

# Anti-IgA antibodies:

# Risks and safety of immunoglobulin substitution

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# Anti-IgA antibodies

IgA deficiency (IgAD) and CVID

- **Anti-IgA antibodies**
  - incidence
  - relevance
  - detection
  - clinical consequence and therapeutic strategy

- IgG substitution therapy (IVIG, SCIG)



# Incidence of **anti-IgA antibodies** in Czech hypogammaglobulinemic patients

Specific anti-IgA antibodies may cause an anaphylactic reaction following an injection or infusion of products containing IgA.

↓

Screening, quantitative, specific and sensitive anti-IgA ELISA assay was established.

# Anti-IgA antibodies in Czech IgA deficient patients

(first results)

| Diagnosis | IgA serum level (g/l) | Number of patients | Patients with anti-IgA Abs | |
|---|---|---|---|---|
| | | | n | % |
| **IgAD** | < 0.01 | 112 | 15 | **13.4** |
| | 0.01-0.05 | 18 | 2 | **11.1** |
| | > 0.05-0.5 | 18 | 0 | 0 |
| Total | | 148 | 17 | 11.5% |



# Anti-IgA antibodies in Czech CVID patients

| Diagnosis | IgA serum level (g/l) | Number of patients | Patients with anti-IgA Abs | |
|---|---|---|---|---|
| | | | n | % |
| **CVID** | < 0.01 | 28 | 3 | **10.7** |
| | 0.01-0.05 | 8 | 0 | 0 |
| | > 0.05-0.5 | 7 | 0 | 0 |
| Total | | 43 | 3 | 7 % |

# www.esid-registry.org

# The red fields…

**PATIENT:** Sex, date of birth, region of residence

**DIAGNOSIS:** Date of diagnosis, onset of symptoms, disease/diagnosis

**THERAPY:** Date, drug, dose per weight, dose interval, route (oral / SC / IV), from, until, side-effects, reason stopped, compliance

**QUALITY OF LIFE:** Days in hospital, days missed at school, days missed at work, body weight, body height

**LABORATORY:** Date, time, label, value (IgG, IgA, IgM, CD3, CD4, CD8, CD19 or CD20, CD56, Leukocytes, Thrombocytes, Erythrocytes, Lymphocytes, Granulocytes, Hb, Eosinophils, Basophils, Macrophages) in percent or/and in absolute values

**+ Anti IgA Abs (red field)**

# THE SPECIFICITY OF DETECTION AND QUANTIFICATION (ELISA)

- **INHIBITION TEST**
  - Reaction of positive serum with positive and negative pool

- **TITRATION**



Anti-IgA Abs were found in patients with low level of serum IgA (< 0.05 g/l, resp. < 0.01 g/l).

# Therapeutic strategy

## Investigation of anti-IgA antibodies in German CVID

(University of Freiburg, Germany and Masaryk University, Brno, Czech Republic)

German **CVID**: n = 88

anti-IgA antibodies were found in 8 patients (9.1 %)

Interestingly, two of the eight patients showed heterozygous mutations in *TNFRSF13b*/TACI.

**Clinical correlation:** Five positive patients had a history of anaphylactoid reactions to IVIG and anti-IgA Ab Titer: 1 : 400 – 1 : 6400.

# Anti-IgA antibodies in Common Variable Immunodeficiency (CVID): Diagnostic workup and therapeutic strategy

Julia Horn[a], Vojtech Thon[b], Dana Bartonkova[b], et al.


Table 1 Summary data of patients with anti-IgA antibodies

| Patient | Age | Sex | Autoimmune phenomena | Granulomatous disease | Lympho-proliferation | TACI | Ig-Therapy | | and Reaction |
|---|---|---|---|---|---|---|---|---|---|
| P#1 | 53 | F | None | No | No | No mutation | Octagam iv | | Generalized flush, acute dyspnoea, hypotension, pruritus, cough |
| | | | | | | | Sandoglobin iv | | |
| | | | | | | | Gammavenin iv | | |
| P#2 | 35 | F | Vitiligo, Alopecia, Psoriasis | No | Tonsillar hyperplasia | No mutation | Beriglobin sc | → | No reaction |
| | | | | | | | Intraglobin F iv | → | General edema, acute dyspnoea, hypotension, cyanosis, unconsciousness |
| | | | | | | | Gammanorm sc | → | No reaction |
| P#3 | 38 | F | None | Yes | NLH[a] | No mutation | Endobuliniv | → | Acute dyspnoea, fever, chills |
| | | | | | | | Pentaglobin iv | → | Acute dyspnoea, fever, chills |
| | | | | | | | Gamunex iv | → | Acute dyspnoea, fever, chills |
| | | | | | | | Gammanorm sc | → | No reaction |
| P#4 | 38 | M | None | Yes | NLH splenomegaly | No mutation | Octagam iv | → | Capillary leak syndrome, acute renal failure, lung oedema |
| | | | | | | | Polyglobin iv | → | No reaction |
| P#5 | 35 | F | None | No | NLH splenomegaly | No mutation | Octagam iv | → | Exanthema of the whole body, enanthem and edema of nose, mouth,bronchi |
| | | | | | | | Gammanorm sc | → | No reaction |
| P#6 | 40 | M | None | No | Splenomegaly | No mutation | Flebogamma iv | → | No reaction |
| | | | | | | | Subcuvia sc | → | No reaction |
| P#7 | 44 | M | Vitiligo | No | NLH hepatosplenomegaly | C104R heterozygote | Octagam iv | → | No reaction |
| P#8 | 31 | F | None | No | NLH splenomegaly | C104R heterozygote | IVIG | → | No reaction |
| | | | | | | | Subcuvia sc | → | Localized Exanthema of the skin |
| | | | | | | | Gammanorm sc | → | No reaction |

Patients P#1–5 with anaphylactoid reactions are highlighted in gray.
[a] Nodular lymphoid hyperplasia (NLH).

*Clin Immunol. 2007;122:156-62*

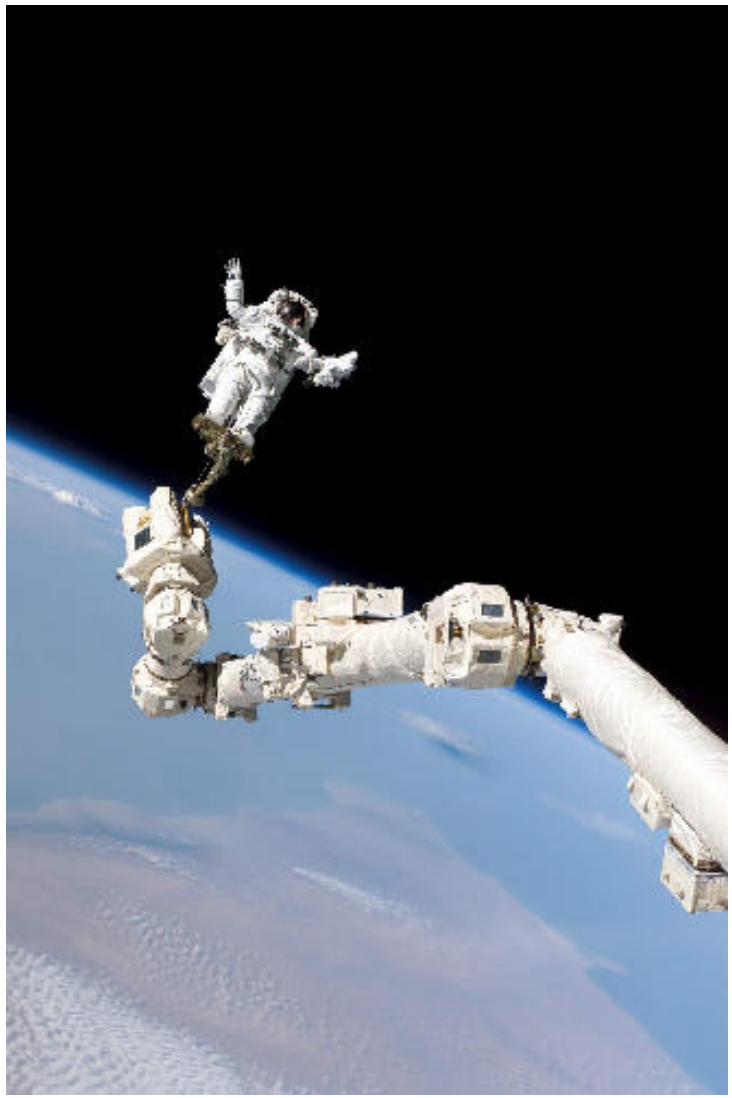
# Lack of IgA+ B cells in CVID patients with anti-IgA antibodies

Table 3 B cell phenotype: $IgA^+$ B cells and CVID classification

| Tests | Normal values | P#1 | P#2 | P#3 | P#4 | P#5 | P#6 | P#7 | P#8 |
|---|---|---|---|---|---|---|---|---|---|
| CD19+ [%] | 4.7-15 | 12.5 | **16.7** | **17.2** | **20.6** | **40.3** | **16.8** | **17.8** | **21.6** |
| IgD+ CD27- cells [%] | 38-80 | 61.9 | 64.9 | **85.9** | **89.7** | 43.8 | 80 | 50.6 | **90** |
| IgD- CD27+ cells [%] | 6.5-33 | **3.7** | **4.5** | **1.7** | **1.2** | **2** | **1.3** | **2.4** | **0.2** |
| IgA+ B cells [%] | 3.1-18 | **0** | **0** | **0** | **0** | **0** | **0** | 0 | **0** |
| IgG+ B cells [%] | ? | n.t. | 7 | 2.7 | n.t. | 0.9 | 1,8 | n.t. | 0 |
| CD21- CD38- cells [%] | 1.1-6.9 | 13 | 5.8 | 1.7 | 1.7 | **45.6** | **10.3** | **26.9** | 4.1 |
| CD10+ cells [%] | 1-12 | n.t. | 6.3 | 6.5 | n.t. | 1.1 | 1,8 | n.t. | 2.4 |
| Transitional B cells [%] | 0.5-3.5 | **5** | 4 | 2.3 | **19.4** | 0.7 | 2.1 | 2 | 2.3 |
| Plasmablasts [%] | 0.5-4.1 | **0** | **0** | **0** | **0.2** | **0.1** | **0** | **0.2** | **0** |
| CVID-Type (Freiburg Classification) | | **II** | **II** | **I** | **I** | **II** | **I** | **II** | **I** |

Pathological values are printed in bold; patients P#1–5 with anaphylactoid reactions are highlighted in gray.

*Horn, Thon et al., Clin Immunol. 2007*



# CVID:
# IgA serum levels correspond to paucity of IgA+ B cells

Table 2 Serum immunoglobulins[a] and IgG anti-IgA Titers

| Tests | Normal values | P # 1 | P # 2 | P # 3 | P # 4 | P # 5 | P # 6 | P # 7 | P # 8 |
|---|---|---|---|---|---|---|---|---|---|
| IgG (g/l) | 7-16 | **1.74** | **2.7** | **3.67** | **<1.5** | **3.21** | **2.13** | **3.45** | Unknown |
| IgM (g/l) | 0.4-2.3 | **0.24** | **0.19** | **0.17** | **<0.2** | **0.22** | 0.74 | 0.5 | **0.2** |
| IgE (IE/ml) | 10-100 | <19.1 | <19 | <16.3 | <19.1 | <19 | <18 | <19.1 | <19 |
| IgA (g/l)[b] | 0.7-4 | **<0.06** | **<0.06** | **<0.06** | **<0.06** | **<0.06** | **<0.06** | **<0.06** | **<0.06** |
| IgA (g/l)[c] | 0.7-4 | **<0.0009** | **<0.0009** | **<0.0009** | **<0.0009** | **<0.0009** | **<0.0009** | **<0.0009** | **<0.0009** |
| IgG anti-IgA titer[d] | Negative | **1:400** | **1:1,600** | **1:400** | **1:6,400** | **1:6,400** | **1:800** | **1:200** | **1:100** |
| IgG anti-IgA titer[e] | Negative | Negative | **1:1,600** | **1:200** | Not done | **1:1,600** | Negative | Negative | Not done |

Pathological values are printed in bold, patients P#1–5 with anaphylactoid reactions are highlighted in gray.

[a] IgG, IgA, and IgM values before treatment with immunoglobulins.

[b] As determined by nephelometry.

[c] As determined by ELISA.

[d] Before IVIG therapy or at the time of anaphylactoid reaction.

[e] Reassessment after start of SCIG or continuous IVIG therapy at different time points.

*Horn, Thon et al., Clin Immunol. 2007*

# CVID:
# IVIG change to SCIG substitution: development of anti-IgA antibodies

Table 2 Serum immunoglobulins[a] and IgG anti-IgA Titers

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| IgA (g/l)[c] | 0.7-4 | **<0.0009** | **<0.0009** | **<0.0009** | **<0.0009** | **<0.0009** | **<0.0009** | **<0.0009** | **<0.0009** |
| IgG anti-IgA titer[d] | Negative | **1:400** | **1:1,600** | **1:400** | **1:6,400** | **1:6,400** | **1:800** | **1:200** | **1:100** |
| IgG anti-IgA titer[e] | Negative | Negative | **1:1,600** | **1:200** | Not done | **1:1,600** | Negative | Negative | Not done |

Pathological values are printed in bold, patients P#1–5 with anaphylactoid reactions are highlighted in gray.

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*Horn, Thon et al., Clin Immunol. 2007*



# Conclusion

In a cohort of 279 hypogammaglobulinemic patients (IgAD, CVID) from the Czech and German population we found 10 % positive with anti-IgA antibodies (28 positive patients from 279 investigated).

Anti-IgA Abs were found in patients with low level of serum IgA (< 0.05 g/l, resp. < 0.01 g/l) and paucity of IgA positive B cells.

The occurrence of anti-IgA Abs in the middle European population is similar to the Scandinavian population (e.g. Koskinen et al.)

# SCIG and IVIG

## Conclusion

In terms of therapeutic management of **CVID patients** with low serum IgA, lacking IgA positive B cells and **with anti-IgA antibodies** we recomend SCIG therapy as a safe therapeutic alternative to IVIG to prevent anaphylactoid reactions.

# Collaboration

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*Thank you for your attention.*