IVIG or Subcutaneous IG ?

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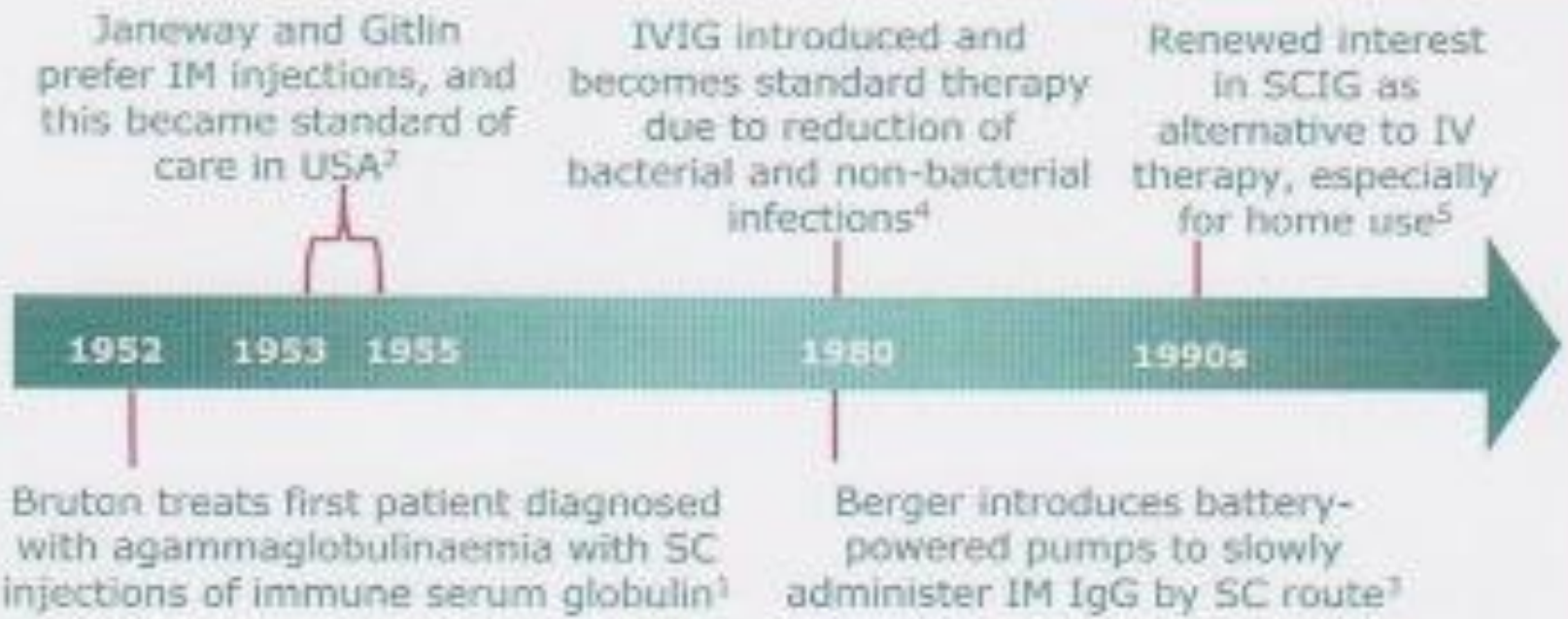
Landmarks in the history of immunoglobulin replacement therapy



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ISTEP

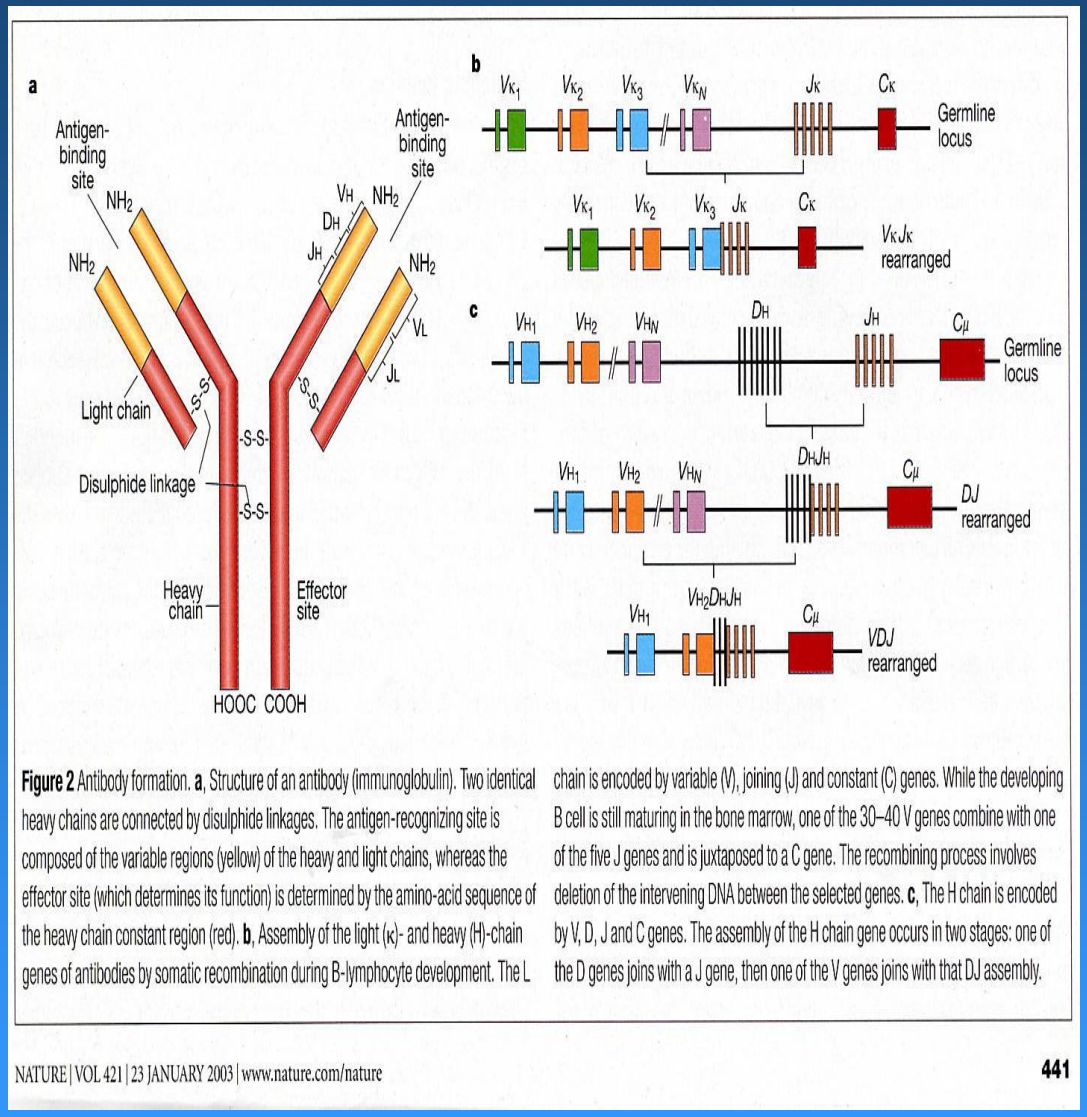
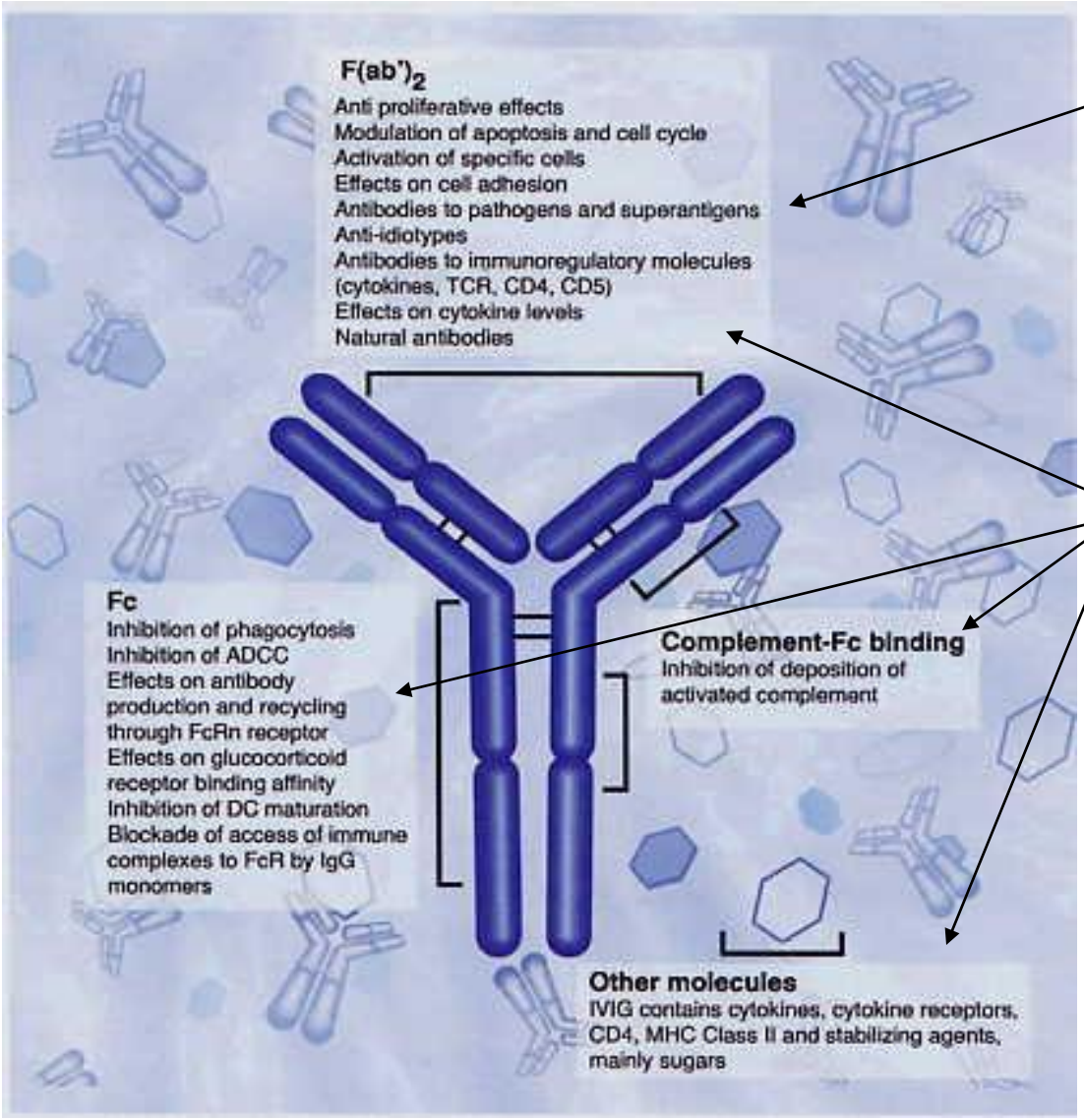


Figure 2 Antibody formation. **a**, Structure of an antibody (immunoglobulin). Two identical heavy chains are connected by disulphide linkages. The antigen-recognizing site is composed of the variable regions (yellow) of the heavy and light chains, whereas the effector site (which determines its function) is determined by the amino-acid sequence of the heavy chain constant region (red). **b**, Assembly of the light (κ)- and heavy (H)-chain genes of antibodies by somatic recombination during B-lymphocyte development. The L chain is encoded by variable (V), joining (J) and constant (C) genes. While the developing B cell is still maturing in the bone marrow, one of the 30–40 V genes combine with one of the five J genes and is juxtaposed to a C gene. The recombining process involves deletion of the intervening DNA between the selected genes. **c**, The H chain is encoded by V, D, J and C genes. The assembly of the H chain gene occurs in two stages: one of the D genes joins with a J gene, then one of the V genes joins with that DJ assembly.

Igs are “live” molecules

Several genes are involved in the synthesis of one molecule

We have the possibility to produce > 10^{14} different antibodies

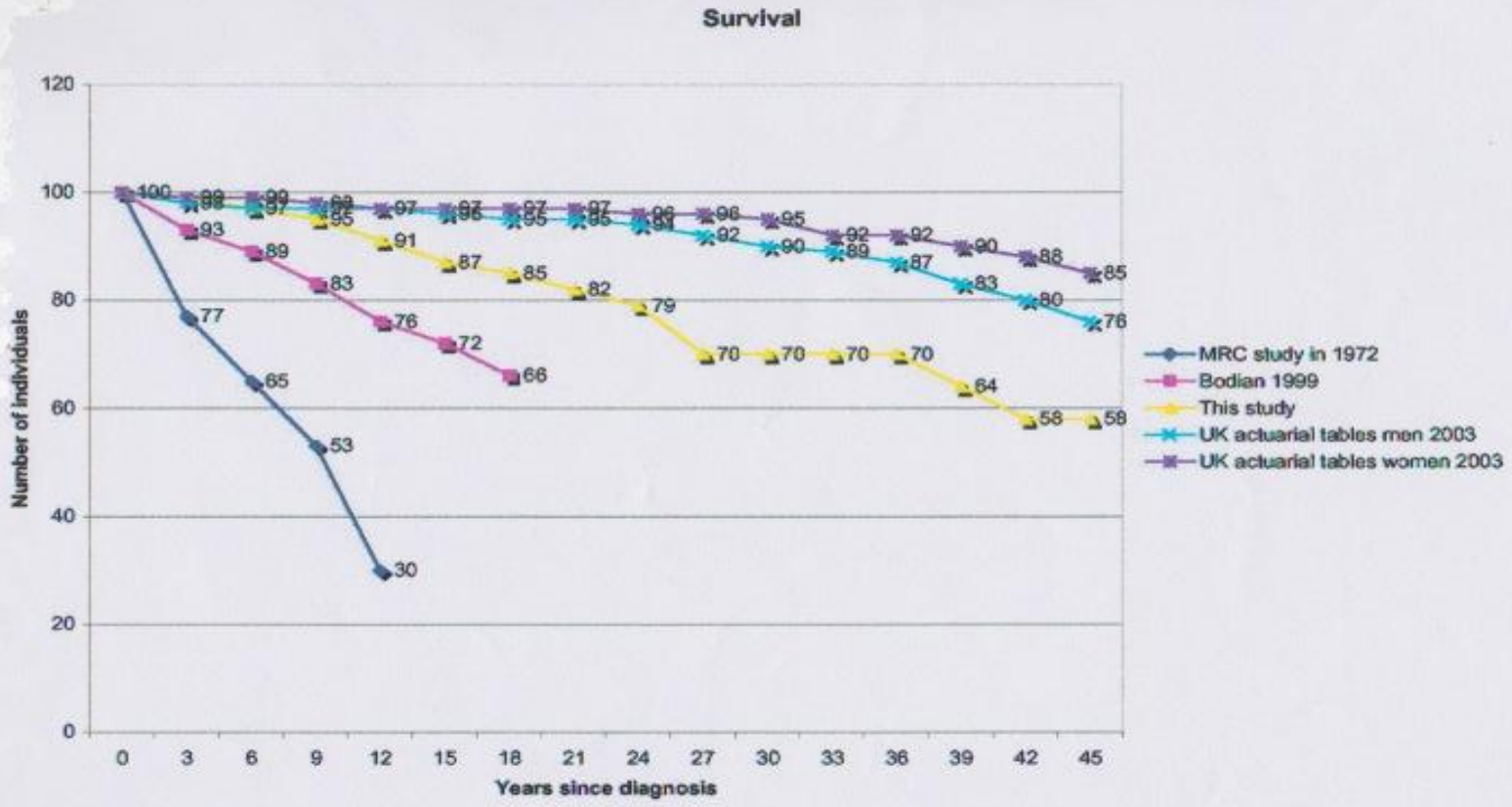


Main function as replacement therapy of Ab deficiencies

Immunomodulatory functions

From Jolles S et al. Clin Exp Immunol 2005

Mortality by year since diagnosis.



Chapel H et al. Blood 2008;112:277-286

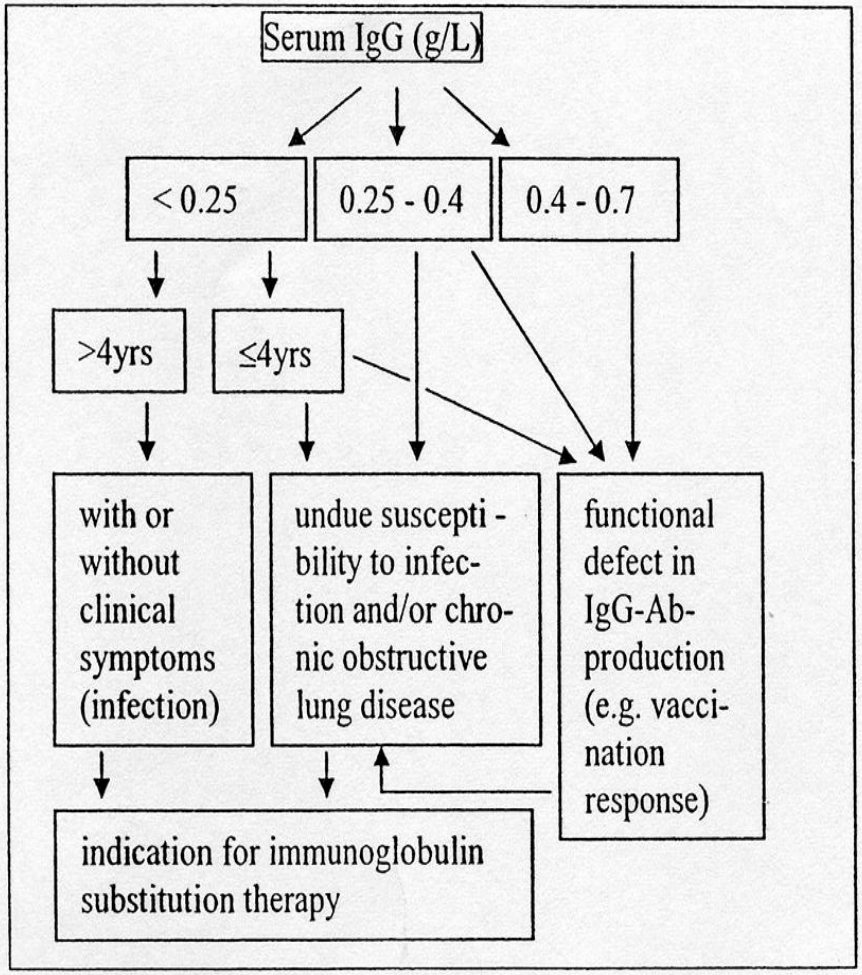


Figure: Indication for immunoglobulin substitution therapy relative to the severity of the hypogammaglobulinemia (i.e. decreased IgG) in patients with primary antibody deficiency

WHEN to begin ?

ESID Educational Symposium
2002 H.Wolf

Journal of Clinical Immunology, Vol. 20, No. 2, 2000

The Comparison of the Efficacy and Safety of Intravenous Versus Subcutaneous Immunoglobulin Replacement Therapy

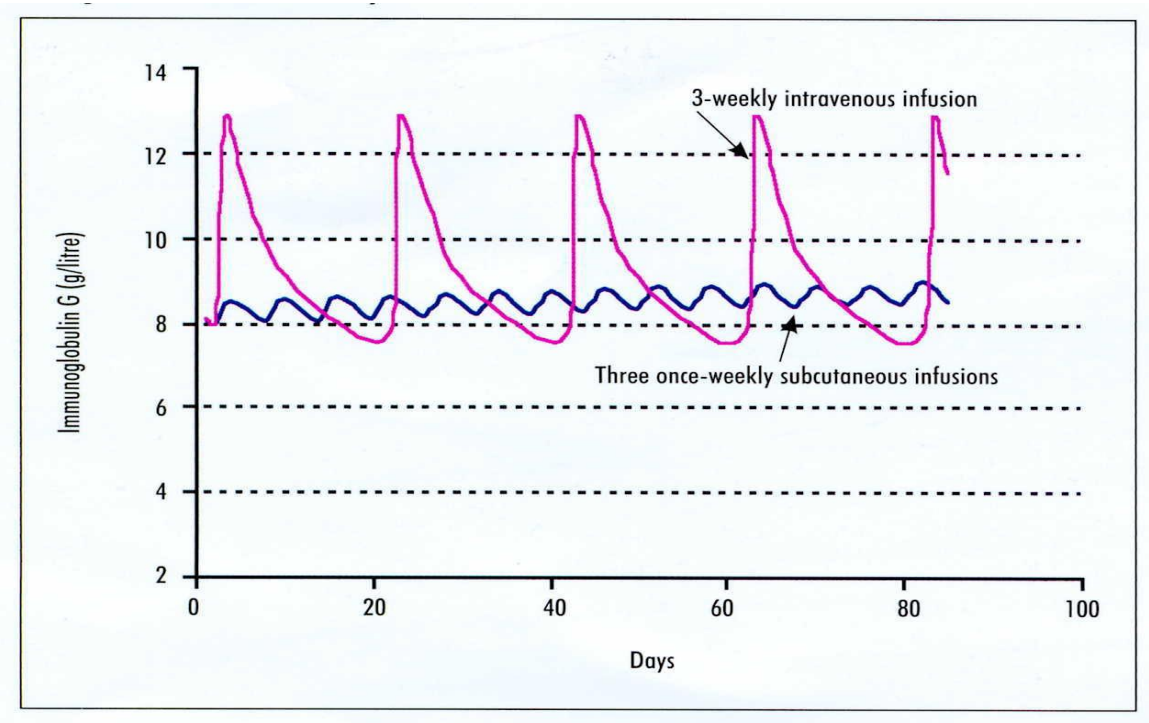
H. M. CHAPEL,[1,6] G. P. SPICKETT,[2] D. ERICSON,[3] W. ENGL,[4] M. M. EIBL,[5] and J. BJORKANDER[3]

Efficacy ands safety of home-based subcutaneous immunoglobulin replacement therapy in paediatric patients with primary Immunodeficiencies.
M. Borte et al 2011 Clin Exp Immunol

Major Advantages and Disadvantages of Subcutaneous and Intravenous Routes of IgG Replacement

Subcutaneous	Intravenous
Advantages	
(1) Lack of requirement for venous access.	(1) Convenient and will tolerated by most patients.
(2) Slow administration or gradual adsorption obviates rapid large swing in serum IgG and reduces severe headaches and other adverse effects.	(2) Ability to give large volume per infusion allows intermittent dosing (every 21-28 days).
(3) Maintenance of more consistent IgG levels eliminates low troughs.	
(4) Facilitates self or home infusion, increasing patient autonomy – may improve patient's self-image and sense of control.	
Disadvantages	
(1) Relatively small volume per infusion and requires frequent dosing – at least once a week in most cases.	(1) Requires venous access and trained personnel in most situations.
(2) Ability to self-infuse requires reliable patient.	(2) Large shift in IgG levels during dosing interval may cause adverse effects at or just after peak, and during low trough.
(3) No preparation currently licensed for subcutaneous use in the US.	

Differences : IVIG / Subcutaneous Ig



Brit J Hosp Med 2007

Advantages: - at-home therapy

- more “physiological” administration

- less “medical “ dependence

Table 1. **Infections in Patients with Primary Hypogammaglobulinemia Treated with Two Different Dosages of Intravenous Immunoglobulin**

Variable	Standard-Dose Therapy (n = 41)	High-Dose Therapy (n = 43)	Difference (95% CI)	P Value
Patients with infections, n	37	36		
Total infections related to immunodeficiency, n*	134	100		
Mild	54	38		
Moderate	17	11		
Severe	63	51		
Mean total immunodeficiency-related infections per patient ± SD (95% CI), n†	3.5 ± 2.6 (2.7–4.3)	2.5 ± 2.4 (1.8–3.2)	1.1 (0.4 to 1.8)	0.004
Median duration of immunodeficiency-associated infections (range), d†	33 (1–185)	21 (1–125)		0.015
Total respiratory infections, n	61	50		
Mean respiratory infections per patient ± SD (95% CI), n†	1.5 ± 1.6 (1.0–2.0)	1.2 ± 1.7 (0.7–1.7)	0.46 (−0.18 to 0.78)	0.18
Median duration of respiratory infections (range), d†	29 (5–178)	22 (2–125)		0.16

* Type of infection was categorized according to the criteria described in reference 18.
† Results are based on data from 41 patients. Two patients did not receive standard-dose intravenous immunoglobulin; therefore, no results were obtained for them during their respective standard-dose periods. Results were compared by using the paired t-test.

Eijkout et al 2001

Use of higher IVIG doses improves the clinical status of patients. Control trials are few, but GENERAL experience supports it !

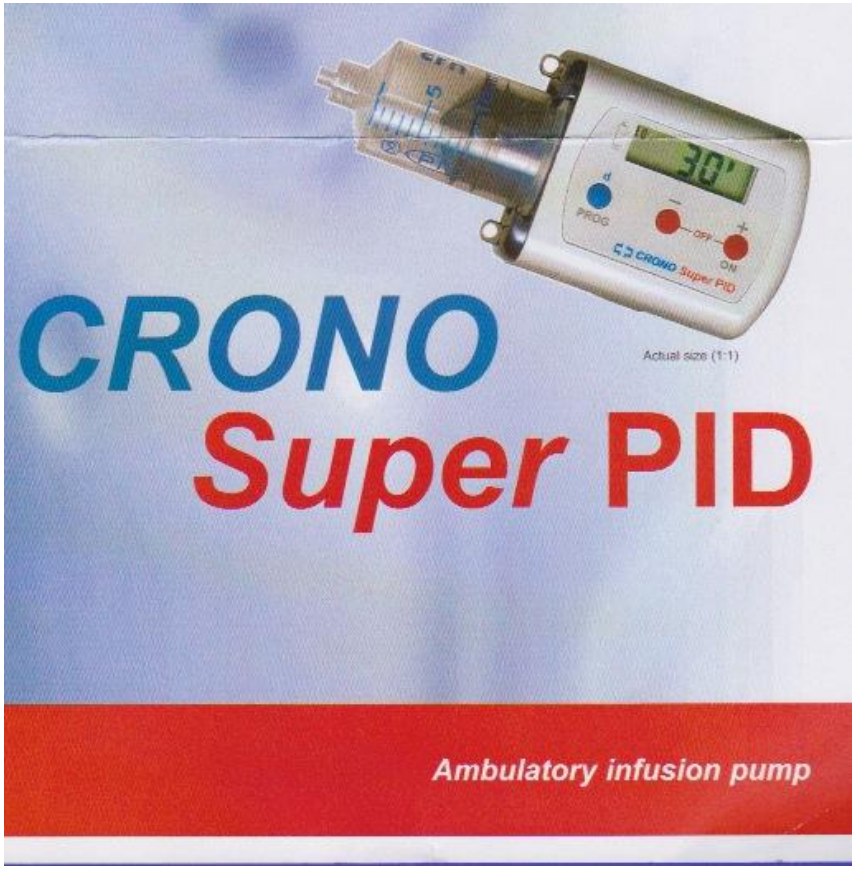
It is the same when using **subcut.IG** "Evaluation of correlation between dose and clinical outcome in subcut. IG replacement therapy" J Orange et al. Clin Exp Immunol 2012

Table V Adverse events[a] irrespective of causality in ≥10% of subjects during SC treatment

Adverse events	All adverse events		Adverse events occurring within 72 h of infusion	
	Number (%) of subjects (N=47)	Number (rate) of adverse events (N=2294 infusions)	Number (%) of subjects (N=47)	Number (rate) of adverse events (N=2294 infusions)
Local reactions	21 (44.7)	56 (0.028)	21 (44.7)	53 (0.027)
Headache	23 (48.9)	45 (0.020)	18 (38.3)	27 (0.012)
Fever	14 (29.8)	22 (0.010)	9 (19.1)	11 (0.005)
Nausea	8 (17.0)	20 (0.010)	3 (6.4)	6 (0.003)
Vomiting	7 (14.9)	12 (0.005)	5 (10.6)	7 (0.003)
Fatigue	7 (14.9)	11 (0.005)	6 (12.8)	10 (0.004)
Diarrhea	5 (10.6)	13 (0.006)	3 (6.4)	3 (0.001)
Asthma	6 (12.8)	9 (0.004)	4 (8.5)	6 (0.003)
Oropharyngeal pain	6 (12.8)	8 (0.003)	3 (6.4)	3 (0.001)
Upper abdominal pain	5 (10.6)	12 (0.005)	5 (10.6)	9 (0.004)

[a] Excluding infections

Very few adverse effects and most of them LOCAL



Pump used at the H. Vall d´Hebron Barcelona
10.5 x 4.5 cm

"Subcutaneous immunoglobulin therapy by rapid push is preferred to infusion by pump: a retrospective analysis"
R. Shapiro 2010 J Clin Immunol.

“Economic evaluation of immunoglobulin replacement therapy in patients with primary antibody deficiencies” J.Beaute et al (French PID study group) May 2010 Clin Exp Immunol.

….significant higher cost for IVIG. ….explained by the higher immunoglobulin mean dose prescribed for IVIG.

Difficulties in accepting subcutaneous IG

From the patient point of view :

- they do not want to be responsible for their therapy (afraid?)
- they do not want to think about the administration and doing it by themselves
- they do not like to use needles so often

From the physicians´ point of view:

-they feel they "lose" control of the patient

-do not like " changes "

It is VERY IMPORTANT to have different products and different ways of administration in order to choose the best for each patient !!!

New presentations and products:

- Subcut. IG 20% , very low IgA and proline as stabiliser (the same for IV preparation of the same pharmaceutical company). Possibility to use both products (e.g. change for holidays !)

- SAN DIEGO, Aug. 1, 2012 /PRNewswire/ -- Halozyme Therapeutics, Inc. (NASDAQ: HALO) ……. HyQ is an investigational product that includes plasma-derived Immune Globulin (IG) 10% and Halozyme's recombinant human hyaluronidase (rHuPH20) for subcutaneous administration in patients with primary immunodeficiency disease.