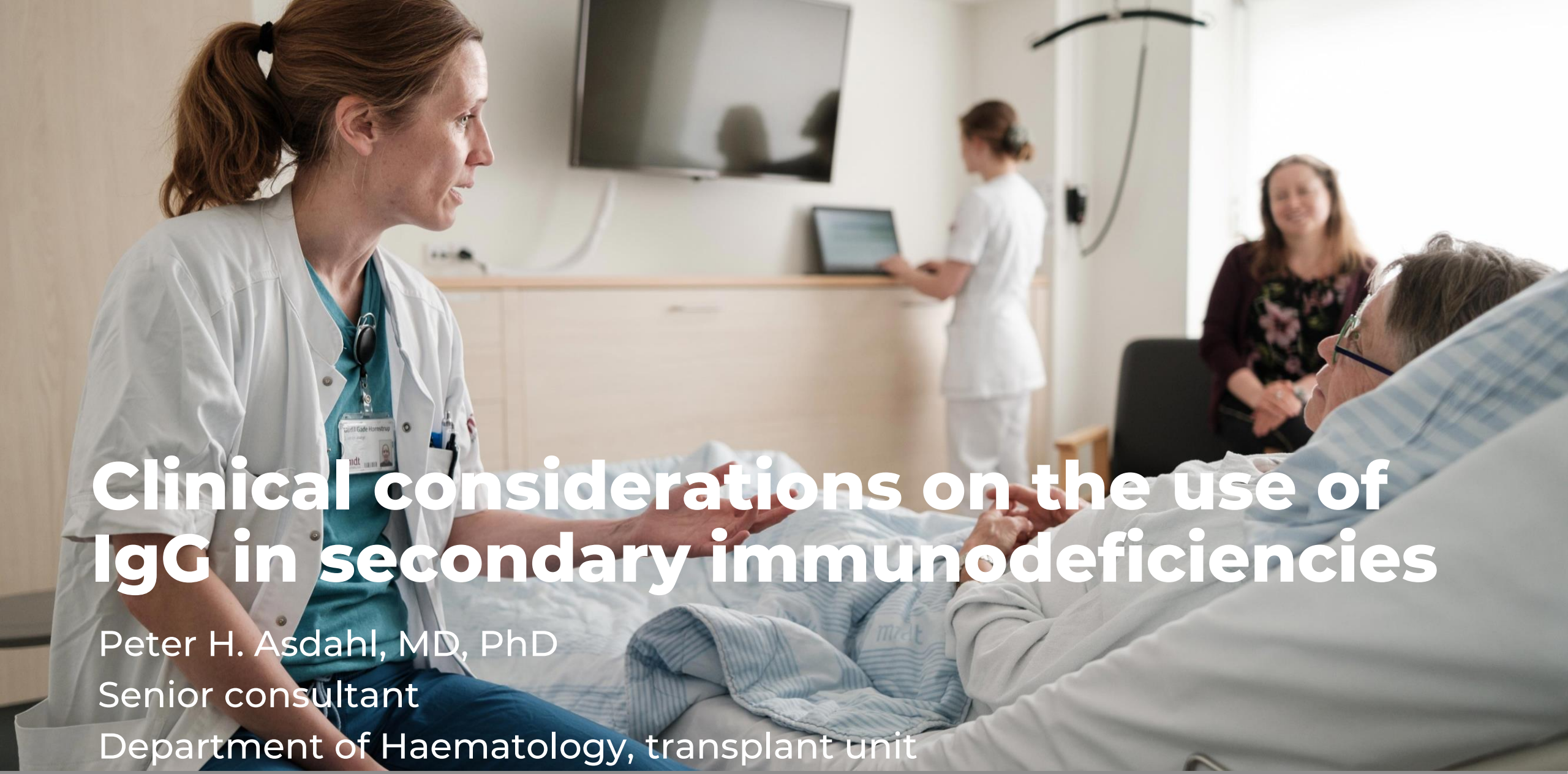

Clinical considerations on the use of IgG in secondary immunodeficiencies

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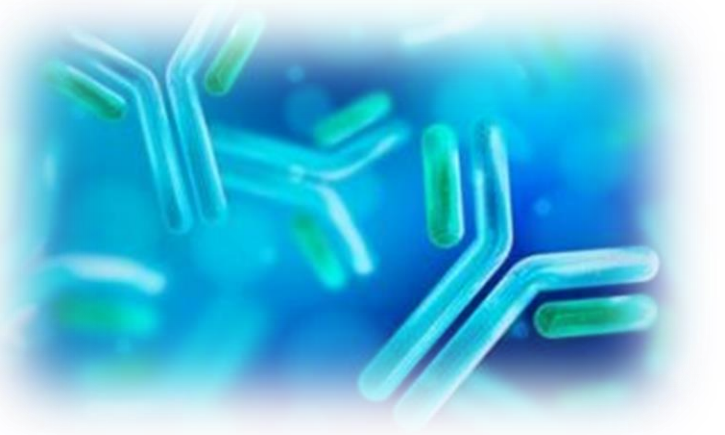
Conflicts of interest

None

Causes of secondary hypogammaglobulinemia

Disease related factors

- Multiple myeloma
- Chronic lymphocytic leukaemia
- Lymphoma



Treatment related factors

- Monoclonal antibodies targeting plasma cells or B-cells
- CAR-T (Chimeric Antigen Receptor T-cells)
- BiTEs (Bispecific T-cell Engagers)
- Lymphocyte-directed chemotherapy
  - *Particular with > 2 lines of therapy*
- Long-term high-dose steroids
- Allo-HSCT
  - *Particular with GvHD*

Case: 62 year old male with chronic lymphocytic leukaemia (CLL)

History:

- >5 lines of treatment including bispecific t-cell engaging therapy in a trial-setting
- Allo-HSCT 18 month ago
- Chronic Graft versus Host disease
- 3 years ago, hypogammaglobulinemia and recurrent pneumonia
  - Treated with IVIg — 0,4 g/kg
  - Shortly after treatment initiation aseptic meningitis

Current time:

- IgG level 2,9 g/l – consistent over the past 6 months
- Standard vaccination program
- Sulfamethoxazole/Trimetroprim prophylaxis
- Admitted with pneumococcal septicimia and pneumonia
- Started on facilitated SCIg, 0,4 g/kg monthly

Requirements for an infection-prophylaxis

- Reduced infection-related and all-cause mortality
- Reduced rate of severe infections
- Reduced rate of any infection
- Reduced admission rate
- Reduced number of hospital bed-days
- Reduction in the use of antibiotics
- Improved quality of life

Population: Adult patients with chronic lymphocytic leukemia, myeloma or non-Hodgkin lymphoma
Intervention: Prophylactic immunoglobulin, antibiotics, vaccinations
Comparator: No intervention, placebo or standard care
Main outcomes: All-cause mortality or clinically documented infections

Immunoglobulin

8 studies (7 before 2000)

370

Clinically documented infections reduced by 28% (RR 0.72, 95% CI 0.54–0.96)

No effect on survival (RR 1.35, 95% CI 0.57–3.18)

Antibiotics

5 studies

1587

No effect on clinically documented infections (RR 0.93, 95% CI 0.79–1.08)

No effect on survival (RR 1.11, 95% CI 0.85–1.45)

Vaccinations

5 studies

3996

Clinically documented infections reduced by 63% (RR 0.37, 95% CI 0.30–0.45)

No effect on survival (RR 0.92, 95% CI 0.75–1.14)

Summary

- Prophylactic immunoglobulin and vaccinations appear to reduce this risk of clinically documented infections, but findings should be interpreted with caution due to high risk of bias, heterogeneity and limited generalizability.
- Only one feasibility trial directly compared between interventions.

Future research

Future studies should compare different interventions, use standardised definitions of infection outcomes and incorporate cost-effectiveness analyses.

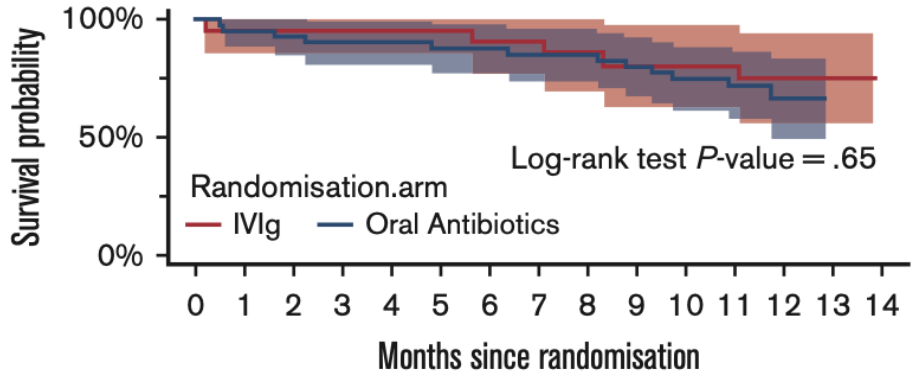
Chai, et al, Blood Advances, 2023

Immunoglobulin replacement vs prophylactic antibiotics for hypogammaglobulinemia secondary to hematological malignancy

McQuilten, Blood Advances, 2024

Conclusions

In this randomized feasibility trial, a similar proportion of participants remained on prophylactic antibiotics at 12 months as those on Ig replacement despite the provision of crossover from prophylactic antibiotics to Ig replacement in the event of grade 3 or higher infection. The rates of major infections were similar between the 2 treatment arms. Our findings support the feasibility of progressing to a larger phase 3 trial.



Requirements for an infection-prophylaxis

1. Reduced infection-related and all-cause mortality 👎
2. Reduced rate of severe infections 👍
3. Reduced rate of any infection 👍
4. Reduced admission rate 👍
5. Reduced number of hospital bed-days 👍
6. Reduction in the use of antibiotics 👍
7. Improved quality of life ?

Selecting the right patients for treatment initiation

Primary prophylaxis

- Low IgG
  - < 2 g/L ?
  - < 4 g/L ?
  - < 6 g/L ?

Secondary prophylaxis

- Low IgG AND
- Recurrent severe Infections
  - How severe ?
  - How many ?
  - Bacterial versus viral ?
  - Antibiotics prophylaxis first ?

Current trial design for BiTEs and CAR-T

“Immunoglobulin replacement should be used to maintain serum IgG levels ≥4 g/L regardless of active or history of infection. It is recommended to administer immunoglobulin i.e., intravenous immunoglobulin 0.4 g/kg every 3 to 6 weeks. After reaching a steady state, IgG levels should be measured at least every 3 months (Hayden 2022; Ludwig 2023).”

Ludwig 2023, myeloma consensus guidelines: *"Prophylactic administration of high-dose (400 mg/kg) immunoglobulin at short intervals of 1–4 weeks is recommended in patients with low IgG concentrations (<400 mg/dL)."*

Lancman, Blood, 2022: "We retrospectively reviewed all (N=37) multible myeloma patients treated with anti-BCMA BiAbs at Mount Sinai from 2019-2022."

Unanswered questions

- Dosing of immunoglobulin?
- Route of administration?
- Alternative prophylaxis?
- Duration of therapy?
    - Is it safe to pause therapy during summer months?

Conclusion

- IgG substitution reduces the rate of infection
- No effect on mortality
- Patient selection is important
- Trials in populations treated on contemporary treatments are needed

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