Clinical use of polyvalent immunoglobulins

Patient factors to consider when treating with immunoglobulin

Isabella Quinti
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Landmarks in the History of Immunoglobulin Replacement Therapy

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

**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

**Additional approved indications with criteria**
- Neuromuscular disorders
  - Guillain–Barre 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

Fab (variable region)

Idiotype

C1q-binding region

C3b- and C4b-binding region

Fc

Fcγ receptor types I, II, and III
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)
• 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.
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
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

Survival probability (SE)

1.00
0.75
0.50
0.25

10-year SURp (SE)
0.98 (0.01)

20-year SURp (SE)
0.96 (0.02)

30-year SURp (SE)
0.69 (0.10)

N. cases N. events
157 12

40-year SURp (SE)
0.60 (0.11)

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

Number of cases at risk:

Years from diagnosis

Clinical Immunology 2012;104:221–30
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)
### Risk factors for CVID-associated conditions

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


IgG replacement

Time in hospital by median IgG level

n = 609 CVID patients

- Time in hospital and serious infections correlate with trough level, but not days unable to perform daily duties and infectious episodes in general
The clinical phenotype characterized by a high infection risk is also associated with a poor response to vaccination.

The example of pneumococcal polysaccharide vaccination.

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

• 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

Adult patients with hypogammaglobulinemia (AFTER exclusion of secondary hypogammaglobulinemias)

Ig dosage repeated

evaluate immuno-phenotype

exclude other PID

2-3 isotypes <2SD

Post vaccination IgG, IgA, IgM anti-PnPs23

persistent Ab response

Hypogammaglobulinemia

FU

2-3 isotypes <3SD

CVID

Start IgG replacement

Post-vaccination IgA, IgM anti-PnPs23

no response to vaccination

CVID

Start IgG replacement
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

**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)
IgG trough levels might be increased by reducing intervals between administrations without need to increase the administration dosage.
Study Design

Enrollment (108 patients)

Group 1
High risk (56)
- Dosage adjusted to 2 weeks interval (48)
- Patient’s assessment relative to the study objective
  - Not achieved (6)
  - Achieved (42)
    - Shift to 1-week interval cumulative IVIG dose adjusted until the study objective
    - Maintain 2-week interval and dosage

Group 2
Fewer disease-associated complications (52)
- Maintain standard treatment with 3 or 4 weeks interval (52)
- Patient’s assessment relative to the study objective
  - Not achieved (4)
  - Achieved (48)
    - Shift to 2-week interval
    - Maintain 3-/4-week interval

3 months
Drop out (8) refuse to reduce IVIG interval

9 months
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.

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,

Resnick ES et al,
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
Longitudinal study on health-related quality of life in a cohort of 96 patients with common variable immune deficiencies

Stefano Tabolli¹, Patrizia Giannantoni¹, Federica Pulvirenti², Fabiola La Marra², Guido Granata², Cinzia Milito² and Isabella Quinti²∗
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.

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

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


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)
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
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.
### Alpha di Cronbach

**Test-Retest**

<table>
<thead>
<tr>
<th>TEST</th>
<th>RHO di Pearson</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCS</td>
<td>-0.73</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PF</td>
<td>-0.52</td>
<td>0.007</td>
</tr>
<tr>
<td>RP</td>
<td>-0.72</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BP</td>
<td>-0.59</td>
<td>0.002</td>
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<tr>
<td>GH</td>
<td>-0.63</td>
<td>0.001</td>
</tr>
<tr>
<td>VT</td>
<td>-0.53</td>
<td>0.006</td>
</tr>
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</table>

### RHO di Pearson: 0.89 (p<0.01)

### EQ5D

<table>
<thead>
<tr>
<th>VAS</th>
<th>RHO Pearson: 0.65</th>
<th>P 0.01</th>
</tr>
</thead>
</table>

### QUEST_TOT (Pearson correlation)

<table>
<thead>
<tr>
<th>GHQ sum</th>
<th>symptoms</th>
<th>activity</th>
<th>impact</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.536</td>
<td>0.206</td>
<td>0.584</td>
<td>0.515</td>
<td>0.526</td>
</tr>
</tbody>
</table>

| P (2-tailed) | 0.007 | ns | 0.002 | 0.008 | 0.007 |
IMMUNODEFICIENZA ANTICORPALE

QUESTIONARIO SULLO STATO DI SALUTE/QUALITÀ DI VITA

COGNOME: ..................................................  CODICE PAZIENTE .................
NOME: ........................................................ 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

Diagram showing the process of Cohn Fractionation Step with additional processing steps and final products.
Manufacture of immunoglobulin products for patients with primary antibody deficiencies – the effect of processing conditions on product safety and efficacy

Albert Farrugia1,2,3 and Isabella Quinti4

Cohn like

- Precipitate I
- Precipitate II+III
- Precipitate III
- Cohn II

Modern

- Precipitate I+II+III
- Octanoic Acid Fractionation
- Chromatography

≥ 2.5 g / L

≥ 3.5 g / L
# On the dark side of therapies with immunoglobulin concentrates: the adverse events

**Peter J. Späth**, Guido Gianata, Fabiola La Marra, Taco W. Kuipers, and Isabella Quinti

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Common (SCIG as well)</th>
<th>“Flu-like” symptoms</th>
<th>Common</th>
<th>Persistent headache</th>
<th>Rare</th>
<th>Vomiting</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Common</td>
<td></td>
<td></td>
<td>Shortness of breath</td>
<td>Common</td>
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<td>Malaise</td>
<td>Common</td>
<td>Anaphylactoid</td>
<td>Rare</td>
<td>Bronchospasm</td>
<td>Common</td>
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<tr>
<td>Fever</td>
<td>Common</td>
<td>complement activation</td>
<td>Immune complexes (presence of acute infection)</td>
<td>Pleural effusion</td>
<td>Rare</td>
<td></td>
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<td>Flushing</td>
<td>Common</td>
<td></td>
<td>Rare</td>
<td>TRALI</td>
<td>Rare</td>
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<td>Chills</td>
<td>Common</td>
<td>Full blown</td>
<td>Rare</td>
<td>Hypotension</td>
<td>Common</td>
<td>Renal failure</td>
<td>Rare</td>
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<td>Anorexia</td>
<td>Common</td>
<td>anaphylaxis</td>
<td>Rare</td>
<td>Hypertension</td>
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<tr>
<td>Myalgia</td>
<td>Common</td>
<td>Headache</td>
<td>Common</td>
<td>Tachycardia</td>
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<td>Arthralgia</td>
<td>Common</td>
<td>Migraine</td>
<td>Common</td>
<td>Chest/back pain</td>
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<td>Joint swelling</td>
<td>Common</td>
<td>Dizziness</td>
<td>Common</td>
<td>Arrhythmia</td>
<td>Rare</td>
<td></td>
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<td></td>
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<td>Aseptic meningitis</td>
<td>Rare</td>
<td></td>
<td></td>
<td>Puritus</td>
<td>Common</td>
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<tr>
<td></td>
<td></td>
<td>Diffuse pain, muscle pain</td>
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<td>Myocardial infarction</td>
<td>Rare</td>
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<td>Dysesthesia</td>
<td>Rare</td>
<td>Anorexia</td>
<td>Common</td>
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<tr>
<td></td>
<td></td>
<td>Weakness</td>
<td>Rare</td>
<td>Nausea</td>
<td>Common</td>
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</table>

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Common (SCIG as well)</th>
<th>“Flu-like” symptoms</th>
<th>Rare</th>
<th>Hypotension</th>
<th>Common</th>
<th>Renal failure</th>
<th>Rare</th>
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<tbody>
<tr>
<td>Cutaneous vasculitis</td>
<td>Rare</td>
<td></td>
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<td>Hemolysis (clinically not significant)</td>
<td>Common</td>
<td></td>
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<tr>
<td>Acute hemolysis/hemolytic anemia</td>
<td>Rare</td>
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<tr>
<td>Thrombotic phenomena (DVT, stroke, cardiac infarction)</td>
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<td>Hyperviscosity</td>
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<td>Neutropenia</td>
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<td>Blood borne infectious disease</td>
<td>Rare</td>
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<tr>
<td>Inappropriate handling before infusion</td>
<td>Common</td>
<td></td>
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*SCIG: subcutaneous immunoglobulin glubulin*
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
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

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

11 Articles  45 Authors
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
Intravenous immunoglobulin and immunomodulation of B-cell – *in vitro* and *in vivo* effects

*Milica Mitrevski*, *Ramona Maramodi*, *Alessandro Campaneschi*, *Filomena Monica Cavaliere*, *Cristina Lazzeri*, *Laura Todi* and *Marcella Visentini*

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**Defective DC differentiation in XLA and CVID**

Defective DC differentiation in XLA and CVID

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**IVIG**

Rescuing differentiation of DC with a semi-mature state but not towards a pro-inflammatory phenotype by default

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**CVID patients with normal B cell functions**

CVID patients with normal B cell functions

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**Delivering T-independent signaling for B cells to proliferate and to produce Immunoglobulins**

Delivering T-independent signaling for B cells to proliferate and to produce Immunoglobulins
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
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!

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