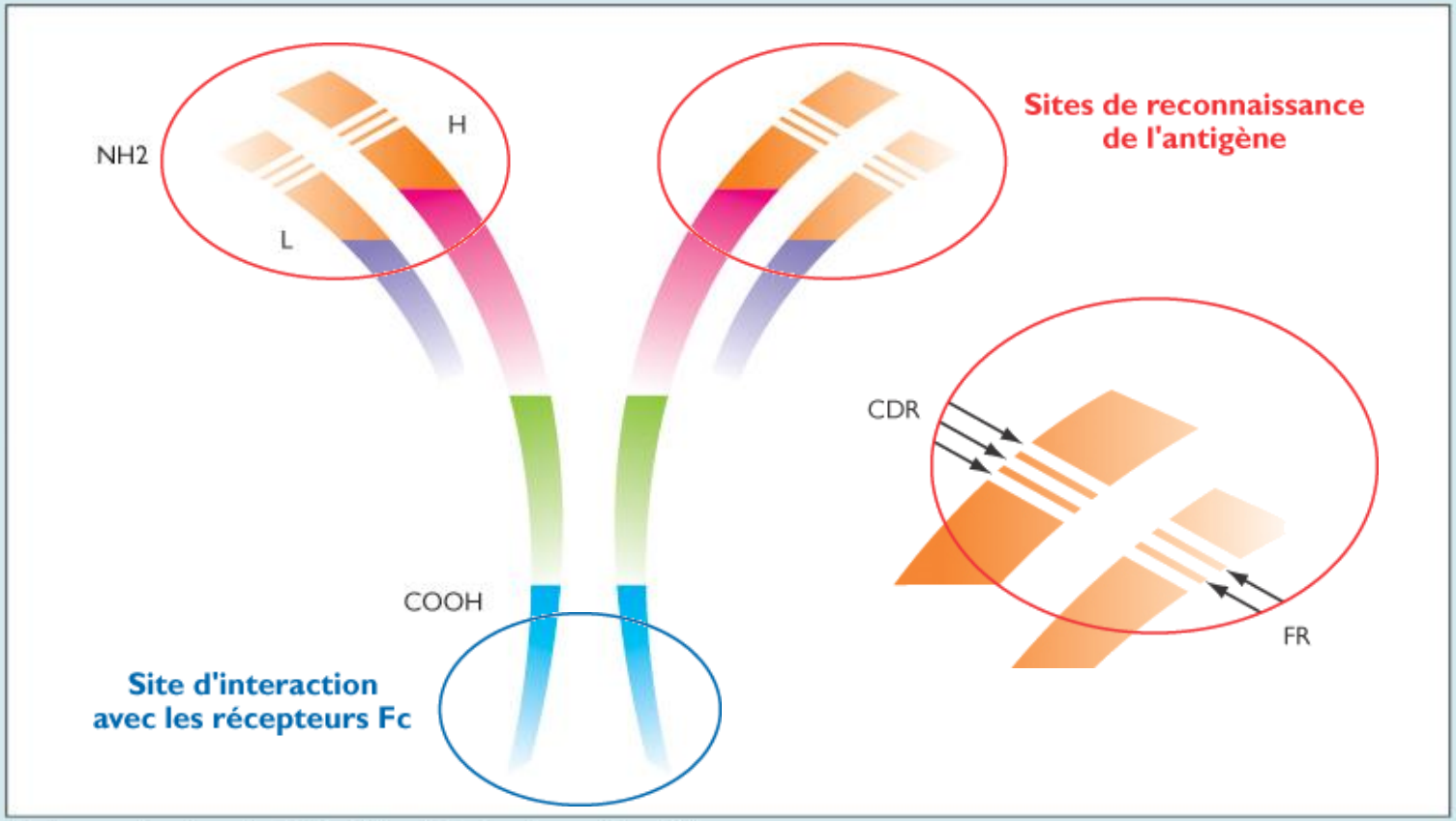
•Augmentation de la vitesse de sédimentation (formation accrue de rouleaux). Peut persister pendant 2 à 3 semaines après la perfusion.

•Positivation transitoire de certaines sérologies pendant une période pouvant aller jusqu'à trente jours après la perfusion.

Quels mécanismes d’action ?

Structure of normal human IgG

Pr Luc MOUTHON - Service de Médecine Interne - Hôpital Cochin - Université Paris V



FR : Framework = charpente - CDR : Régions déterminant la complémentarité

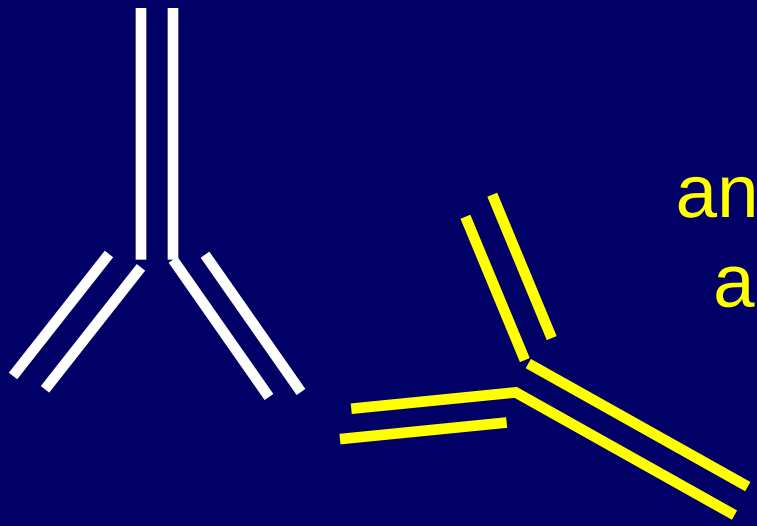
64667-OCTOBRE 2006

Mechanisms of action of IVIg in auto-immune diseases

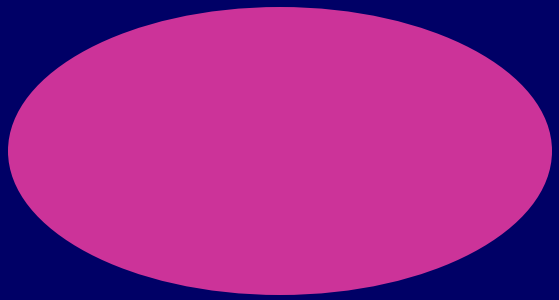
- **Modulation of the expression of Fc receptors at the cell surface**
- **Inhibition of complement dependent cytolysis; solubilisation of circulating immune complexes**
- **Direct modulation of lymphocyte proliferation**
- **Remyelinisation**
- **Neutralisation of circulating antibodies through interactions with variable regions of IVIg**
- **Selection of repertoires through stimulation and/or inhibition of B or T cell clones**
- **Modulation of production of cytokines and their natural antagonists**

Neutralisation of circulating autoantibodies through interaction with V regions of IVIg

Pathogenic autoantibodies



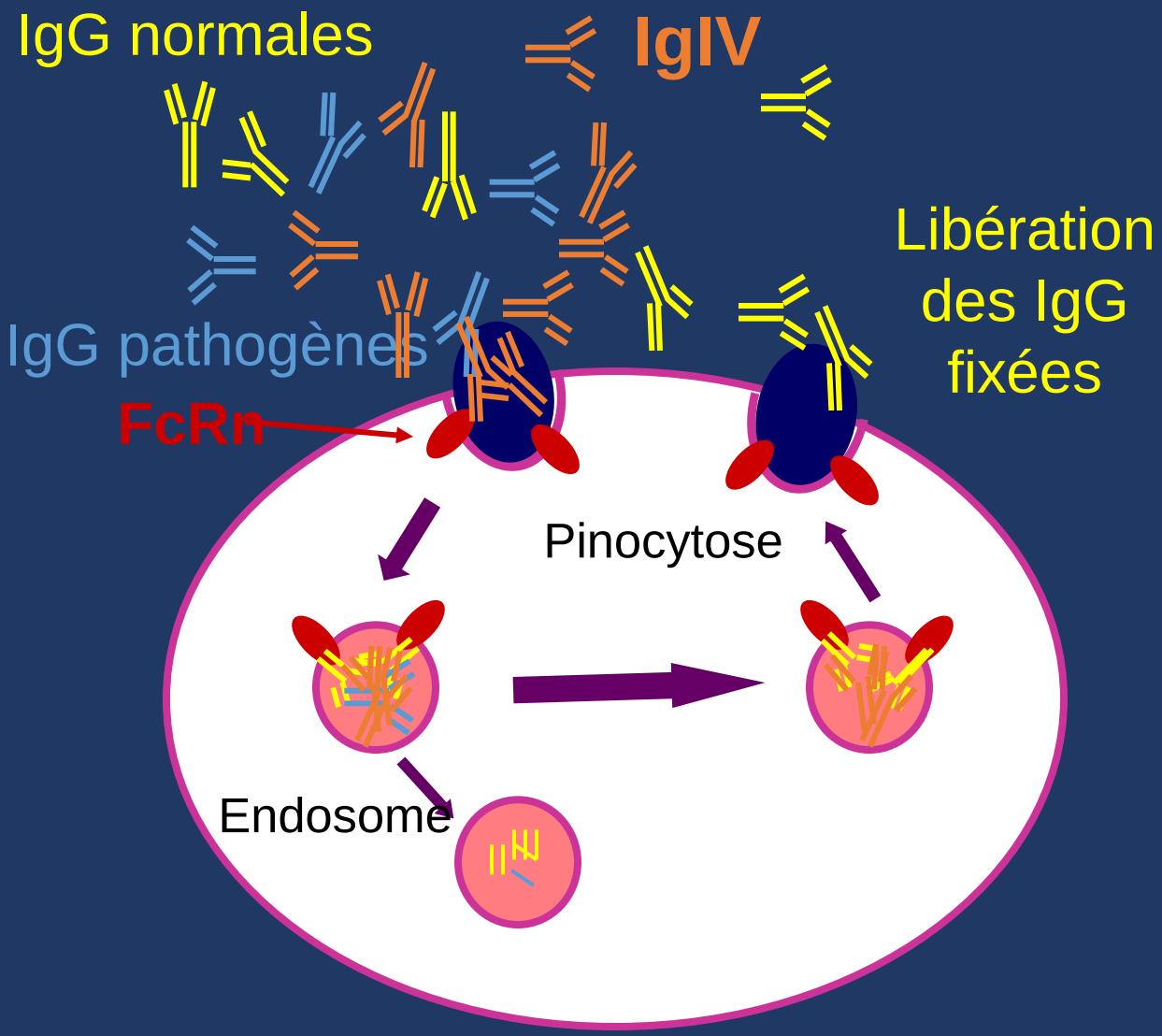
IVIg: anti-idiotypic antibodies



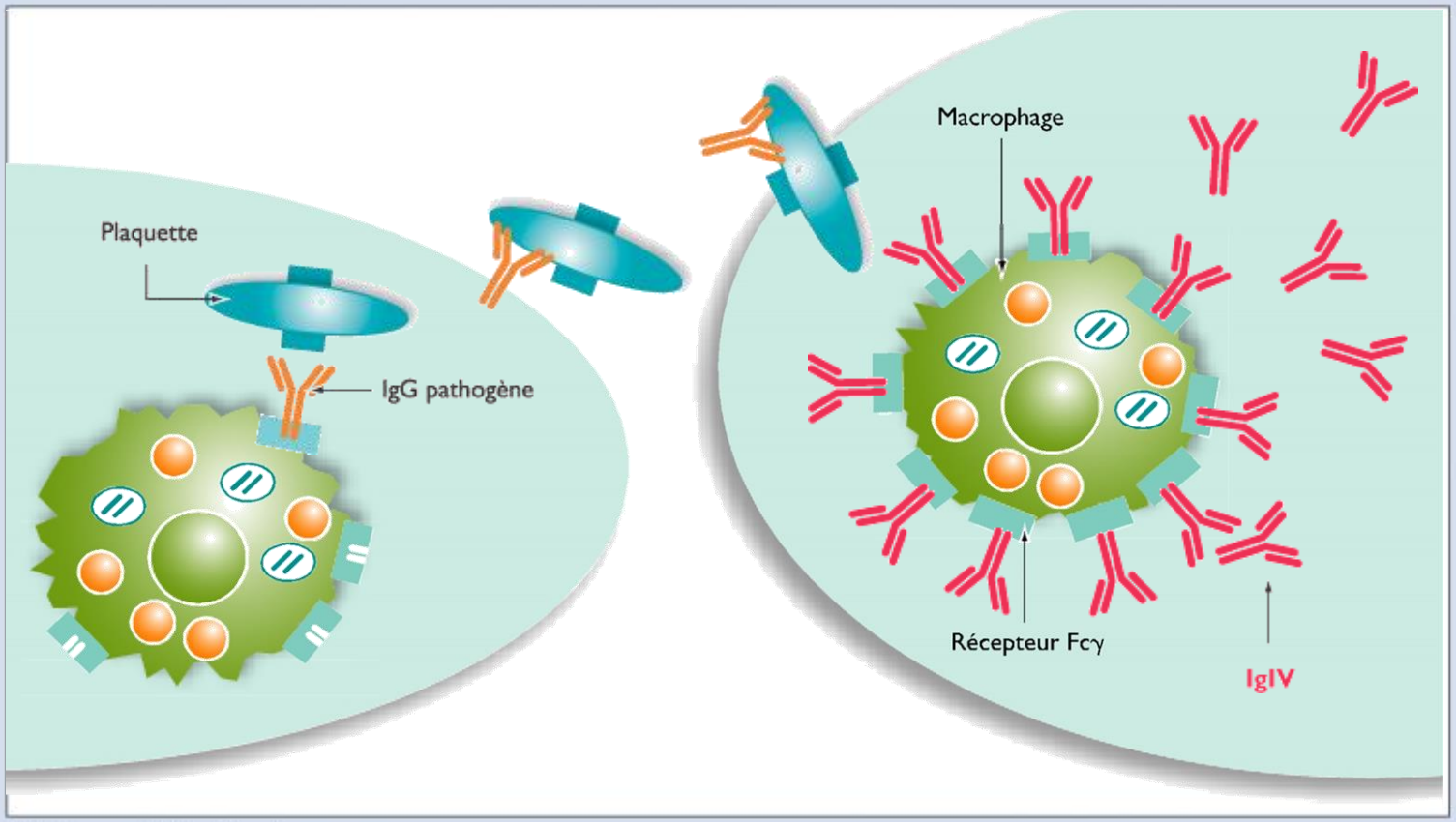
Auto-antigen

Catabolisme des IgG humaines

Yu Z, Lennon VA. N Engl J Med 1999; 340:227-8



Blockade of Fcγ receptors at the surface of macrophages



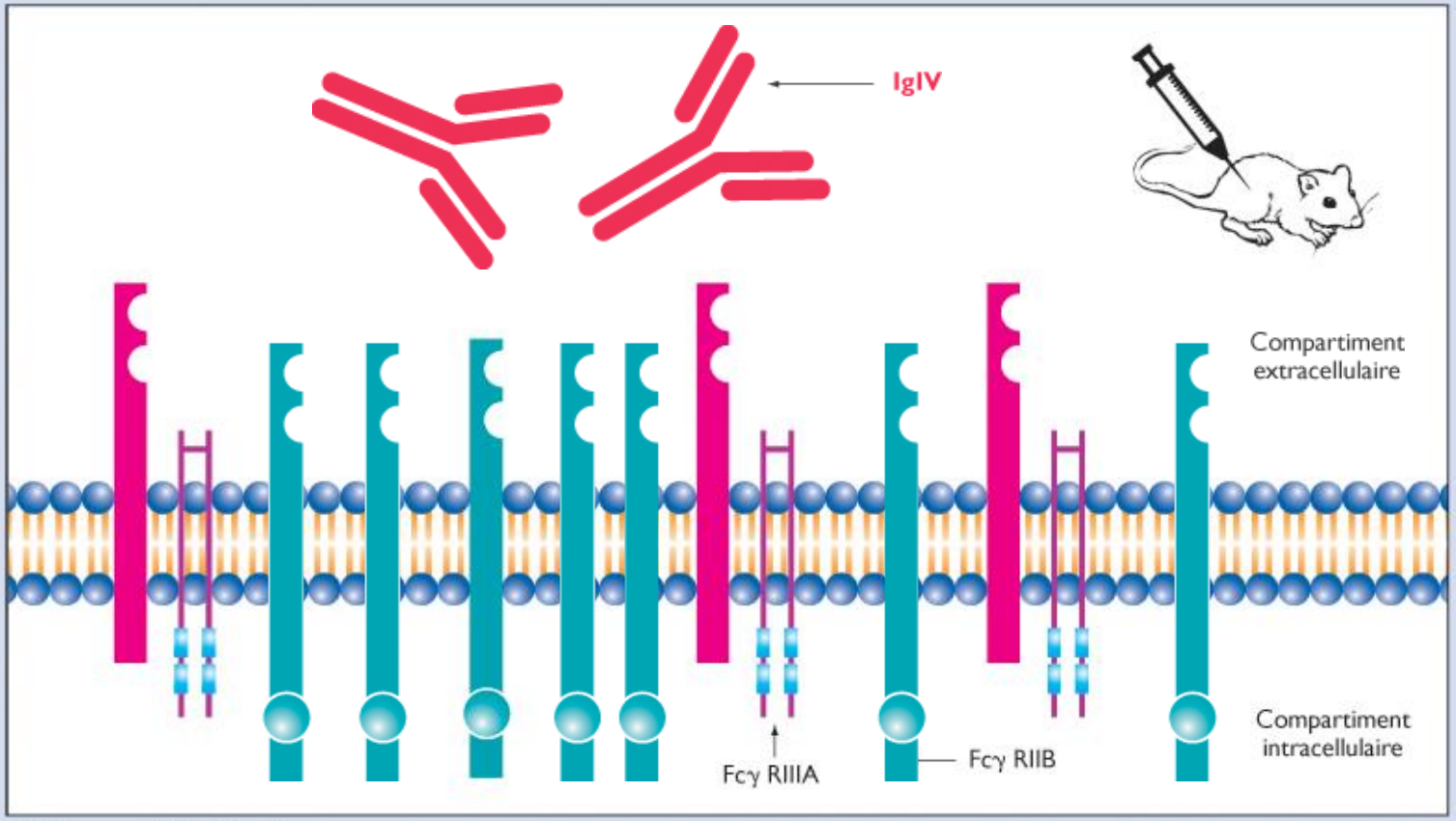
IgIV : Immunoglobuline intraveineuse

64667-OCTOBRE 2006

Induction of the inhibitory receptor FcγRIIB at the surface of macrophages

Samuelson A. et al. Science 2001 ; 291 : 484-6

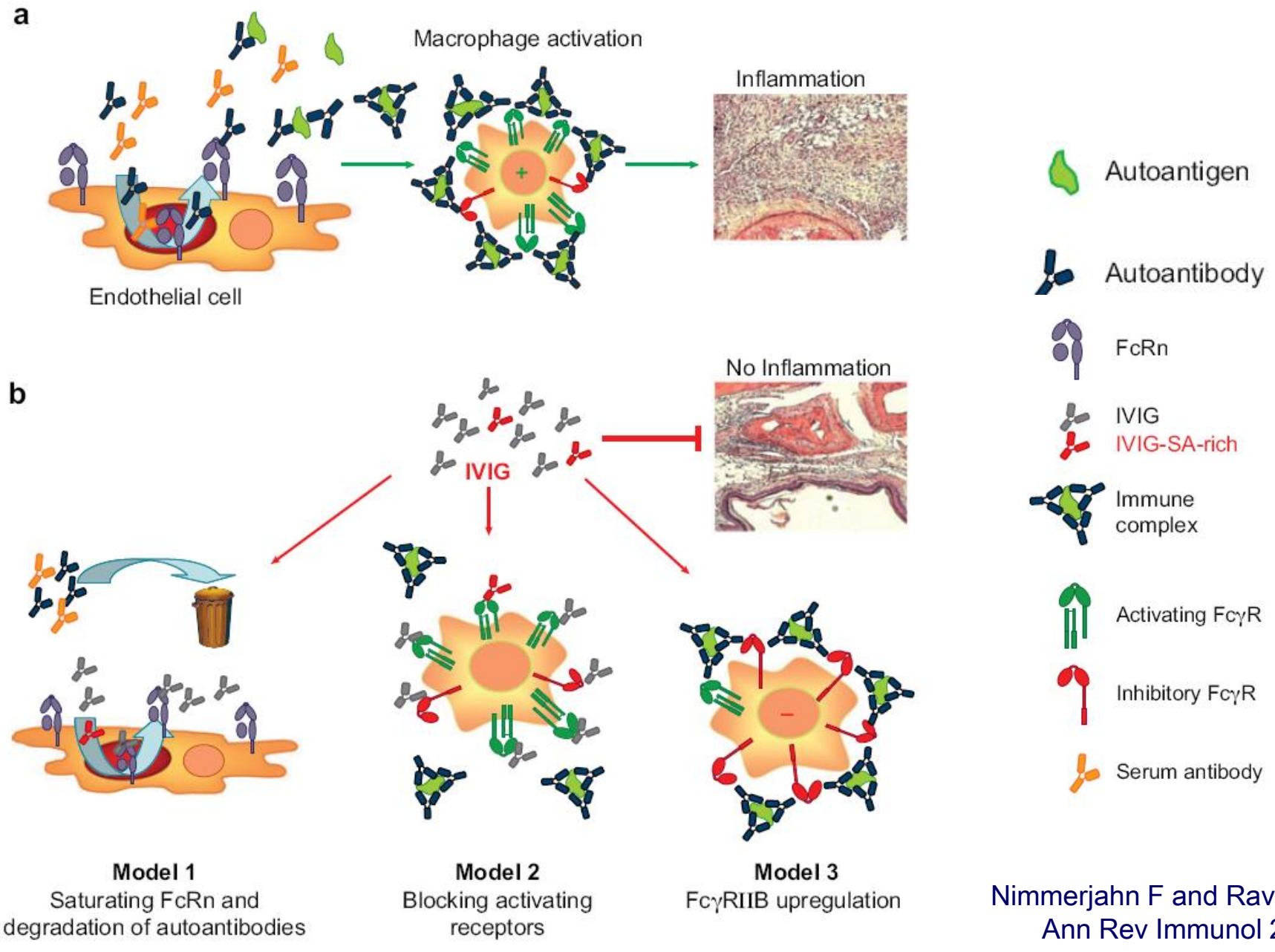
Pr Luc MOUTHON - Service de Médecine Interne - Hôpital Cochin - Université Paris V



IgIV : Immunoglobuline intraveineuse

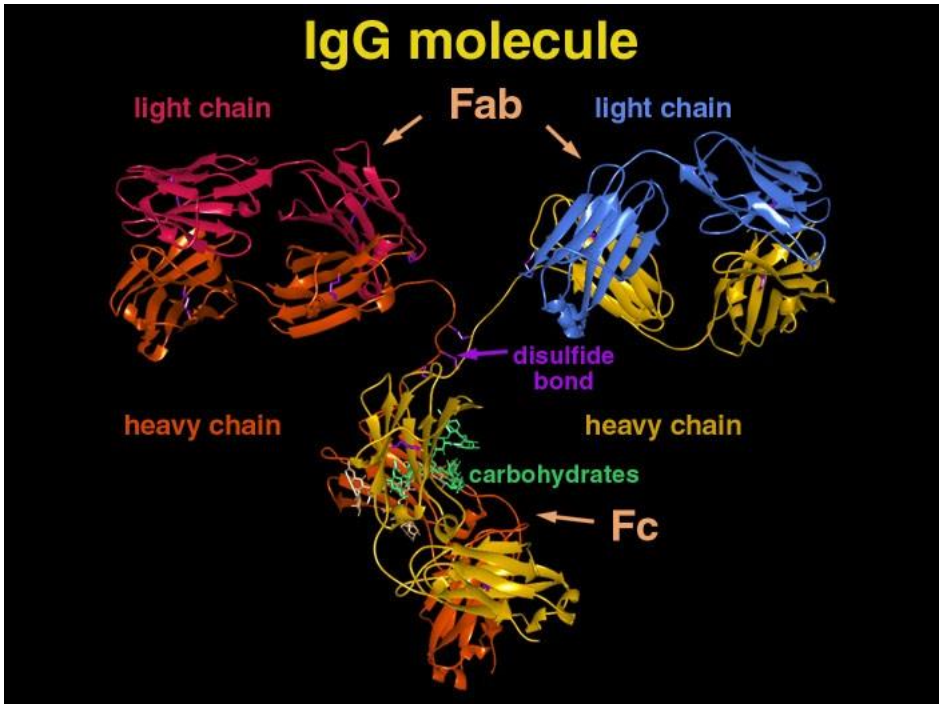
64667-OCTOBRE 2006

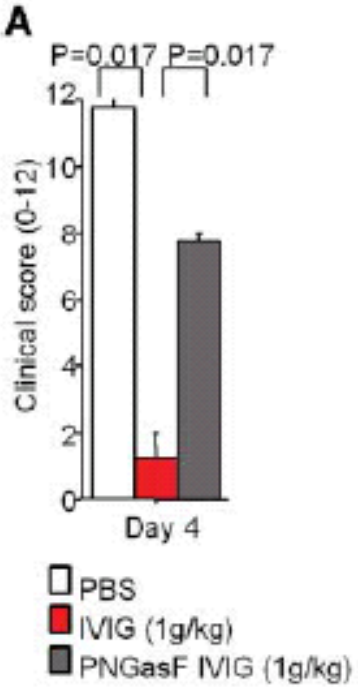
Proposed Fc fragment–dependent mechanisms of IVIg activity

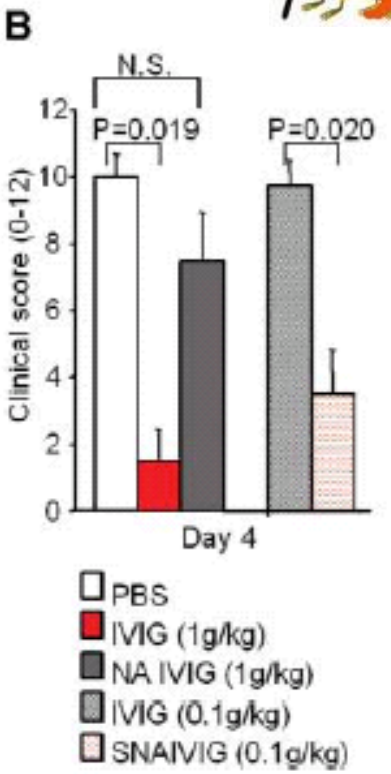


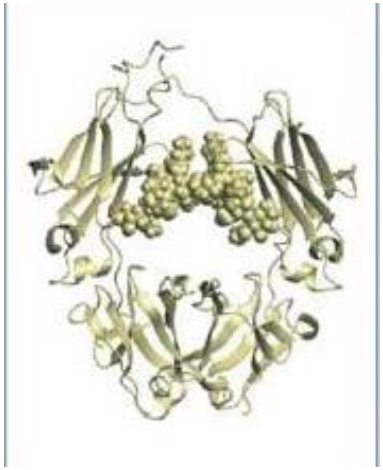
Nimmerjahn F and Ravetch JV, Ann Rev Immunol 2008

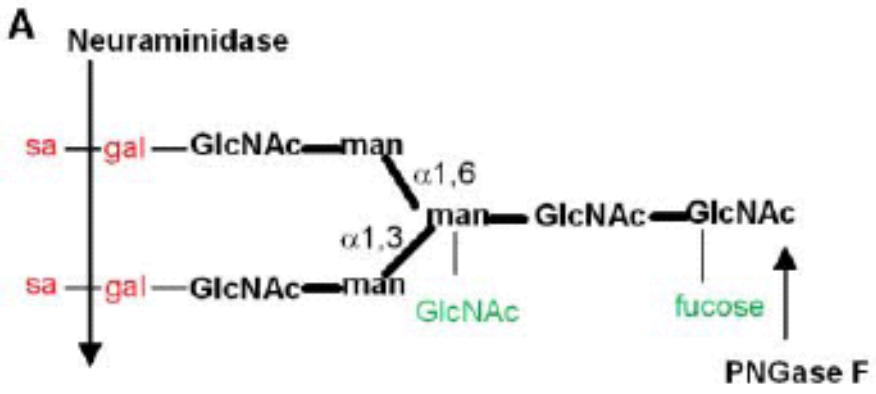
The anti-inflammatory activity of IVIg requires sialic acid







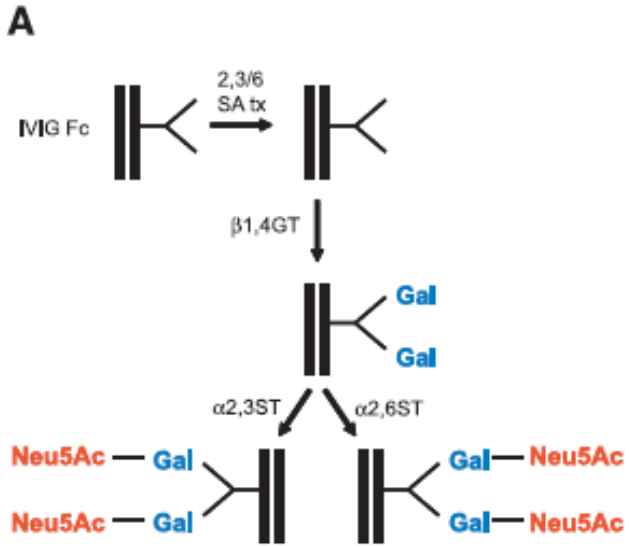


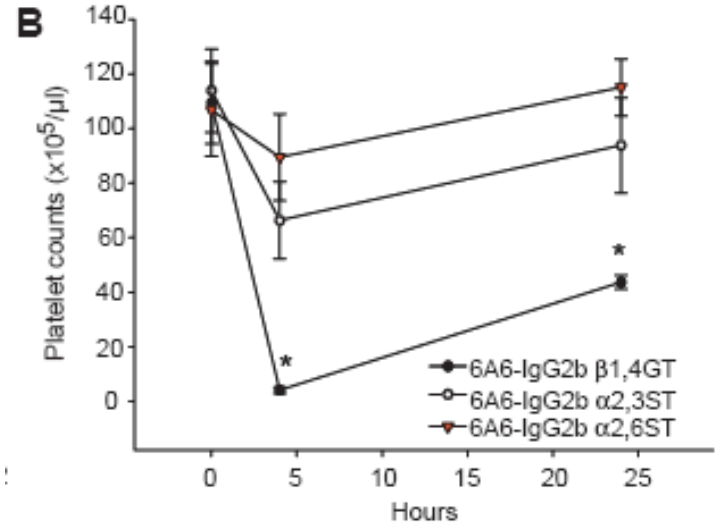


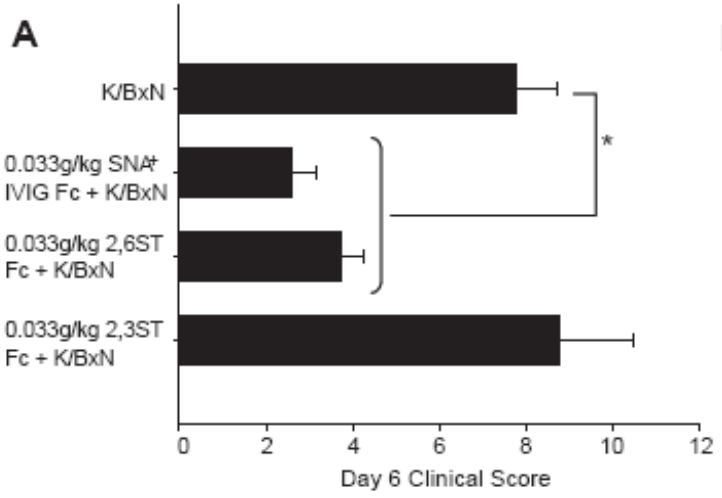
Kaneko Y, Science 2006

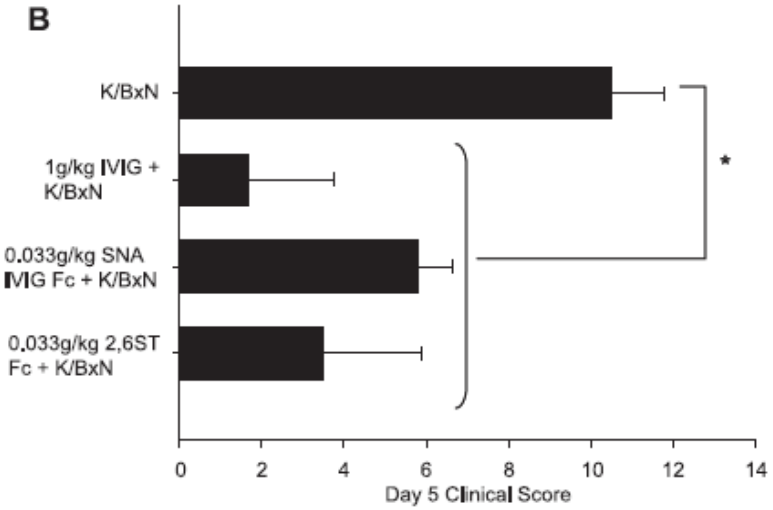
Recapitulation of IVIg Anti-Inflammatory Activity with a Recombinant IgG Fc

Anthony RM. Science 2008









CONCLUSIONS

- **Les IgIV ont été proposées dans le traitement d'un nombre important de pathologies autoimmunes ou inflammatoires chroniques**
- **Cependant, elles apportent un bénéfice démontré dans un nombre limité de pathologies**
- **Nécessité de réaliser des études randomisées (en cross over)**
- **La dose et la fréquence des perfusions peut être optimisée**
- **Nécessité d'études prenant en compte les polymorphismes des Récepteurs Fc**
- **Nécessité d'identification d'autres marqueurs prédictifs d'efficacité**

French Vasculitis Study Group

CMR
CENTRE MALADIES RARES
VASCULARITES | SCLÉRODERMIES
GOUGEROT-SJÖGREN | LUPUS

Hôpital Cochin
Paris

www.vascularites.org

Luc.mouthon@cch.aphp.fr

Referral Center for
Rare Systemic and
Autoimmune Diseases