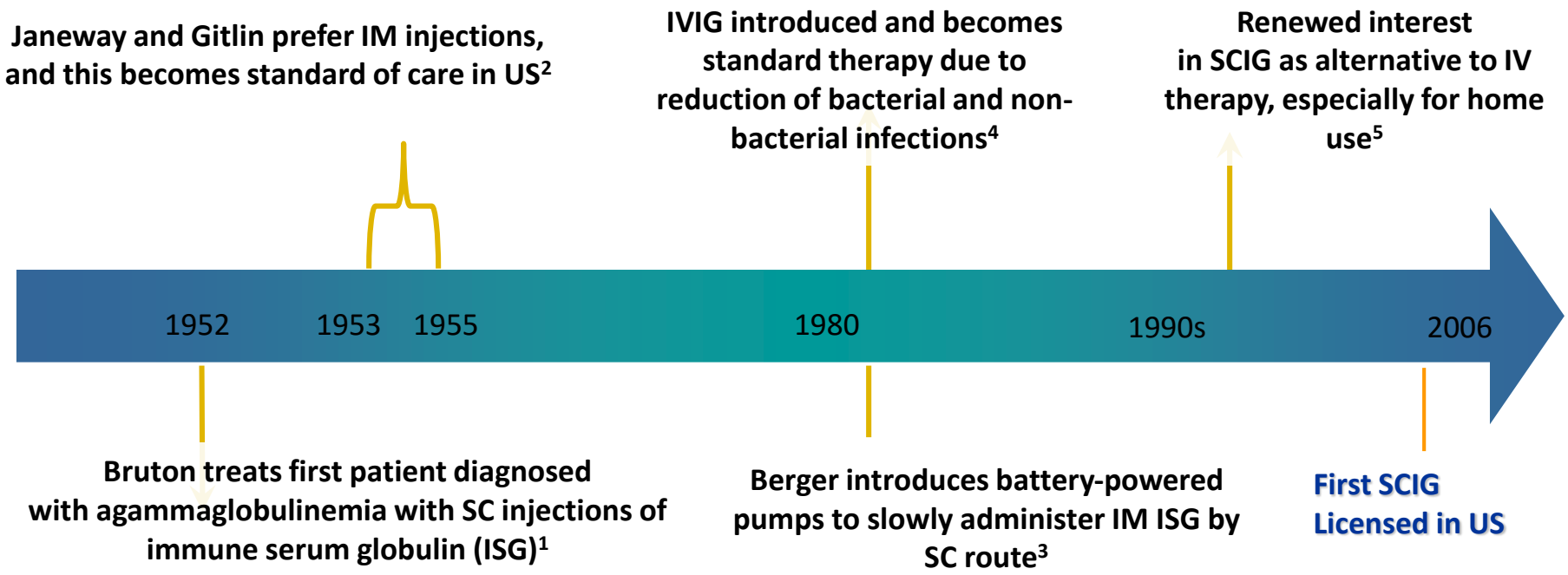
Clinical use of polyvalent immunoglobulins

Patient factors to consider when treating with immunoglobulin

Isabella Quinti
Sapienza University of Rome, Italy

Landmarks in the History of Immunoglobulin Replacement Therapy



1. Bruton OC. *Pediatrics.* 1952;9:722-728.
2. Berger M. *Clin Immunol*. 2004;112:1-7.
3. Berger M. et al. *Ann Intern Med.* 1980;98:55-56.
4. Quartier P. et al. *Jour Pediatrics.* 1999;134:5:589-596.
5. Abrahamsen TG. *Et al. Pediatrics.* 1996;98:1127-1131.

FDA-approved indications

Primary immunodeficiency disease

Chronic lymphocytic leukemia

Pediatric HIV infection

Kawasaki's disease

Allogeneic bone marrow transplantation

Chronic inflammatory demyelinating polyneuropathy

Kidney transplantation involving a recipient with a high antibody titer or an ABO-incompatible donor

Multifocal motor neuropathy

Requiring documentation of contraindications to or a lack of response to conventional therapies

Additional approved indications with criteria

Neuromuscular disorders

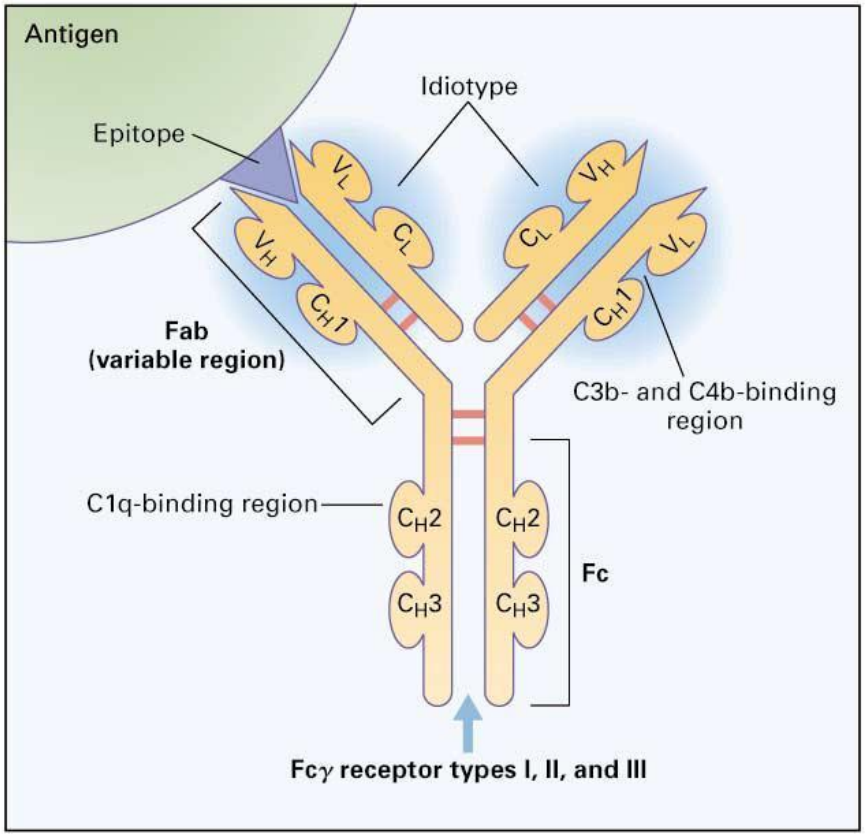
- Guillain–Barré syndrome
- Relapsing–remitting multiple sclerosis
- Myasthenia gravis
- Refractory polymyositis
- Polyradiculoneuropathy
- Lambert–Eaton myasthenic syndrome
- Opsoclonus–myoclonus
- Birdshot retinopathy
- Refractory dermatomyositis

Dermatologic disorders

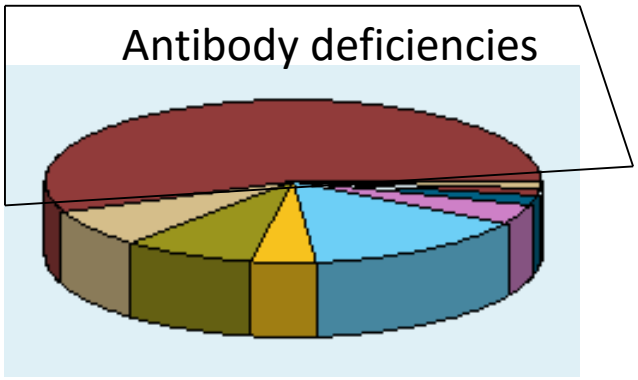
- Pemphigus vulgaris
- Pemphigus foliaceus
- Bullous pemphigoid
- Mucous-membrane (cicatricial) pemphigoid
- Epidermolysis bullosa acquisita
- Toxic epidermal necrolysis or Stevens–Johnson syndrome
- Necrotizing fasciitis

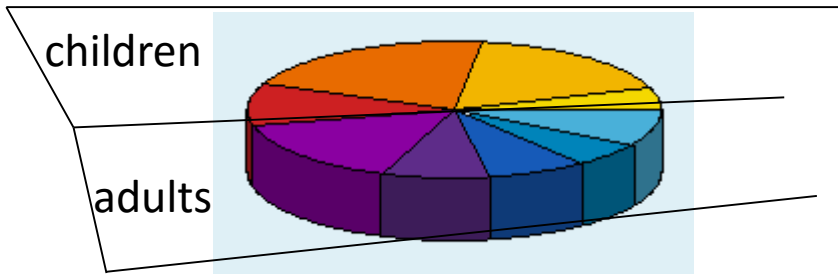
Hematologic disorders

- Autoimmune hemolytic anemia
- Severe anemia associated with parvovirus B19
- Autoimmune neutropenia
- Neonatal alloimmune thrombocytopenia
- HIV-associated thrombocytopenia
- Graft-versus-host disease
- Cytomegalovirus infection or interstitial pneumonia in patients undergoing bone marrow transplantation


Antigen
Epitope
Idiotype
V_L
V_H
C_L
C_L
V_H
V_L
C_H1
C_H1
Fab
(variable region)
C3b- and C4b-binding
region
C1q-binding region
C_H2
C_H2
C_H3
C_H3
Fc
Fcγ receptor types I, II, and III

ESID, 2012





Predominantly antibody disorders	**55.86%**
Predominantly T-Cell deficiencies	**7.83%**
Phagocytic disorders	**8.61%**
Complement deficiencies	**4.26%**
Other well defined PIDs	**15.06%**
Autoimmune Syndr.	**3.88%**
Autoinflammatory syndromes	**1.94%**
Defects in innate immunity	**1.06%**
Unclassified PIDs	**1.50%**

Under 5 years	**6.70% (n=740)**
5 – 9 years	**21.99% (n=2,428)**
10 – 15 years	**26.36% (n=2,911)**
16 - 19 years	**12.61% (n=1,392)**
20 - 29 years	**19.58% (n=2,162)**
30 - 39 years	**10.79% (n=1,191)**
40 - 49 years	**9.84% (n=1,087)**
50 - 59 years	**7.48% (n=826)**
Over 59 years	**10.60% (n=1,171)**

(Total number of patients: 15,781)

Patient's outcome

Τα αποτελέσματα στους ασθενείς

- Health care delivery systems are quickly changing in response to economic pressures and concerns about quality of care. **The system of care is itself an important determinant of patient outcomes.**
- Elucidating the effects of the system of care on **patient outcomes** requires new methodologic approaches in order to identify **what works in which setting and under what conditions.**
- **Personalized health research** presents further methodologic challenges, since emphasis is placed on the individual response rather than on the population.

N Engl J Med 367;9, august 30, 2012

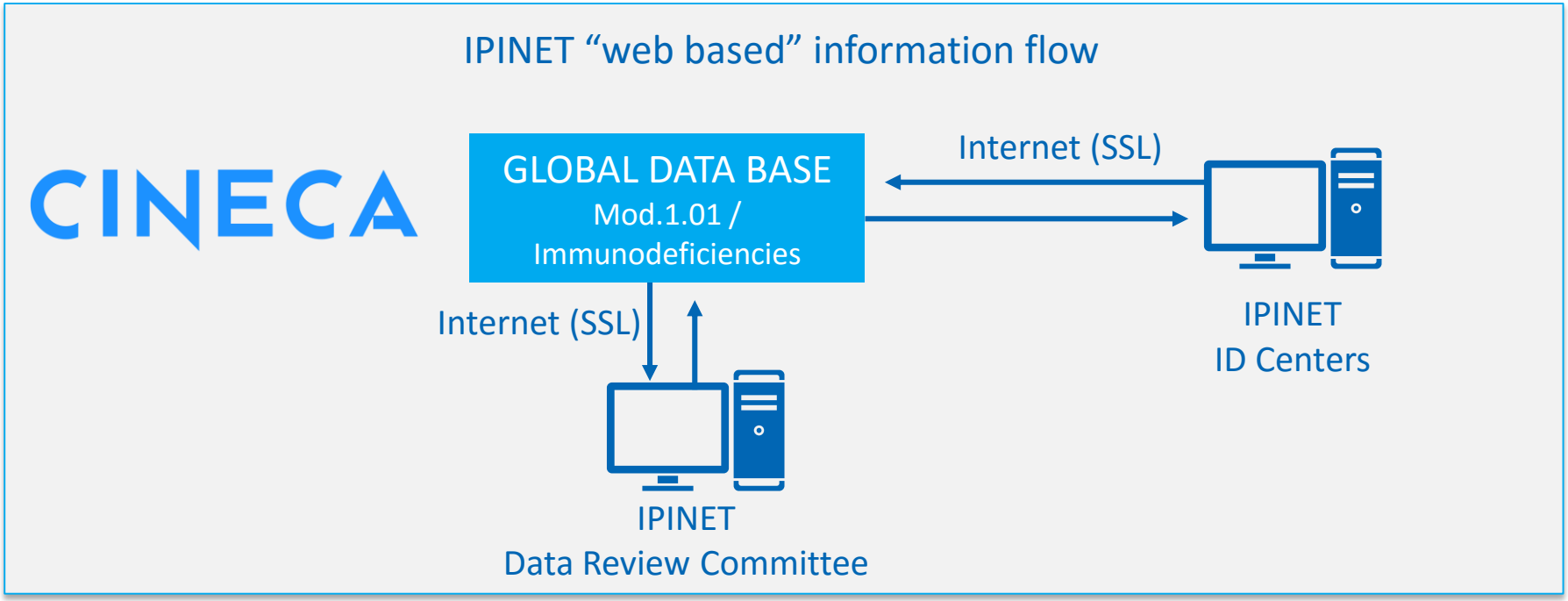
Factors to Consider When Individualizing Immunoglobulin Treatment
Παράγοντες που πρέπει να ληφθούν υπόψη στην εξατομίκευση θεραπείας με ανοσοσφαιρίνη

1. Disease Heterogeneity
2. Optimizing the IG Dose
3. Patient Quality of life

Primary Immune Deficiency Heterogeneity

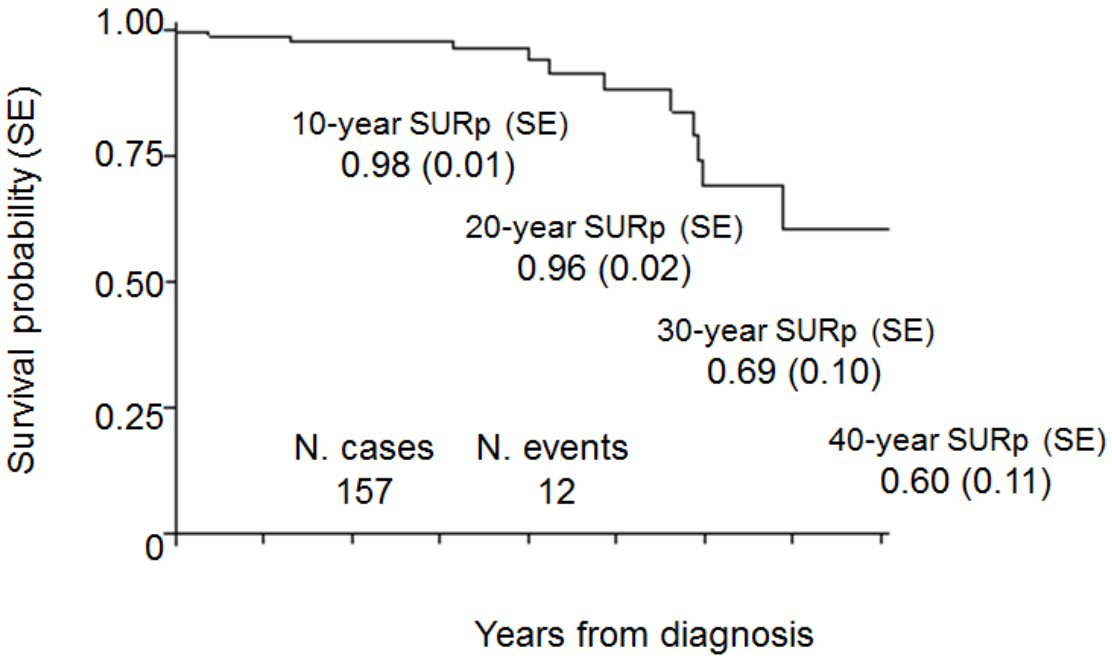
Πρωτοβάθμια Ετερογένεια Ανοσοποιητικής Ανεπάρκειας

Italian Network on Primary Immunodeficiencies (IPINET)

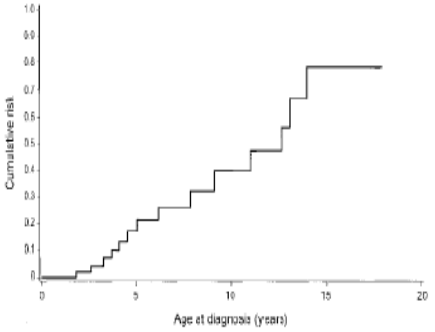


- ✓ In 1999, 57 Italian centers established a collaborative group involving both pediatric and adult immunological centers (**Italian Network of Primary Immunodeficiencies, IPINET**) with the aim of collecting data at diagnosis and on a yearly basis during follow-up
- ✓ **More than 1300 patients** have been enrolled in these prospective multicenter studies of 6 PIDs (**XLA, CVID, WAS, Del22, AT, CGD**)

AIEOP XLA
Overall Survival



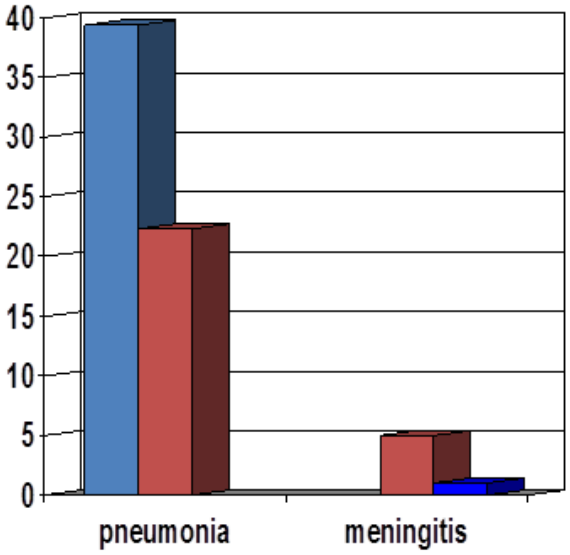
Cumulative risk of developing chronic lung disease in relation to age at diagnosis



Age at diagnosis	Cumulative risk	Standard error
5 yrs	0.17	0.07
10 yrs	0.40	0.11
15 yrs	0.78	0.13

Clinical Immunology 2002;**104**:221–30

CVID

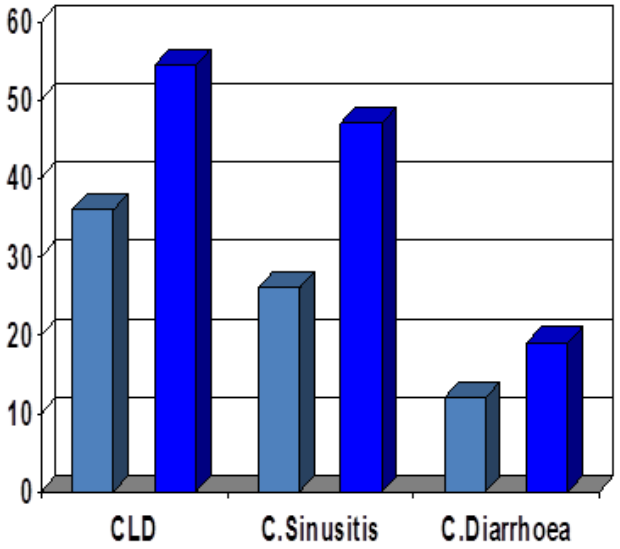


Reduction in the prevalence of pneumonia, after initiation of Ig replacement therapy:

-from 39.4% to 22.3%, (p<0.0001).

After Ig replacement, the incidence of pneumonia remained relatively constant:

-range 0.06-0.10 episodes/patient/year).



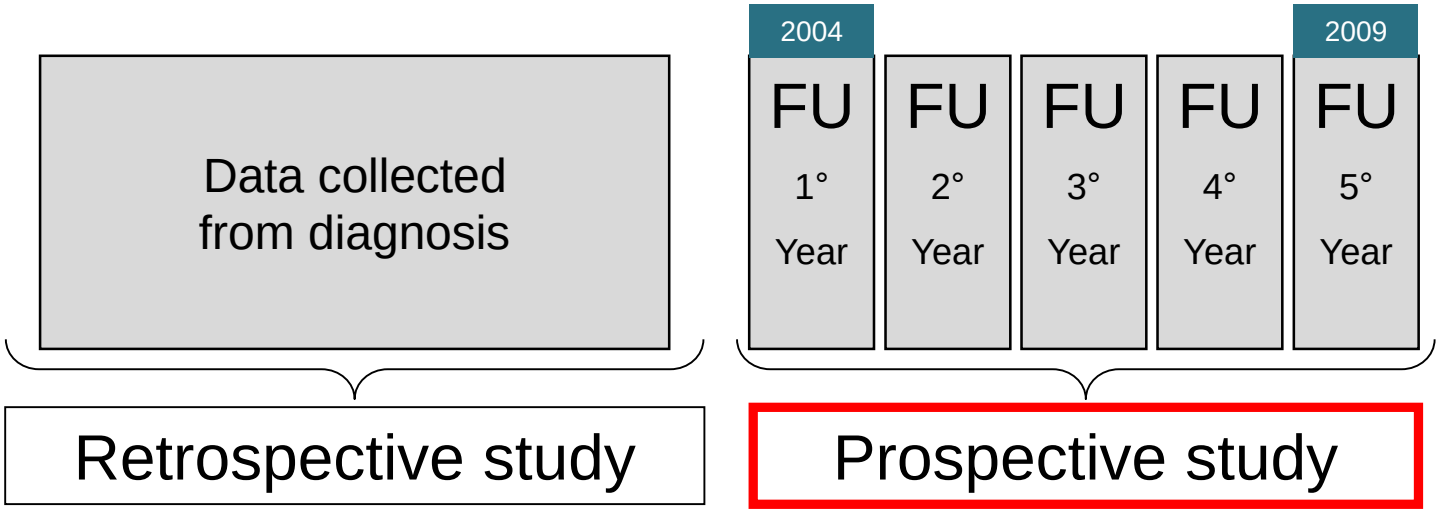
Increase in bronchiectasis prevalence (by a CT scan performed every four years):

-from 36.2% to 54.5% patients (p=0,009)

Study Design

Patients enrolled:
XLA: 101
CVID: 201

Mean age at diagnosis (years)		Mean age at study end (years)
4.9± 6.2	XLA	21± 5
28.7±18.4	CVID	40.5±18.9



Effectiveness of immunoglobulin replacement therapy on clinical outcome in patients with primary antibody deficiencies: results from a multicenter prospective cohort study. J Clin Immunol. 2011 Jun;31(3):315-22

Risk factors for CVID-associated conditions

CVID

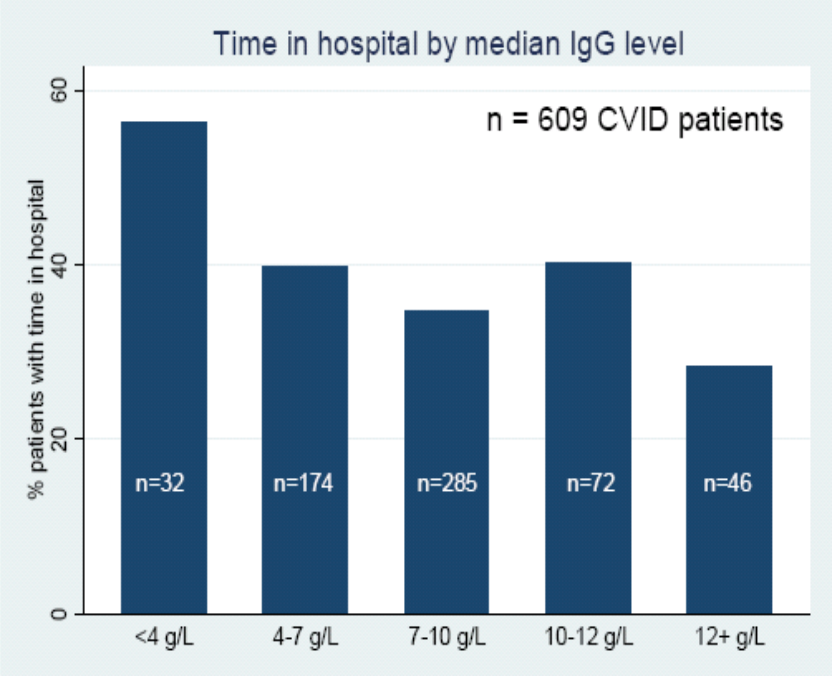
Multiple regression

Clinical condition	Risk factor	HR	p
Pneumonia	IgG <400 mg/dL	5.1	0.0009
	bronchiectasis	3	0.007
	IgA< 7 mg/dL	2.6	0.03
Acute sinusitis	chronic sinusitis	11.4	<0.0001
	bronchiectasis	1.6	0.02
Bronchiectasis	IgA < 7 mg/dL	2.4	0.04
	age	1,5 (10-year intervals)	0.0007
Chronic sinusitis	acute sinusitis	11.5	<0.0001
	IgA <7 md/dL	3.7	0.02
	pneumonia	3.6	0.05
Chronic diarrhea	IgA	1.1	0.04
	Age (10-year intervals)	1.2	0.01
Splenomegaly	bronchiectasis	2.6	0.0003
	IgA <7 mg/dL	2.2	0.02

Effectiveness of immunoglobulin replacement therapy on clinical outcome in patients with primary antibody deficiencies: results from a multicenter prospective cohort study. J Clin Immunol. 2011 Jun;31(3):315-22

Clinical picture and treatment of 2212 patients with common variable immunodeficiency.
European Society for Immunodeficiencies Registry Working Party.
J Allergy Clin Immunol. 2014 Jul;134(1):116-26

IgG replacement

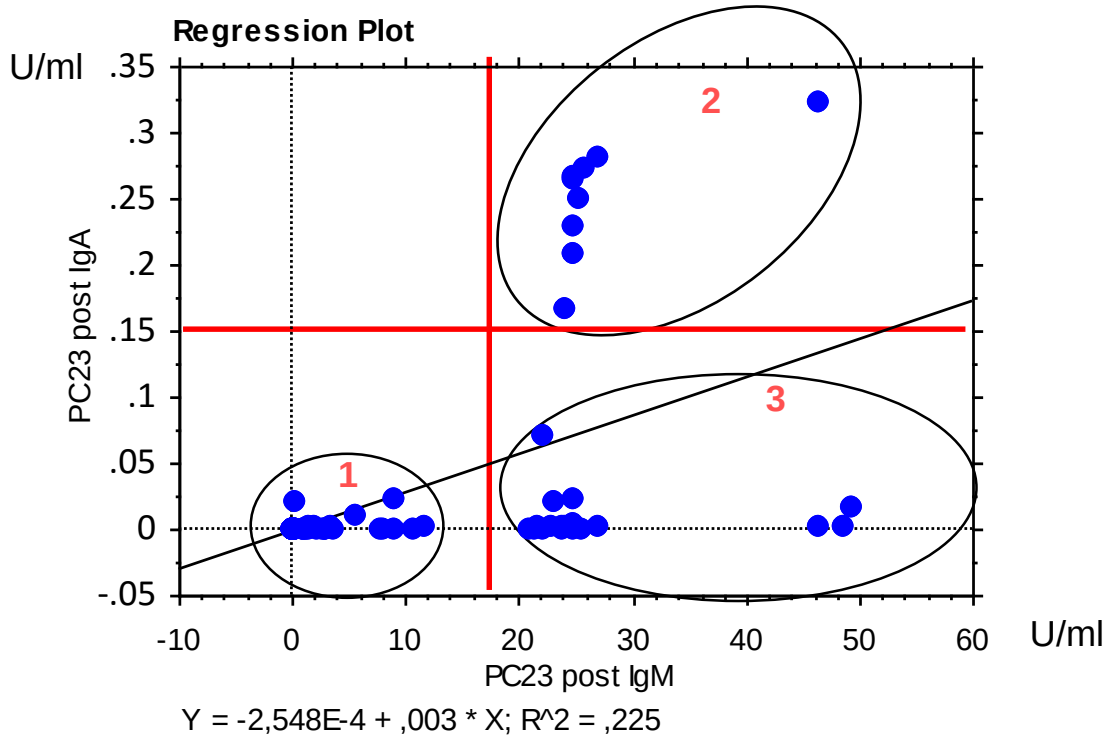


→Time in hospital and serious infections correlate with trough level, but not days unable to perform daily duties and infectious episodes in general

CVID patients grouped according to IgM and IgA pneumococcal polysaccharides response

The clinical phenotype characterized by a high infection risk is also associated with a poor response to vaccination

The example of pneumoccoccal polysaccharide vaccination



Quantification of IgM and IgA anti-pneumococcal capsular polysaccharides by a new ELISA assay: a valuable diagnostic and prognostic tool for common variable immunodeficiency. J Clin Immunol. 2013 May;33(4):838-4

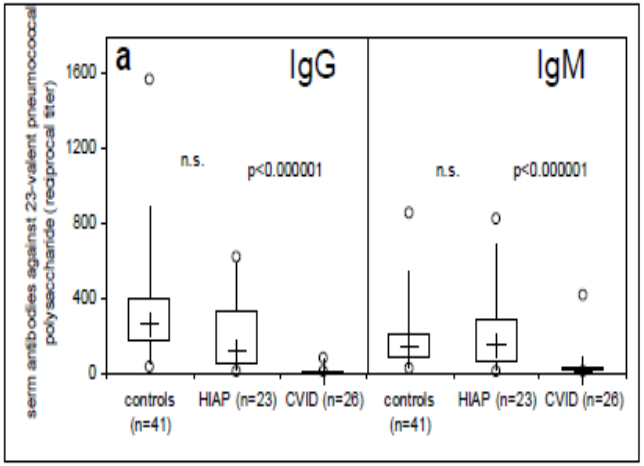
frontiers in IMMUNOLOGY

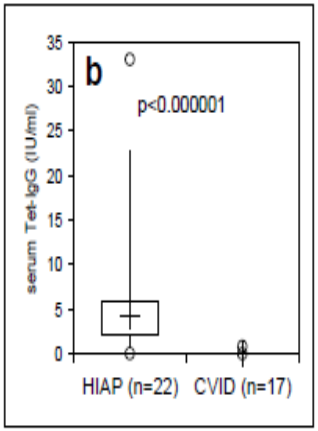
ORIGINAL RESEARCH ARTICLE
published: 02 February 2015
doi: 10.3389/fimmu.2015.00032

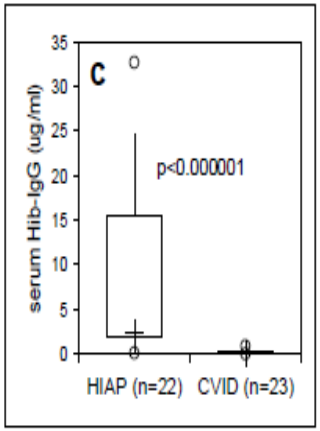
Detection of impaired IgG antibody formation facilitates the decision on early immunoglobulin replacement in hypogammaglobulinemic patients

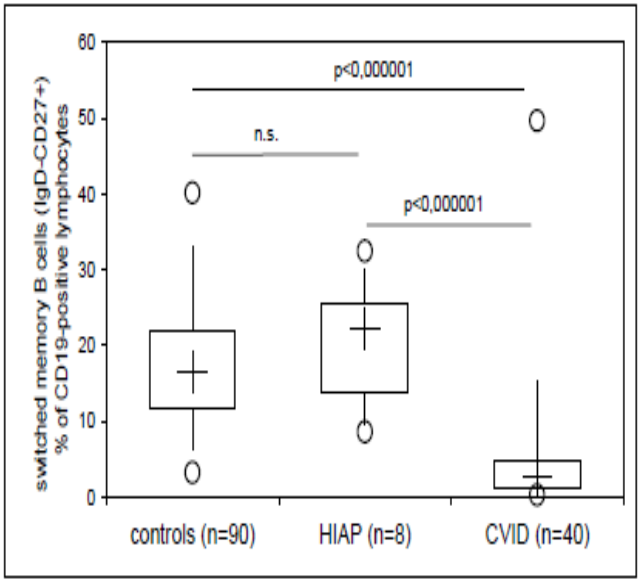
Hermann M. Wolf[1], Vojtech Thon[2,3], Jiri Litzman[2,3] and Martha M. Eibl[1]*

To facilitate early treatment before recurrent infections may lead to organ damage the antibody formation capacity should be examined in hypogammaglobulinemic patients and the decision to treat should be based on the finding of impaired IgG antibody production

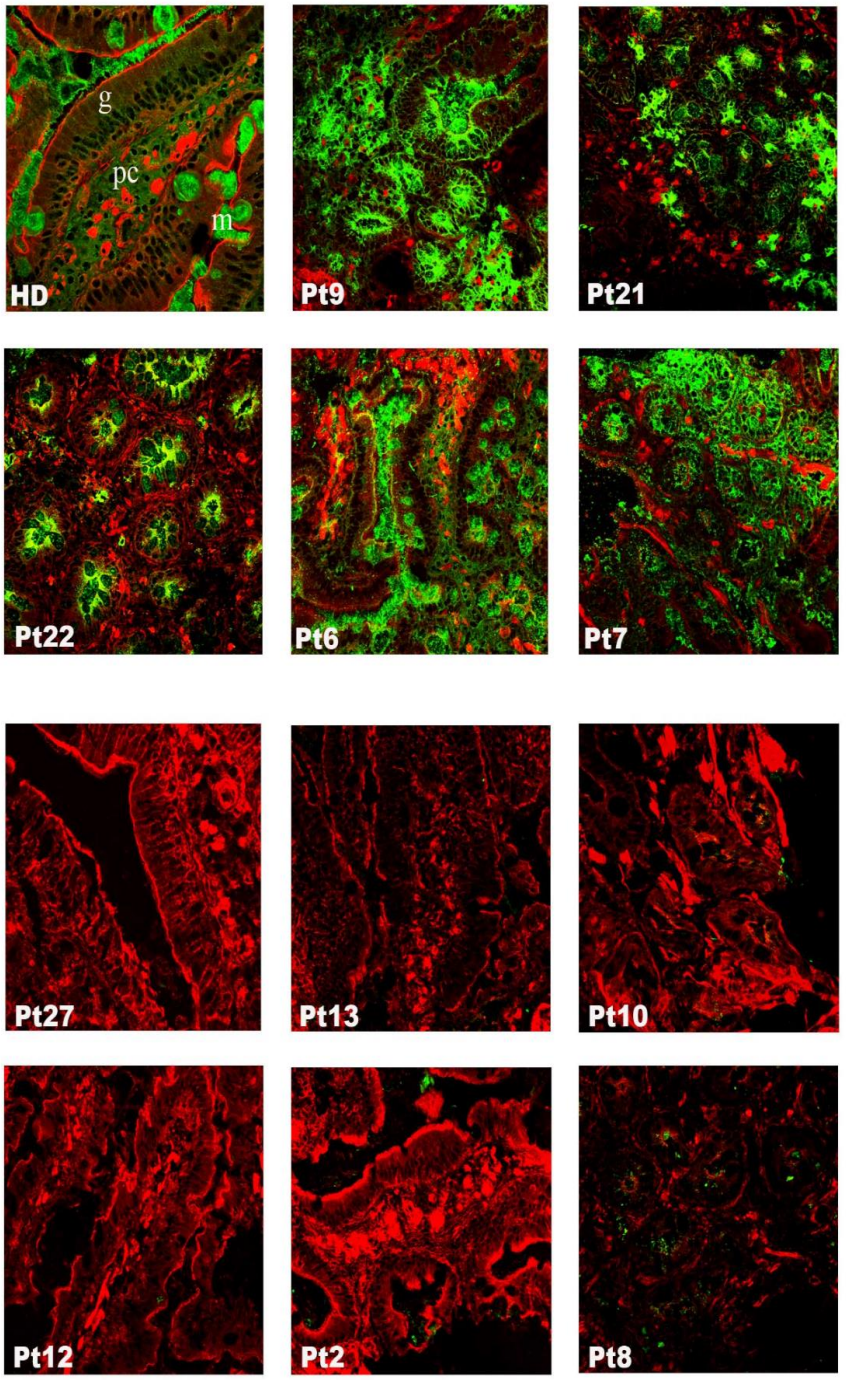








PAD patients with similar severity of serum hypogammaglobulinemia show different severity of mucosal abnormalities



Cryostat sections of the duodenum stained in red with phalloidin (a toxin that binds and stains filamentous actin) and in green with antibodies against IgA

Biopsies of one healthy donor (HD) and 11 representative CVID patients are shown.

CVID patients at high risk for severe respiratory infections

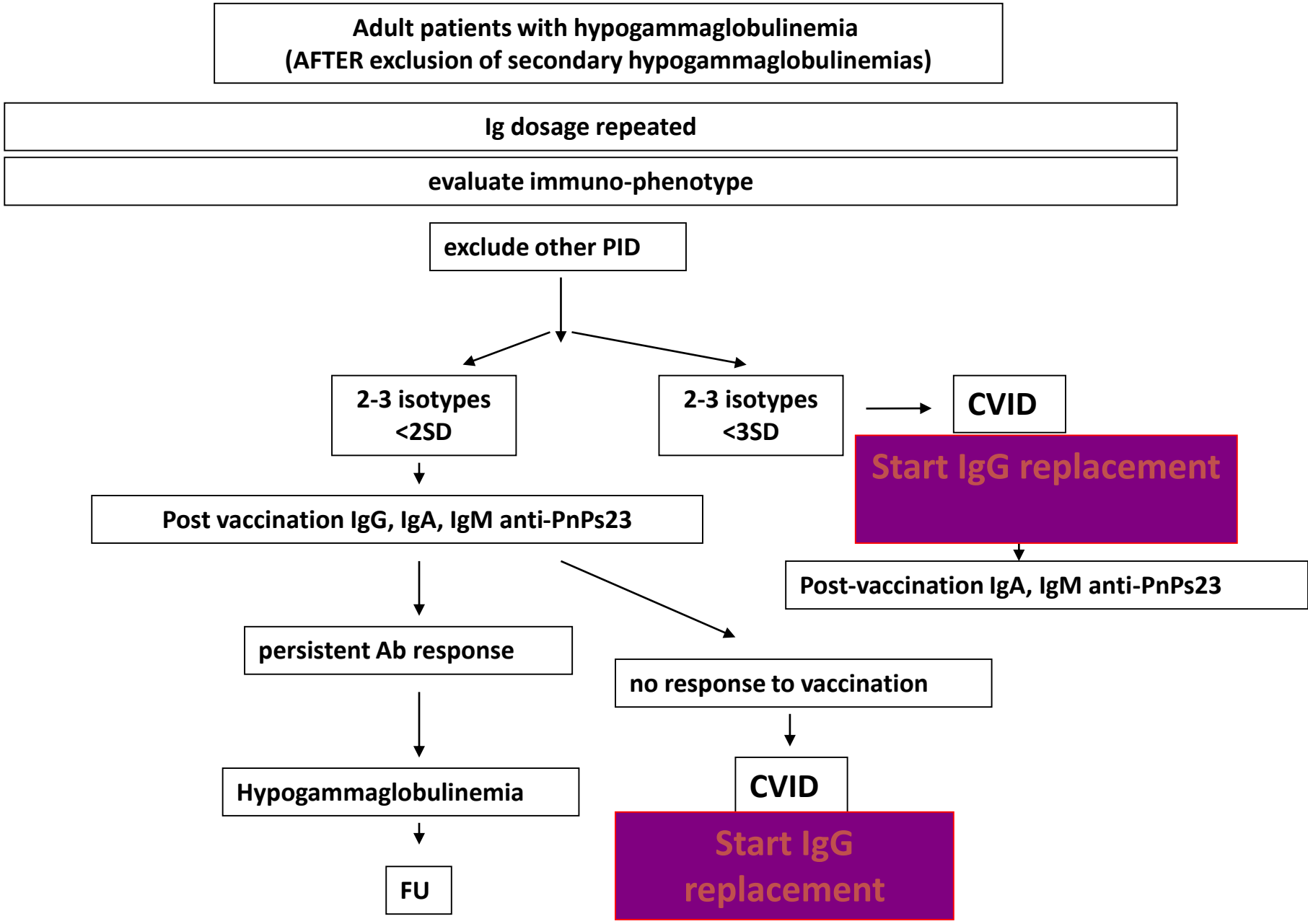
ασθενείς με υψηλό ρίσκο για σοβαρές αναπνευστικές λοιμώξεις

- Up to now, risk factors for the increased susceptibility to severe respiratory infections in CVID patients have been poorly defined

  - Presence of bronchiectasis
  - IgG serum trough levels < 400 mg/dL
  - A low frequency of memory B cells
  - Very low IgA serum level (<7 mg/dL)

  …are risk factors for recurrent pneumonias

Quinti I et al. *J Clin Immunol*. 2011.


Adult patients with hypogammaglobulinemia
(AFTER exclusion of secondary hypogammaglobulinemias)
Ig dosage repeated
evaluate immuno-phenotype
exclude other PID
2-3 isotypes
<2SD
2-3 isotypes
<3SD
CVID
Start IgG replacement
Post vaccination IgG, IgA, IgM anti-PnPs23
Post-vaccination IgA, IgM anti-PnPs23
persistent Ab response
no response to vaccination
Hypogammaglobulinemia
CVID
Start IgG
replacement
FU

Optimizing Immunoglobulin Dose

The Oxford experience

- The Oxford choice is to increase the IVIG dose by 0.15 g/kg/month when patients present with a serious infection, or 3 or more moderate infections over a year.

- This recommendation could be an alternative to patients who have persistent infections; although other factors contributing to infections such as airway inflammation may need to be assessed before these increased doses are made permanent for a specific patient.

Adequate Patient Outcomes Achieved with Short Immunoglobulin Replacement Intervals in Severe Antibody Deficiencies

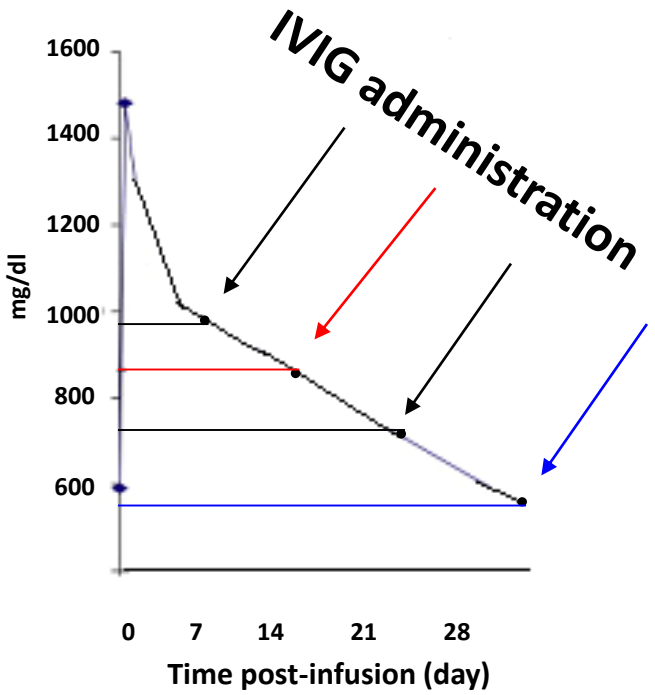
Cinzia Milito, Federica Pulvirenti, Anna Maria Pesce, Maria Anna Digiulio, Franco Pandolfi, Marcella Visentini, Isabella Quinti

J Clin Immunol (2014) 34:813–819

Objective:
To determine for each patient the best interval between immunoglobulin administration in order to:

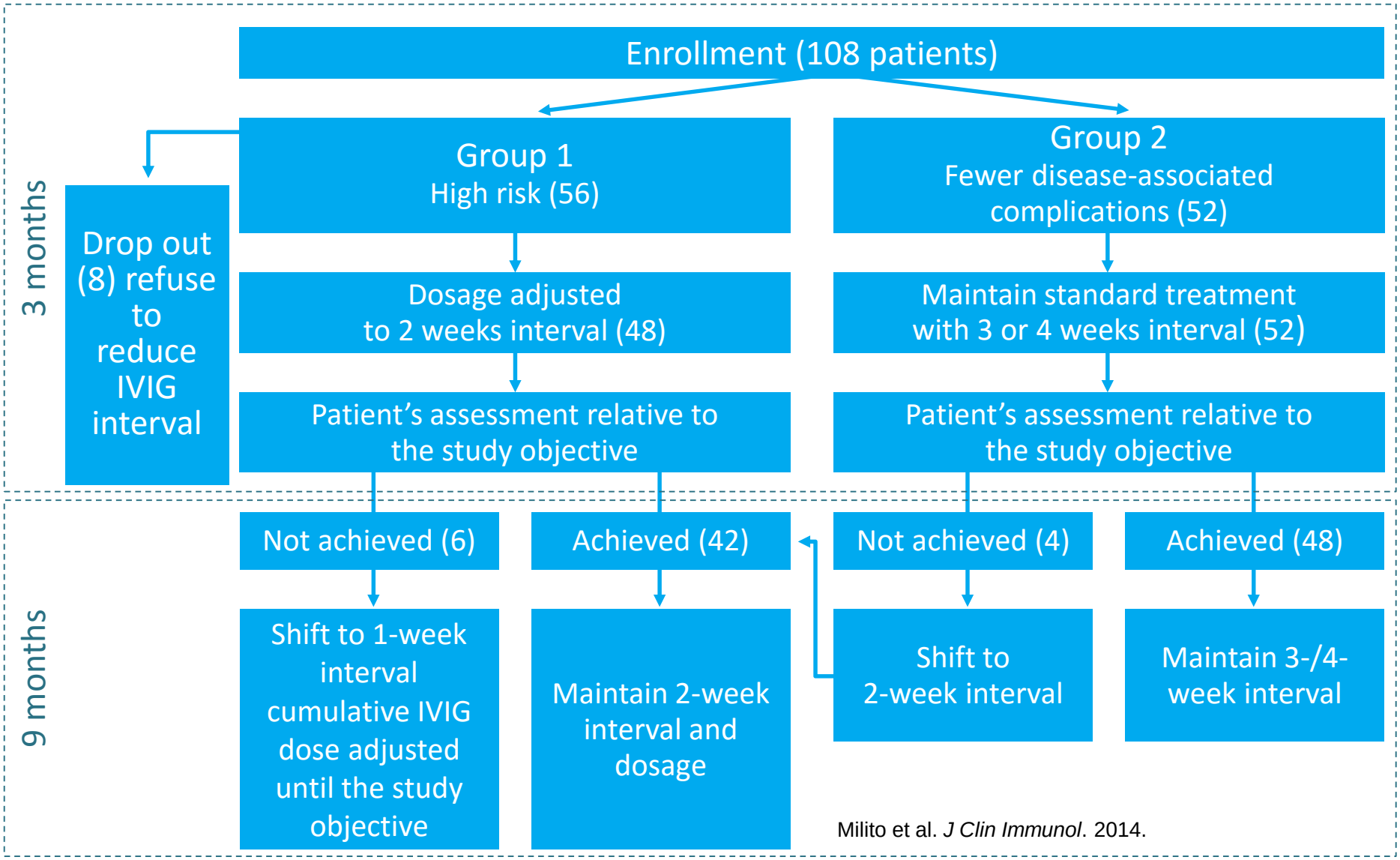
- Keep IgG trough levels >500 mg/dL
- Minimize major infections (pneumonias and infections requiring hospitalization)
- Minimize adverse events (AEs)

Which interval?



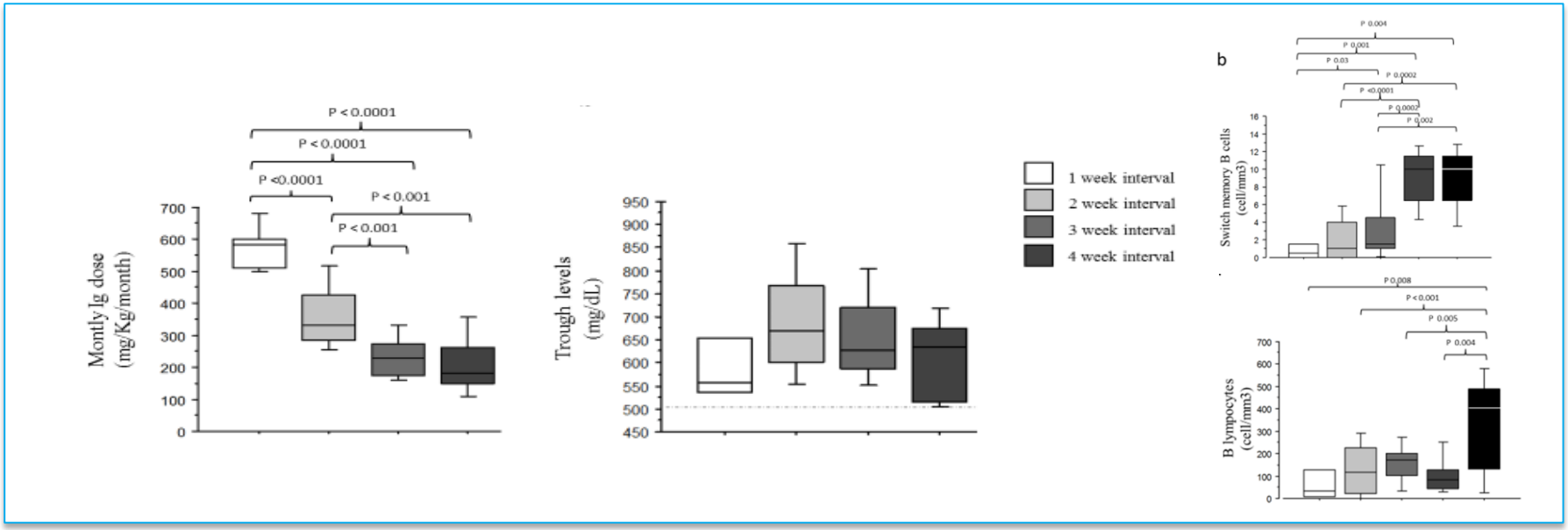
IgG trough levels might be increased by reducing intervals between adiministrations without need to increase the administration dosage

Study Design



Milito et al. *J Clin Immunol*. 2014.

High risk CVID patients benefit from the reduction of the dosing interval



98% of patients achieved the study objective

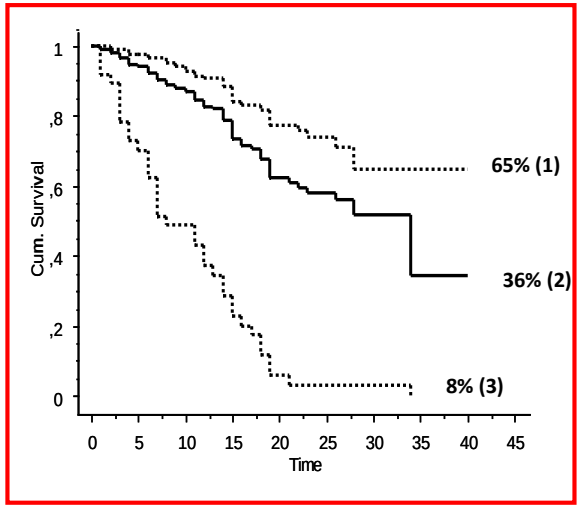
- ✓ Patients who had **low switched memory B cells and low IgA serum levels** and/or were affected by **bronchiectasis** and/or **enteropathy** and/or **continued to experience adverse events despite premedications** achieved the study objective by shortening the administration intervals to 2 week or to 1 week without the need to increase the monthly cumulative immunoglobulin dosage and its relative cost.
- ✓ The adverse events were reduced by administering low Ig dosages in a single setting.
- ✓ Patients without risk factors achieved the study objective with immunoglobulin replacement administered with the widely used interval of 3 or 4 weeks.

Malignancies are the major cause of death in patients with adult onset CVID

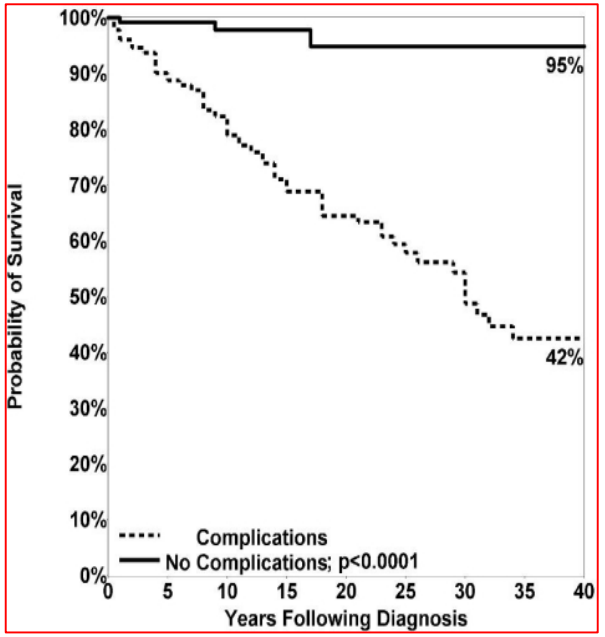
Morbidity and mortality in CVID over 4 decades

Probability of survival

Analysis of survival: 40 years follow-up



Kaplan-Meier curves for patients with CVID:
(1) cumulative; (2) without cancers; (3) with cancer



Quinti I. et al,

Blood. 2012 Aug 30;120(9):1953-4.

Resnick ES et al,

Blood. 2012 Feb 16;119(7):1650-7.

Conclusions
Συμπεράσματα

- Clinical phenotypes of primary antibody deficiencies are quite variable also within the same disease

This might explain the different results on dosing and efficacy.

- Therefore, the suggested “protective high trough IgG levels” might not be considered a general goal and only large prospective multicenter studies might help to identify CVID subgroups of patients at high infection risk.

Patient Quality of Life

Research Topic:
Immunoglobulin Therapy in the 21st Century: The Dark Side of the Moon

frontiers in IMMUNOLOGY

OFFICIAL JOURNAL OF THE IUIS

ORIGINAL RESEARCH ARTICLE
Published: 26 November 2014

Longitudinal study on health-related quality of life in a cohort of 96 patients with common variable immune deficiencies

Stefano Tabolli[1], Patrizia Giannantoni[1], Federica Pulvirenti[2], Fabiola La Marra[2], Guido Granata[2], Cinzia Milito[2] and Isabella Quinti[2*]

Health-Related Quality of Life

- The health-related quality of life (HRQoL) is a multidimensional concept that encompasses measurements of physical, psychological and well being and assesses the individual's perception of the impact of illness on his/her life.
- There are several critical reasons to evaluate the available data on HRQoL in patients with primary antibody deficiencies:
  - The absence of a disease-specific questionnaire is a major limitation.
  - Only observational or short-term longitudinal studies on small cohorts have been performed and differences between patients have been mainly evaluated to compare treatment regimens and routes of immunoglobulin administration.

Outcome Measures

- SF-36: generic health status indicator for use in population survey and health policy evaluation studies. 36 items addressing physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health. Scores for each domain range from 0 to 100.
- GHQ-12: self administered 12-item general health questionnaire designed to measure the psychological distress and to detect current non-psychotic psychiatric disorders such as depression and anxiety.
- TAS-20: 20-item Toronto Alexithymia Scale questionnaire designed to evaluate alexithymia, i.e. the difficulty in identifying and describing feelings. Three subscales: difficulty in identifying feelings, difficulty in describing and communicating feelings, the tendency to focus on the concrete details of external events rather than on feelings and patient's own inner experience.
- PGA: clinical severity evaluation of the disease given by the physician and the patient.

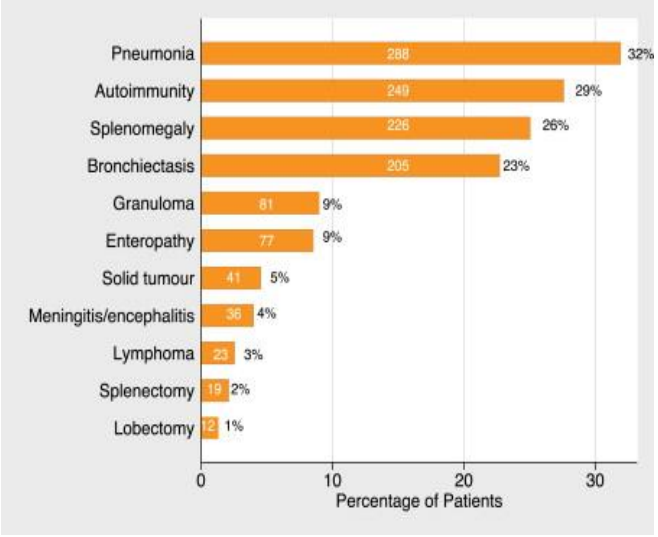
Quinti I, et al. *Yonsei Med J*. 2012.

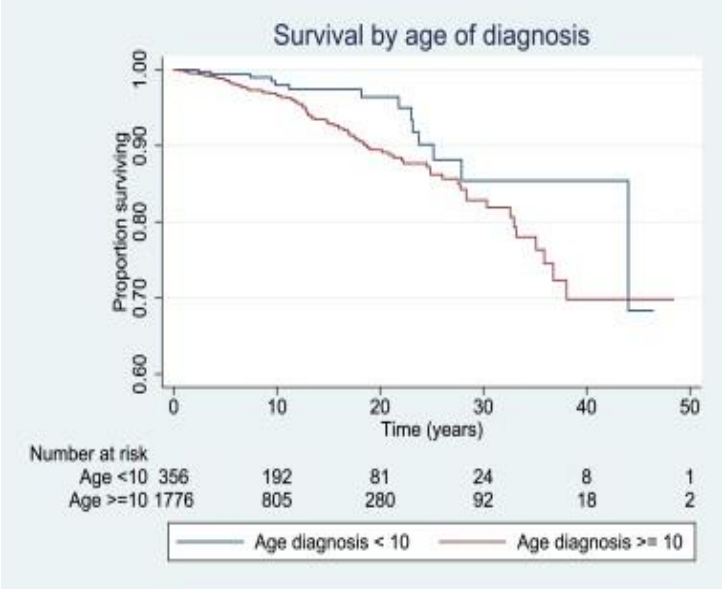
Activity, severity and impact of respiratory disease in primary antibody deficiency syndromes.

Hurst JR, Workman S, Garcha DS, Seneviratne SL, Haddock JA, Grimbacher B

J Clin Immunol. 2014 Jan;34(1):68-75.

SF36 and respiratory SGRQ questionnaires: much of the quality of life impact in PAD relates to respiratory involvement, specifically the severity of airflow obstruction, respiratory exacerbation frequency and dyspnoea.





Clinical picture and treatment of 2212 patients with common variable immunodeficiency (ESID, 2014)

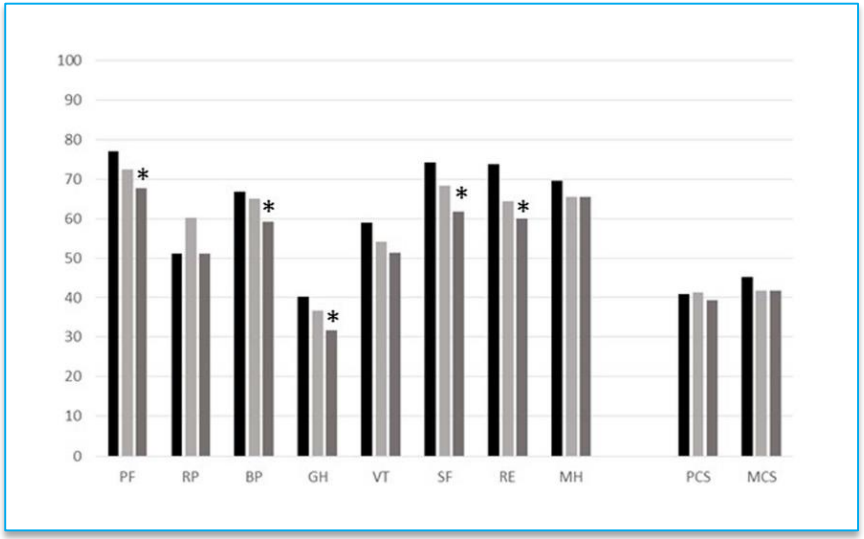
Longitudinal study on health-related quality of life in a cohort of 96 patients with common variable immune deficiencies

frontiers in IMMUNOLOGY

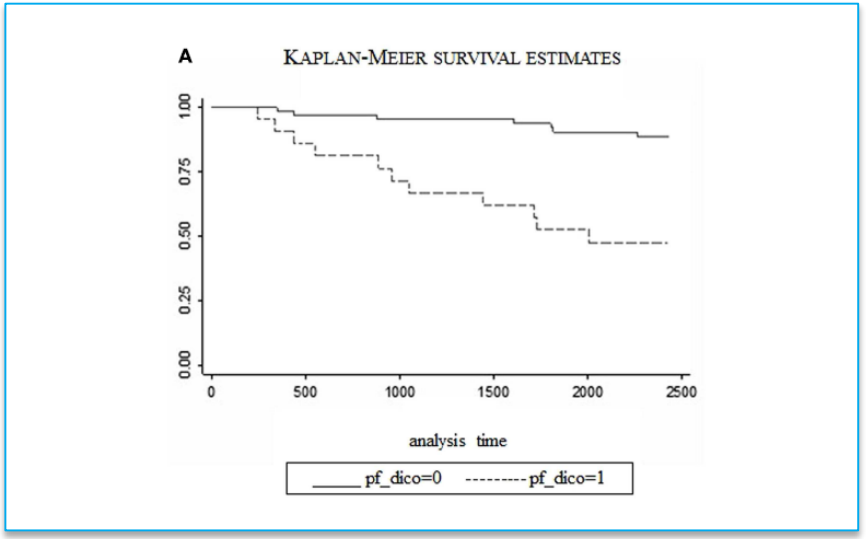
ORIGINAL RESEARCH ARTICLE
published: 26 November 2014
doi: 10.3389/fimmu.2014.00605

Longitudinal study on health-related quality of life in a cohort of 96 patients with common variable immune deficiencies

*Stefano Tabolli[1], Patrizia Giannantoni[1], Federica Pulvirenti[2], Fabiola La Marra[2], Guido Granata[2], Cinzia Milito[2] and Isabella Quinti[2]**



Profile of the mean values for each scale of SF-36 for the group of 66 CVID patients observed at different times (T0, black column, T1 pale-gray column, T2, gray column



Survival rates for CVID patients ("at-risk" vs. "not at-risk") considering SF-36 scales:
Physical Functioning, cut-off at 50 (A) and Social Functioning cut-off at 37.5 (B).

Do We Need a Disease-Specific Instrument?

Each QOL tool covers a number of domains (measurements of different characteristics) and they measure quantitative outcome

Questionnaires designed to be **applicable for general population** such as the SF-36, SF-12, the Nottingham Health Profile (used for primary care), the European Quality of Life Instrument - EQ-5D, the McGill QOL (MQOL) scale and GHQ- 12 and GHQ-28.

Examples of **disease-specific questionnaires:**

- St George respiratory questionnaire (SGRQ)
- Inflammatory Bowel Disease Questionnaire (IBDQ)
- Dialysis Symptom Index (DSI), the Kidney Disease Quality of Life Instrument Short Form-KDQOL-SF36
- AQLQ, **Asthma** Quality of Life Questionnaire
- FAQL-PB, Food Allergy Quality of Life – Parental Burden, FAQLQ-PF, **Food Allergy Quality** of Life Questionnaire – **Parent Form,** FAQLQ-AF, Food Allergy Quality of Life Questionnaire – **Adult Form,** FAQLQ-CF, Food Allergy Quality of Life Questionnaire **– Child Form,** FAQLQ-TF, Food Allergy Quality of Life Questionnaire – **Teenager Form,** FAQL-teen, Food Allergy Quality of Life Assessment Tool for **Adolescents,** PFA-QL, Paediatric Food Allergy Quality of Life Questionnaire,
- RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire

Development and Validation of a Questionnaire To Measure Quality Of Life In Adult Patients With Primary Antibody Deficiencies.

The CVID_QoL Questionnaire/Το ερωτηματολόγιο CVID_QoL

Focus group (10 patients) to define the first 30 items. Open and registered discussion with the team psychologist on the most relevant issues related to physical, mental and social behavior aspects. Definition of a 3 point answers for each question.

Individual interview to determine the correct understanding of the question and specific terms used

Focus group with the same 10 patients to re-define the first 30 items. Open and registered discussion with the team psychologist on the most relevant issues related to physical, mental and social behavior aspects

Individual administration of the questionnaire to a second group of 30 patients by the psychologist. At the same setting the SF36 (gold standard) will be administered.

Individual administration of the questionnaire in 3 additional groups of patients (20 patients each) in 3 different Italian Centres for adults PAD on Ig replacement At the same setting the SF36 (gold standard) will be administered

For the purposes of the results analysis, the emotions and functioning scales of the PAD-related questionnaire will be compared with the widely used SF-36 questionnaire by transforming them to a linear scale of 100, to allow direct comparability of scores between the instruments.

To verify that responses to individual items are affected by diagnosis in a comparable way in the two instruments, we will perform a DIF analysis on random subsamples (n=230) of our study population. DIF analysis verifies whether a given construct has a similar meaning across different subgroups of patients.

Each patient filled: - the new questionnaire twice 2 weeks apart; - the SF-36; - the St George questionnaire; - the GHQ-12 questionnaire; the EuroQoL; PGA

Alpha di Cronbach	Alpha: 0,939
Test-Retest	RHO di Pearson: 0,89 (p<0.01)

TEST	RHO di Pearson	P value
PCS	-0,73	<0.0001
PF	-0,52	0.007
RP	-0,72	<0.0001
BP	-0,59	0.002
GH	-0,63	0.001
VT	-0,53	0.006

	GHQ sum	symptoms	activity	impact	total
QUEST_TOT (Pearson correlation)	,536	,206	,584	,515	,526
P (2-tailed)	0,007	ns	0.002	0.008	0.007

EQ5D	VAS	RHO Pearson: 0,65	P 0.01

IMMUNODEFICIENZA ANTICORPALE

QUESTIONARIO SULLO STATO DI SALUTE/QUALITÀ DI VITA

COGNOME : .....
NOME: .....

CODICE PAZIENTE .....
DATA .....

Per favore, metta una crocetta sul ciascuna delle seguenti affermazioni che meglio descrive la sua condizione, considerando il suo stato di salute e la sua qualità di vita

It is universally accepted that immunoglobulin therapy is a life-saving treatment in patients with humoral PID

Currently the consumption of immunoglobulin for PID represents a small fraction of the total IVIg market

In the recent past we have been observing:

- An increase in the demand for plasma and in the consequent need to increase the number of donors
- Changes in methods to improve IgG recovery and to increase productivity as a response to growing clinical demand
- Introduction of immunoglobulin treatments with higher concentration
- Changes in the timing of administration with an increase in the rate of infusion
- Introduction of immunoglobulin treatment administered subcutaneously mainly confined initially to patients with PID and later extended to other clinical indications which often require higher volumes of infusion.

OPTIMAL USE OF COAGULATION FACTORS & IMMUNOGLOBULINS MEETING

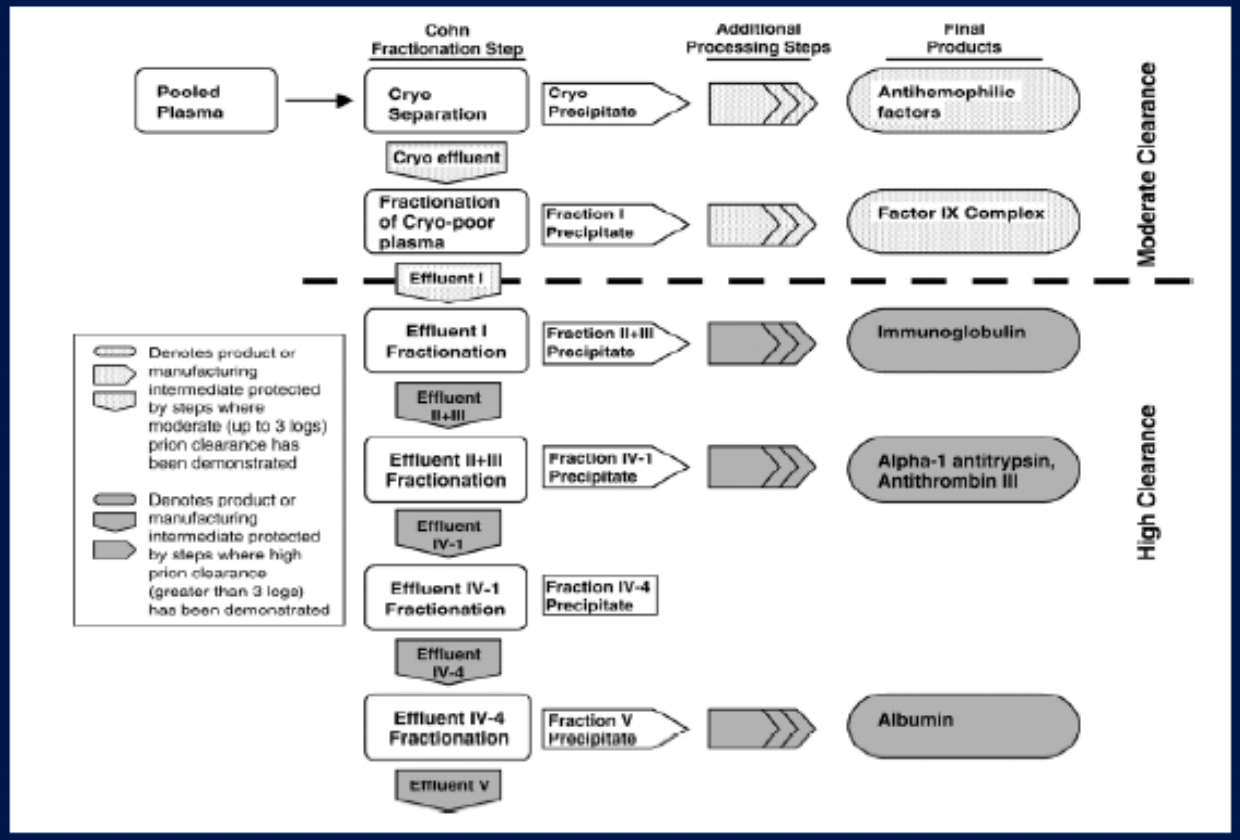
(Kreuth III)

26-27 April 2013

FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
CENTER FOR DRUG EVALUATION AND RESEARCH

Washington, D.C.
Wednesday, January 29, 2014

Cold Ethanol Fractionation



frontiers in IMMUNOLOGY

REVIEW ARTICLE
published: 23 December 2014
doi: 10.3389/fimmu.2014.00665

Manufacture of immunoglobulin products for patients with primary antibody deficiencies – the effect of processing conditions on product safety and efficacy

Albert Farrugia[1,2,3] and Isabella Quinti[4]*

Cohn like	Modern
Precipitate I	Precipitate I+II+III
Precipitate II+III	Octanoic Acid Fractionation
Precipitate III	Chromatography
Cohn II	
≥ 2.5 g / L	≥ 3.5 g / L

frontiers in IMMUNOLOGY

REVIEW ARTICLE
published: 05 February 2015
doi: 10.3389/fimmu.2015.00011

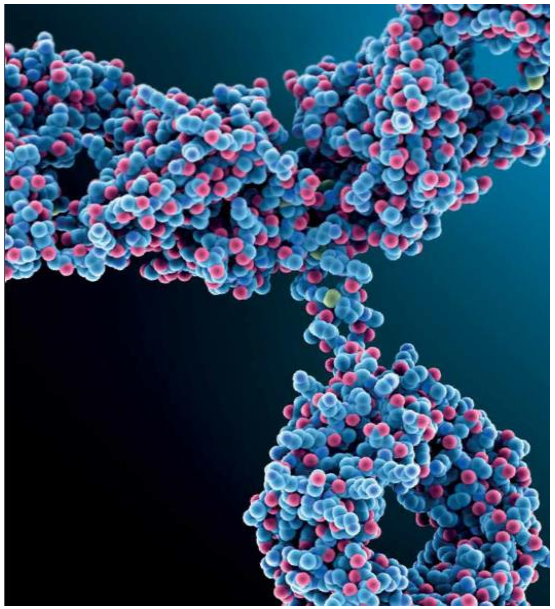
On the dark side of therapies with immunoglobulin concentrates: the adverse events

*Peter J. Späth[1], Guido Granata[2], Fabiola La Marra[2], Taco W. Kuijpers[3] and Isabella Quinti[2]**

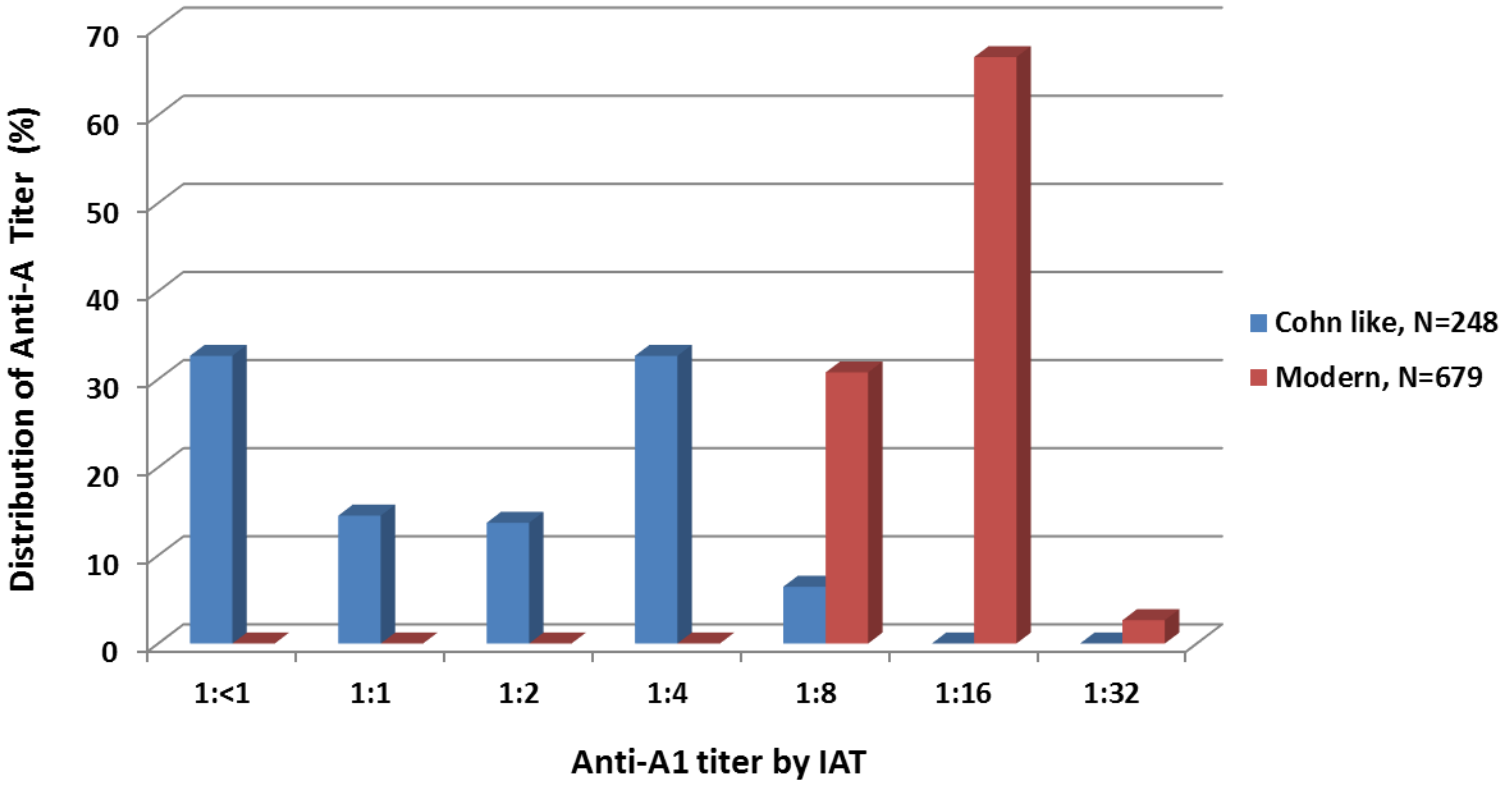
Fatigue	Common (SCIG as well)	"Flu-like" symptoms	Common	Persistent headache	Rare	Vomiting	Common	Cutaneous vasculitis	Rare
Malaise	Common	Anaphylactoid symptoms	Rare	Shortness of breath	Common	Cramping	Common	Hemolysis (clinically not significant)	Common
Fever	Common		Complement activation	Bronchospasm	Common	Diarrhea	Common	Acute hemolysis/hemolytic anemia	Rare
Flushing	Common		Immune complexes (presence of acute infection)	Pleural effusion	Rare	Colitis	Rare		
Chills	Common	Full blown anaphylaxis	Rare	TRALI	Rare	Tubular swelling	Rare	Thrombotic phenomena (DVT, stroke, cardial infarction)	Rare
Anorexia	Common		Complement activation (in the presence of acute infection)	Hypotension	Common	Renal failure	Rare	Hyperviscosity	Rare
Myalgia	Common	Headache	Common	Hypertension	Common	Infusion site pain, swelling, erythema	Common (SCIG more frequent)	Neutropenia	Rare
Arthralgia	Common	Migraine	Common	Tachycardia	Common	Urticaria	Common	Blood borne infectious disease	Rare
Joint swelling	Common	Dizziness	Common	Chest/back pain	Common	Non-specific macular or maculopapular eruptions/eczema	Common	Inappropriate handling before infusion	
		Aseptic meningitis	Rare	Arrhythmia	Rare	Pruritus	Common		
		Diffuse pain, muscle pain	Rare	Myocardial infarction	Rare	Erythema multiforme	Rare		
		Dysesthesia	Rare	Anorexia	Common				
		Weakness	Rare	Nausea	Common				

IVIG treatment and hemolysis

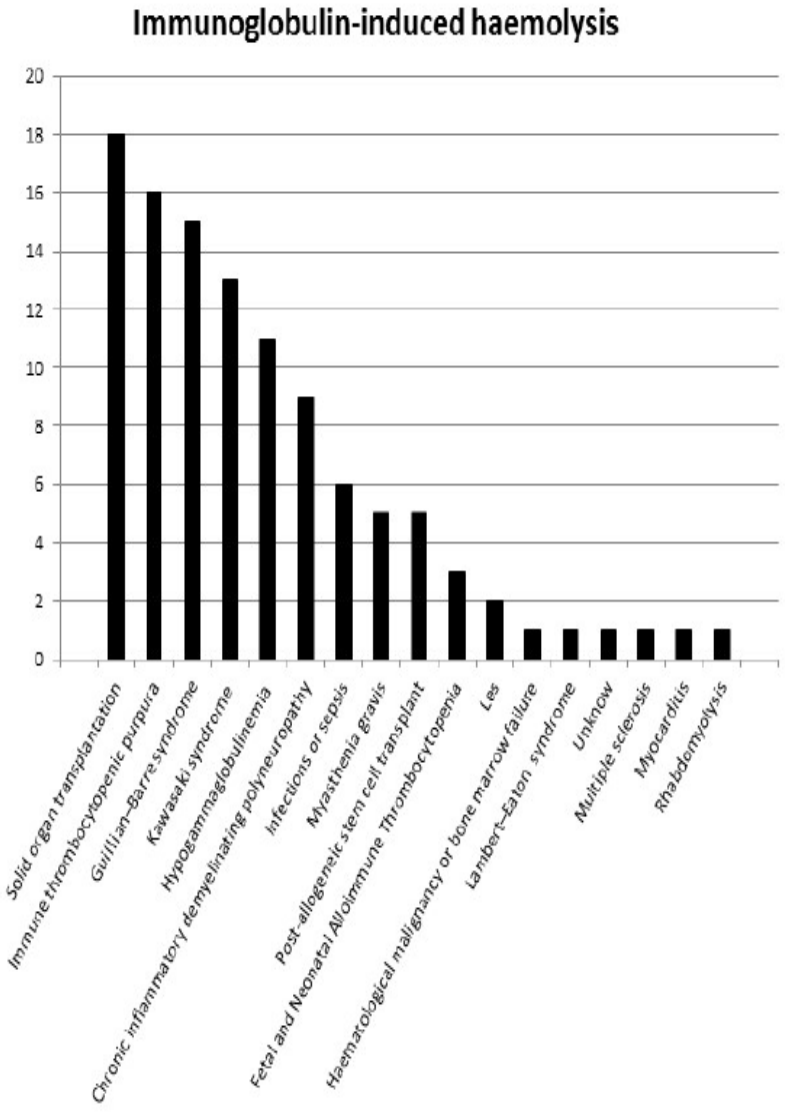
- IVIG is used to treat a range of conditions:
  - Primary and secondary immune deficiencies
  - Chronic inflammatory demyelinating polyneuropathy
  - Immune thrombocytopenia
- Hemolysis has been reported following IVIG treatment
- Risk factors for hemolysis
  - High cumulative doses of immunoglobulins
  - Non-O blood group of patients
  - Underlying inflammatory condition

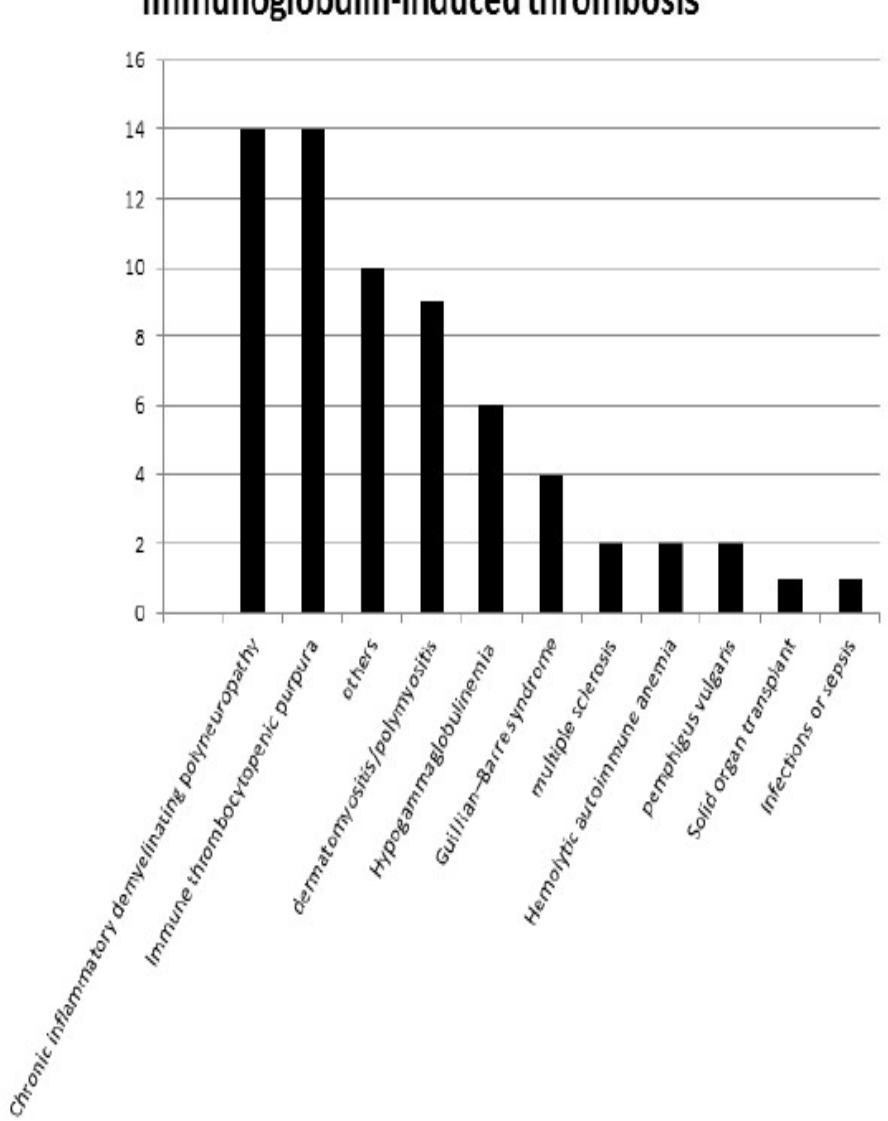


Anti-A in Cohn like versus Modern Processes



- Cohn like processes have ≥ 2 titer step reduction capacity


Immunoglobulin-induced haemolysis
20
18
16
14
12
10
8
6
4
2
0
Solid organ transplantation
Immune thrombocytopenic purpura
Guillian–Barre syndrome
Kawasaki syndrome
Hypogammaglobulinemia
Chronic inflammatory demyelinating polyneuropathy
Infections or sepsis
Myasthenia gravis
Post-allogeneic stem cell transplant
Fetal and Neonatal Alloimmune Thrombocytopenia
Haematological malignancy or bone marrow failure
Lambert–Eaton syndrome
Unknow
Multiple sclerosis
Myocarditis
Rhabdomyolysis


Immunoglobulin-induced thrombosis
16
14
12
10
8
6
4
2
0
Chronic inflammatory demyelinating polyneuropathy
Immune thrombocytopenic purpura
others
dermatomyositis/polymyositis
Hypogammaglobulinemia
Guillian–Barre syndrome
multiple sclerosis
Hemolytic autoimmune anemia
pemphigus vulgaris
Solid organ transplant
Infections or sepsis

Transfusion. 2015 May;55(5):1067-74

ORIGINAL ARTICLE

Hemolysis in patients with antibody deficiencies on immunoglobulin replacement treatment

Isabella Quinti,[1] Federica Pulvirenti,[1]* Cinzia Milito,[1] Guido Granata,[1] Gianluca Giovannetti,[2] Fabiola La Marra,[1] Anna M. Pesce,[1] Albert Farrugia,[3,4,5] Serelina Coluzzi,[2] and Gabriella Girelli[2]*

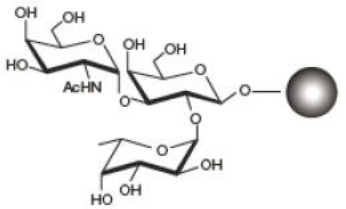
- Post-Immunoglobulin haemolysis can occurred in PAD patients receiving Ig at replacement dosages.
- Polyvalent Ig preparations can contain multiple clinically significant antibodies that could have unexpected haemolytic consequences, as anti-C and anti-c
- Mild haemolytic reactions can be easily missed and the true incidence of such reactions is difficult to document without careful clinical and laboratory follow-up.
- In terms of safety the issue of acute and chronic haemolysis in long term recipients of immunoglobulin treatment administered at replacement dosages should be more widely recognized
- The effects of the recent changes in the immunoglobulin production and schedules of administration should be assessed in studies of drug surveillance

Measures to reduce the Anti-A and Anti-B titers

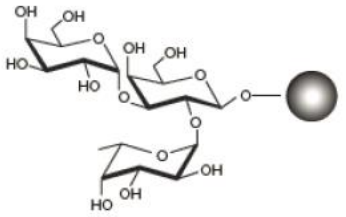
1. Screening of Plasma Donors (Anti-A)
-5% of donors were identified as 'high titer' and their plasma screened out

2. Introduction of an immunoaffinity chromatography (IAC) step

Blood group A trisaccharide



Blood group B trisaccharide



Reference: Siani *et al.* (2014) Biologics in Therapy

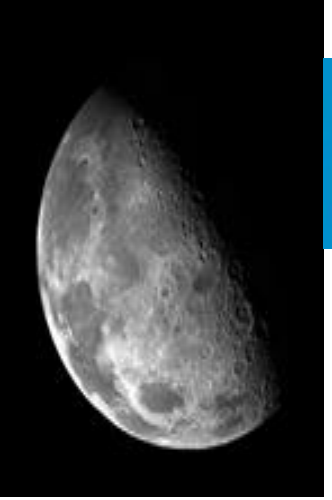
Concerns on the idea of gasoline-like treatment in primary antibody deficiencies (PAD)

The idea of a mere replacement function in patients with PAD might possibly be borrowed from the model of other clinical conditions requiring a replacement such as haemophilia.

In primary antibody deficiencies, immunoglobulin treatment is obviously replacing a missing feature. However, beside the antibody deficiency, complex immune alterations are responsible for the large number of PID-associated diseases.

Moreover, the immunomodulatory effects of immunoglobulin administered at replacement dosages on multiple cells and immune system functions are still largely to be checked in in vitro studies and in vivo.

A wide debate between experts is necessary to afford the new challenge on immunoglobulin usage



frontiers in IMMUNOLOGY

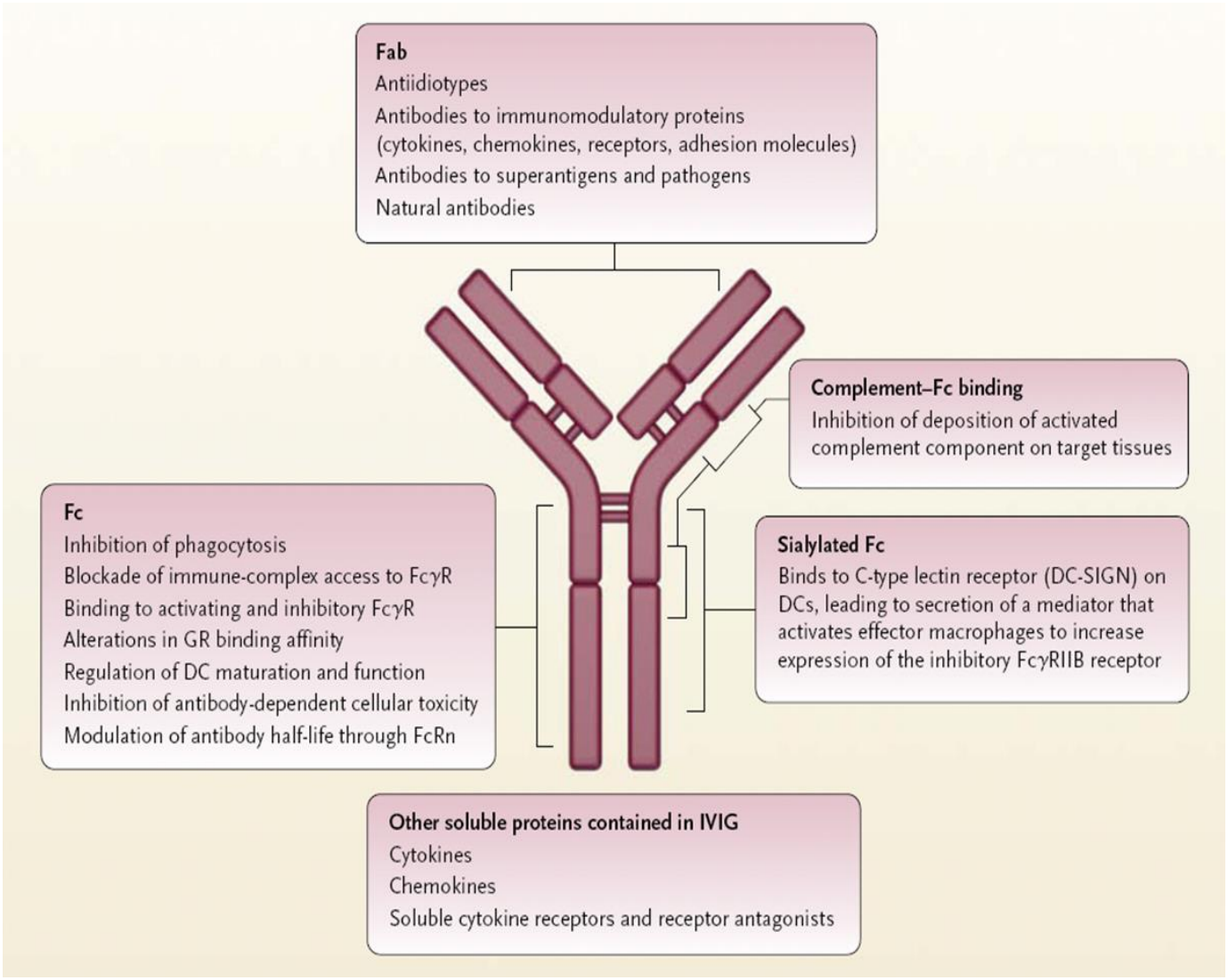
OFFICIAL JOURNAL OF THE IUIS

Research Topic:

Immunoglobulin therapy in the 21st century : the dark side of the moon

11 Articles 45 Authors

Immunomodulatory effects of IVIg at replacement doses



IVIg 'replacement therapy' in PAD is not a mere passive transfer of antibodies to prevent exclusively the recurrent infections;

rather it has an active role in regulating autoimmune and inflammatory responses through modulating B cell functions and thus imposing dynamic equilibrium of the immune system.

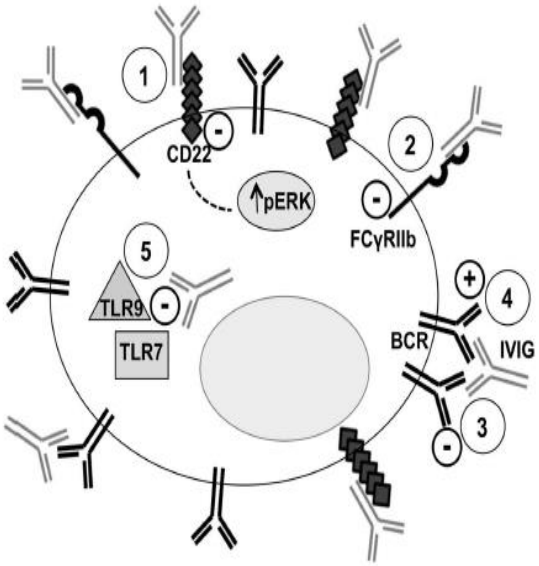
J Autoimmun. 2011;36:9-15

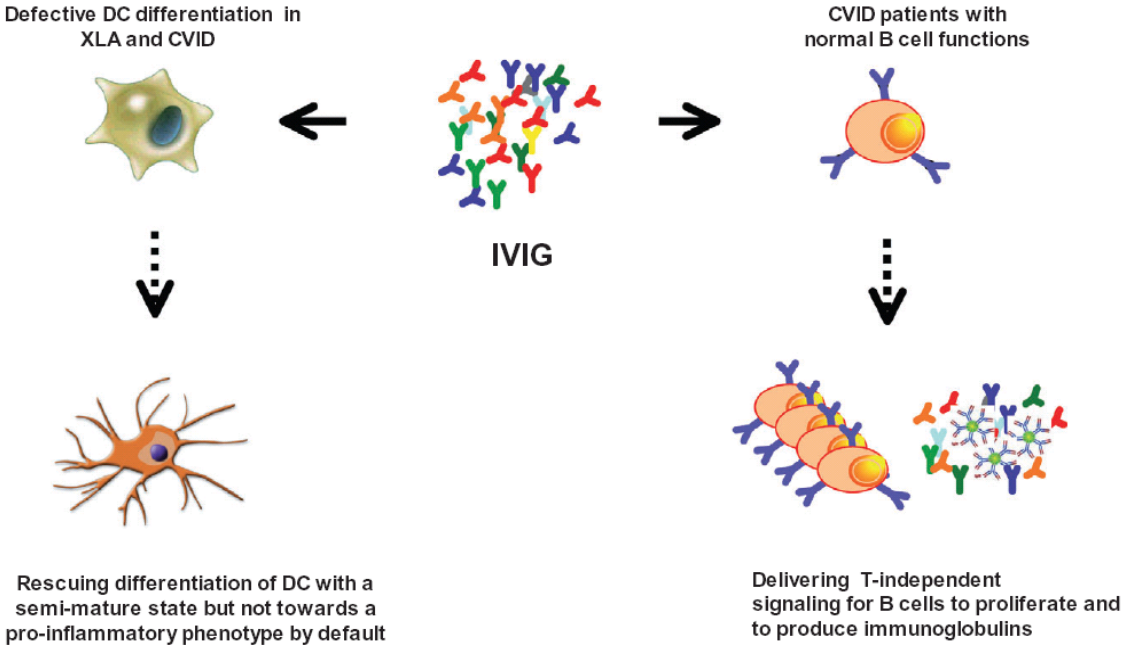
frontiers in IMMUNOLOGY

MINI REVIEW ARTICLE
published: 22 January 2015
doi: 10.3389/fimmu.2015.00004

Intravenous immunoglobulin and immunomodulation of B-cell – *in vitro* and *in vivo* effects

Milica Mitrevski[1], Ramona Marrapodi[1], Alessandro Camponeschi[1], Filomena Monica Cavaliere[2], Cristina Lazzeri[1], Laura Todi[1] and Marcella Visentini[1]*





frontiers in
IMMUNOLOGY

MINI REVIEW ARTICLE
published: 16 December 2014
doi: 10.3389/fimmu.2014.00637

Persistent immune activation in CVID and the role of IVIg in its suppression

*Dominic Paquin-Proulx and Johan K. Sandberg**

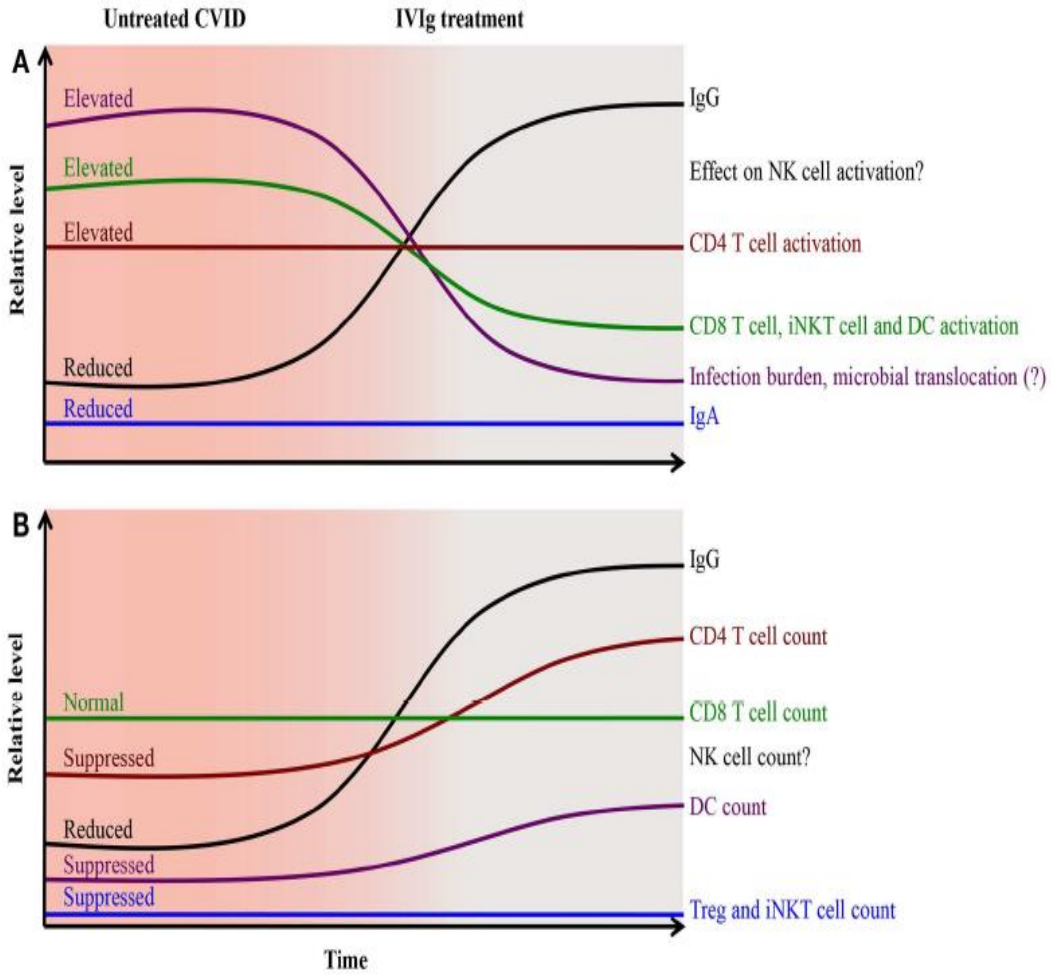


FIGURE 1 | Pathological changes and activation of cellular immunity in CVID is partially alleviated after immunoglobulin replacement therapy. IgG replacement therapy restores humoral immunity and provides better control of microbes and pathogens, reducing the infection burden on the immune system. This together with triggering of the FcR-mediated inhibitory effects on antigen presenting cells leads to reduced activation of CD8 T cells, iNKT cells, and DCs **(A)** and improvement in CD4 T cell counts and DC count **(B)**.

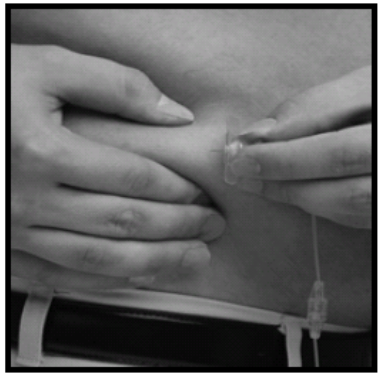
The administration of immunoglobulins induces multiple effects on the immune system functions

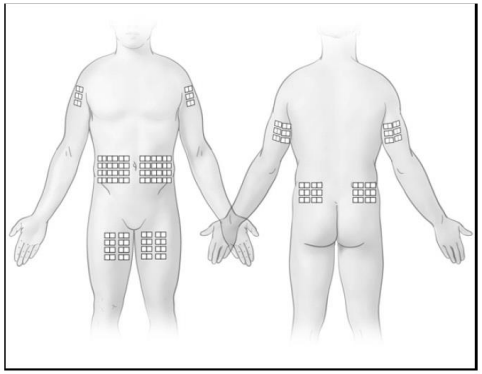
The knowledge of these effects must be better evaluated, must guide future decisions and treatment choices, should guide clinical and basic research

Therapy should be individualized

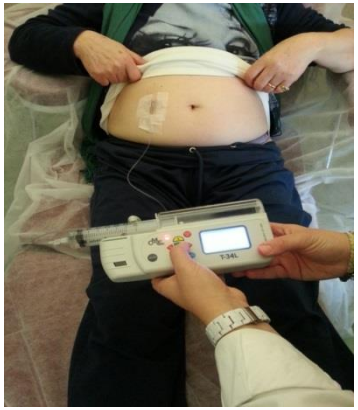
Immunoglobulins can not be considered a generic drug

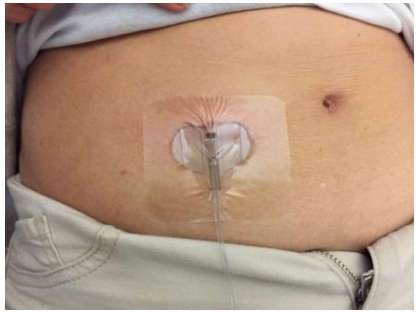
Subcutaneous IgG





Facilitated subcutaneous IgG





New prospective

- Immunoglobulins with high IgA and IgM content
- Nebulized IgA and IgM for Prevention of Respiratory Tract Infection in PID

Συμπεράσματα

Conclusions

Since its introduction in the early ’80 the Ig replacement did a great job in that the mortality for infections is no more the major clinical problem.

Our attention must now be paid to early diagnosis of lymphoid and non lymphoid cancers

Thank you for your attention

Σας ευχαριστώ για την προσοχή σας!

Thanks to:

European Commission

Agenzia
Italiana del Farmaco

Jeffrey Modell
Foundation

Centre for Primary Immunodeficiencies
Sapienza Università di Roma

isabella.quinti@uniroma1.it
Tel +39-06-49972007