Differences in Ig replacement therapy dosing in patients with Common Variable Immunodeficiency in Europe: Results from the ESID Database

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Abstract

Rationale

- Common variable immunodeficiency (CVID) is characterised by low levels of serum immunoglobulins and increased susceptibility to infections. Standard therapy for patients is immunoglobulin (Ig) replacement.

Methods

- In a retrospective analysis by country, we analysed CVID patients within the ESID Database for Primary Immunodeficiencies. Actual dosing with intravenous (IVIg) and subcutaneous (SCIg) products was compared to the recommended dose. We used 600 mg/kg bw/month as the recommended dose, as this is the midpoint between the recommended 400 and 800 mg/kg bw/month. Results represent the median percentage difference from this figure for IVIg (n=547 patients), SCIg (n=273) and total Ig patients (IVIg and/or SCIg route, n=647) for each country.

Results

- There was wide regional variation in values for IVIg (p<0.001), SCIg (p=0.004) and total Ig patients (p<0.001). The majority of countries prescribed doses lower than 600 mg/kg bw/month for IVIg such as Czech Republic (-46%) and Germany (-43%). The Netherlands (-5%) and Greece (+5%) showed the least variation. The prescribed doses for SCIg showed a similar picture, with the lowest doses in Czech Republic (-64%), Germany (-32%), France (-25%), the UK (-22%) and Sweden (-16%), whilst dosing levels were slightly higher only in Greece (+8%). Overall, the variations in dosing were similar with IVIg and SCIg (median: -22% vs. -26%; p=0.02).

Conclusions

- This analysis indicates a wide regional variation in dosing of Ig replacement therapy across Europe which requires further investigation of clinical phenotypes, adjunctive treatments (e.g., antibiotics), Ig serum levels achieved, and, most importantly, clinical outcomes.

Introduction

- Common variable immunodeficiency (CVID) is a primary immunodeficiency disease (PID) characterised by low levels of serum immunoglobulins (Ig) and increased susceptibility to infections.
- Ig replacement therapy is the treatment of choice for CVID. It can be administered either intravenously (IVIg) or subcutaneously (SCIg).
- The European Society for Immunodeficiencies (ESID) has established an internet-based patient database which is a collaboration between treatment centres across Europe.
- The aim of this analysis was to compare the recommended and actual doses of Ig replacement therapy received by patients with CVID in different patient subgroups, using data from the ESID Database.

Methods

Study design

- Originally, data collected by the ESID Database between 2004 and 2010 were retrospectively analysed. Patients were included in the cohort based on the availability of the necessary data items. For this poster, we repeated the original analysis and included additional data collected in the meantime (September 2010 to January 2011). In total, we analysed 1562 intervals from 841 patients.
- As stated in the abstract, we used a recommended dose of 600 mg/kg bodyweight (bw)/month as a benchmark in the original analysis and the results were presented as deviations from this. However, the results suggested that this benchmark did not reflect the reality of Ig dosing. Therefore, we have decided to present the results as absolute numbers.
- Patients were analysed in three groups according to the route of Ig administration: IVIg, SCIg and the total cohort (note: a subset of the total cohort received both IVIg and SCIg in their lifetime, but not simultaneously).
- Dosing variations were compared between:
  - Countries
  - Ig treatment routes
  - Age groups (patients aged <12 years, 12–17 years and ≥18 years)
  - Patients with bronchiectasis versus patients without bronchiectasis

Statistical methods

- Doses of Ig were converted to a relative unit of dose/kg bw. Dose frequency was calculated as mg/kg bw/month.
- SCIg concentrations were assumed to be 160 mg/mL (three out of the four currently available SCIg products have a concentration of 160 mg/mL, one has a concentration of 165 mg/mL).
- Many patients changed their doses throughout their treatment, therefore, data were analysed at the treatment dose level (i.e., one value every time the dose or drug changed).
- The Kruskal-Wallis test was used to compare dosing differences between countries and between age groups.
- The Mann-Whitney test was used to compare the dosing difference between: 1) the IVIg and SCIg groups; and 2) patients with or without bronchiectasis.
- Statistical significance was defined as p<0.05.

Results

Dosing comparison between countries

- There was a significant difference between countries in the median doses of Ig received by patients treated with IVIg, SCIg and by those in the total cohort (all p<0.001).
- The Czech Republic presented with the lowest median doses of Ig in patients who received IVIg (328 mg/kg bw), SCIg (365 mg/kg bw) and in those in the total cohort (329 mg/kg bw) [Figure 1].
- The highest median doses were recorded in Greece, both in patients with IVIg (619 mg/kg bw), SCIg (655 mg/kg bw) and in patients in the total cohort (650 mg/kg bw) [Figure 1].

Comparison between treatment routes

- Both the IVIg (n=655) and SCIg (n=361) groups had similar median doses of Ig (476 and 478 mg/kg bw, respectively; p=0.56).

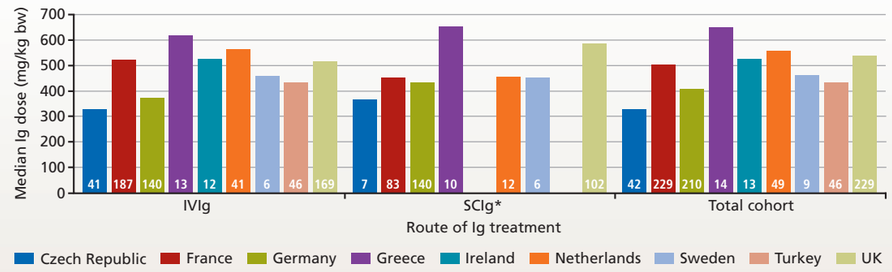
Comparison between age groups

- Across the three age groups, there was no significant difference in median Ig dose received by patients in the IVIg group (p=0.43) [Figure 2].
- Significant differences between the age groups were observed in the median Ig doses of patients in the SCIg group (p=0.007) and the total cohort (p=0.01). In both groups, patients aged <12 years received the highest Ig doses (Figure 2).

Comparison between patients with or without bronchiectasis

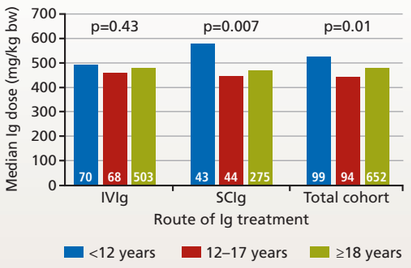
- Patients with bronchiectasis received significantly higher median Ig doses than patients without bronchiectasis, regardless of treatment route (IVIg, p<0.001; SCIg, p=0.002; total cohort, p<0.001) [Figure 3].

Figure 1. Median dose of Ig administered by country in each treatment group



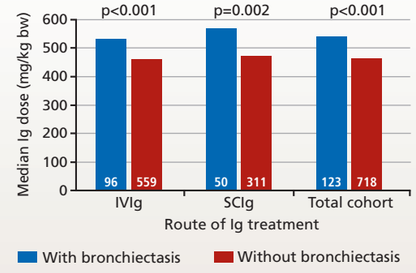
Ig, immunoglobulin; IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin.
White numbers at base of each column refer to the number of patients assessed in each country.
Individual patients could be included in both the IVIg and SCIg groups.
No SCIg data were reported in Turkey.
*Ireland had insufficient data for analysis; only one patient provided information.

Figure 2. Comparison of median Ig dose by treatment group between patients aged <12 years, 12–17 years and ≥18 years



Ig, immunoglobulin; IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin.
White numbers at base of each column refer to the number of patients assessed in each group.
Individual patients could be included in both the IVIg and SCIg groups.

Figure 3. Comparison of median Ig doses by treatment group in patients with or without bronchiectasis



Ig, immunoglobulin; IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin.
White numbers at base of each column refer to the number of patients assessed in each group.
Individual patients could be included in both the IVIg and SCIg groups.

Conclusions

- There is a wide regional variation in doses used for Ig replacement across Europe.
- Regional variation may reflect national health policies and treatment protocols.
- Ig dose varies with patient characteristics.
- SCIg doses were highest in children aged <12 years, possibly due to increased susceptibility to infection in infants and pressure to treat.
- SCIg doses were lowest in adolescents aged 12–17 years, which may reflect inadequate dose adjustment to increased body weight.
- Patients with bronchiectasis received higher Ig doses, suggesting that physicians tailor treatment to clinical severity/infection profile.
- Further investigation into clinical phenotypes, adjunctive treatments, Ig serum levels and clinical outcomes is required to establish the factors determining differences in Ig dosing.

This study was supported by:

PPTA CSL Behring Biotherapies for Life™ Federal Ministry of Education and Research PiA Octapharma

Editorial assistance was provided by Meridian HealthComms, Middlewich, UK.

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