# Dosing Strategies of Immunoglobulins (IgG) Replacement Therapies in Obese and Overweight Patients with Primary Immunodeficiency Diseases (PIDDs)

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## Abstract

Patients with primary immunodeficiency diseases (PIDDs) are susceptible to recurrent infections because of underlying immune defects. Replacement of serum IgG with human immune globulin products has become the standard treatment for PIDDs since the 1950s. However, since late 2018, the United States experienced a shortage of both intravenous immunoglobulin (IVIG) and subcutaneous immunoglobulin (SCIG) products. The shortage could be exacerbated by the COVID-19 pandemic because some COVID-19 patients are receiving IG as treatment for the pro-inflammatory syndrome and high doses of IgG products are being investigated for potential in patient with pneumonia caused by COVID-19. The current dosing regimens of IVIG and SCIG in the U.S. are based on total body weight. To ameliorate the shortage of IVIG and SCIG products, there are reports proposing that the dosing of IVIG and SCIG should be based on adjusted (or ideal) body weight. Despite no randomized controlled studies for establishing the optimal dosing strategy, adjusted body weight dosing strategy is employed in some countries such as Canada, Australia and the United Kingdom. In this study, we conducted a meta-analysis of the data submitted as part of some IVIG or SCIG BLA applications to the Center for Biologics Evaluation and Research (CBER) to assess the relationships between dose and IgG trough level, between IgG trough level and infection, and to indirectly address whether obese subjects should be dosed according to adjusted body weight or total body weight. We found a smaller increase in trough level in obese or overweight subjects compared to subjects with normal BMIs when treated with the same dose. Increase in trough level after 10g/L was found to be associated with fewer overall infections. The meta-analysis did not provide compelling evidence to justify changing the dosing of obese subjects based on BMIs.

## Introduction

- PIDDs include over 150 immune disorders
  - Predispose patients to recurrent infections
- Treated with immunoglobulins (IgG) replacement therapies
  - Intravenous IgG (IVIG): administered every 3 or 4 weeks
  - Subcutaneous IgG (SCIG): administered every week

- A national shortage of both IVIG and SCIG products since late 2018 that could be exacerbated by COVID-19
  - Some COVID-19 patients are receiving IgG products for treatment of pro-inflammatory syndrome
  - High doses are being investigated for treatment of pneumonia caused by COVID-19

## Research Questions

Can we optimize use of IgG products?

Should obese and overweight patients be dosed based on their ideal or adjusted body weight?

We conduct a meta-analysis of the data submitted as part of IVIG or SCIG BLA applications to CBER to address these questions

## Materials and Methods

**Assess the relationship between dose and trough level in normal vs overweight or obese subjects**

- Subjects received infusion every 1, 3, or 4 weeks and trough levels were measured before some (but not all) of these infusions
- A linear mixed model to account for multiple observations from each subject was used :
- For each subject $i$ in treatment cycle $j$ of study $k$, the model is as follows:

$$Y_{ijk} = \beta_{0k} + \beta_{1k}X_{1ik} + \beta_{2k}X_{2ik} + \beta_{3k}X_{3ik} + \beta_{4k}X_{4ik} + \beta_{5k}X_{5ik} + \beta_{6k}X_{6ijk} + \beta_{7k}X_{7ijk} + \beta_{8k}X_{8ijk} + \mu_{oik} + \varepsilon_{ijk}$$

- $X_1$ baseline trough level; $X_2$ baseline age; $X_3$ indicator for common variable immune deficiency (CVID) disease type; $X_4$ indicator for 25 ≤ BMI <30; $X_5$ indicator for BMI ≥ 30; $X_6$ dose per week associated with each treatment cycle; $X_7$ interaction between dose per week and 25 ≤ BMI <30; and $X_8$ interaction between dose per week and BMI ≥ 30
- $Y_{ijk}$ the trough level for subject $i$ in treatment cycle $j$ of study $k$

- *Parameters of interest:*
- $\beta_{6k}$: the increase in trough level for 1 gram (g) increase in dose per week in subjects with BMI < 25 in study $k$
- $\beta_{6k} + \beta_{7k}$ : the increase in trough level for 1 g increase in dose per week in subjects with 25 ≤ BMI <30 in study $k$
- $\beta_{6k} + \beta_{8k}$: the increase in trough level for 1 g increase in dose per week in subjects with BMI ≥ 30 in study $k$

**To assess the relationship between trough level and overall infection count**

- For each subject $i$ in study $k$, a Poisson model was used:

$$\log(\mu_{ik}) = \beta_{0k} + \beta_{1k}X_{1ik} + \beta_{2k}X_{2ik} + \beta_{3k}X_{3ik} + \beta_{4k}X_{4ik} + \beta_{5k}X_{5ik} + \beta_{6k}X_{6ik} + +\log(obsLen_{ik}) \text{ and } Y_{ik} \sim Poisson(\mu_{ik})$$

- $X_1$ baseline age; $X_2$ indicator for common variable immune deficiency (CVID) disease type; $X_3$ indicator for 25 ≤ BMI <30; $X_4$ indicator for BMI ≥ 30; $obsLen$ length of observation in year; $X_5$ mean trough level during the study; $X_6 = (X_5 - 10)_+ = (X_5 - 10)$ if mean trough level is > 10; and = 0 if mean trough level ≤ 10
- $Y_{ik}$ the overall infection count for subject $i$ in study $k$
- Orange et. al. (2010) showed that pneumonia risk can be reduced by higher trough IgG levels up to at least 10 g/L,
- Thus, we include a piecewise linear relationship with a knot at 10 g/L

- *Parameters of interest:*
- $\exp(\beta_{5k})$: for 1 g/L increase in trough level (up to 10 g/L), the expected number of infections changes by a multiplicative factor of $\exp(\beta_{5k})$
- $\exp(\beta_{5k} + \beta_{6k})$: for 1 g/L increase in trough level (after 10 g/L), the expected number of infections changes by a multiplicative factor of $\exp(\beta_{5k} + \beta_{6k})$

**Conduct a meta-analysis of the study results**

- The estimates of the parameters of interest and the standard errors are obtained from the models
- Meta-analyze the study specific results using a random-effects model

## Results and Discussion

**Relationship between dose and trough level in normal vs overweight or obese subjects**

- As shown in Table 1, adjusting for baseline trough level, age and BMI, one gram increase in dose per week is associated with
  - 0.22 g/L increase in trough level in subjects with BMI < 25
  - 0.15 g/L increase in trough level in subjects with 25 ≤ BMI <30
  - 0.14 g/L increase in trough level in subjects with BMI ≥ 30

- A higher dose is statistically significantly associated with a higher trough level
- A higher dose is needed in subjects with BMI > 25 to achieve the same trough level compared to subjects with normal BMI

**Relationship between trough level and overall infection count**

- As shown in Table 2, for one g/L increase in trough level up to 10g/L, the expected number of overall infections does not statistically significantly change

- However, for one g/L increase in trough level after 10 g/L, the expected number of overall infections reduces by 11% with a 95% confidence interval of [2%, 19%]

**Table 1.** Meta-analysis results on the relationship between dose per week and trough level in normal, overweight and obese subjects

| BMI categories | Estimate (g/L) | Lower 95% Confidence Interval | Upper 95% Confidence Interval |
|---|---|---|---|
| BMI <25 | 0.22 | 0.10 | 0.33 |
| 25 ≤ BMI <30 | 0.15 | 0.09 | 0.21 |
| BMI ≥ 30 | 0.14 | 0.03 | 0.24 |

**Note: these results were obtained using the 6 studies for which we have permission from the sponsors to use. Study specific results are not shown here because we have not submitted this to the sponsors for review as part of the data use agreement.**

**Table 2.** Meta-analysis results on the relationship between trough level and overall infection count: The slope associated with trough level for when trough level ≤ 10 g/L and for trough level > 10 g/L.

| Trough level (g/L) | Estimate | Lower 95% Confidence Interval | Upper 95% Confidence Interval |
|---|---|---|---|
| ≤ 10 | 1.04 | 0.94 | 1.14 |
| >10 | 0.89 | 0.81 | 0.98 |

**Note: these results were obtained using the 6 studies for which we have permission from the sponsors to use. Study specific results are not shown here.**

**Limitation of existing data:**

- Trough levels were not measured for all treatment cycles
- Aggregating trough levels over entire follow-up period (using mean trough level) could attenuate the relationship with infection
  - Subjects could be at higher risk for infections when trough levels drop too low but that is not captured in the data
- Heterogeneity of infections across subjects and studies

## Conclusion

- A smaller increase in trough level was found in obese or overweight subjects compared to subjects with normal BMIs when treated with the same dose
- Increase in trough level after 10g/L was associated with a decrease in the risk of overall infection
- The meta-analysis did not provide compelling evidence to justify changing the dosing of obese subjects based on BMIs

## Reference

1. Orange JS, Grossman WJ, Navickis RJ, Wilkes MM. Impact of trough IgG on pneumonia incidence in primary immunodeficiency: A meta-analysis of clinical studies. Clin Immunol. 2010 Oct;137(1):21-30. doi: 10.1016/j.clim.2010.06.012. Epub 2010 Aug 1. PMID: 20675197.

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