

The ratio of mean daily IgG increment/mean daily dose in immunoglobulin replacement therapy in primary antibody deficiencies

Mary Lucas, BSc^a, Martin Lee, PhD^b,

Eric Oksenhendler, MD, PhD^c, and Helen Chapel, MD, MA^a

Clinical Implications

- Reduced dosages of therapeutic immunoglobulin at greater frequency increases increment:dose ratios (immunoglobulin efficiency) in several primary antibody failures. The data confirm that patients with inflammatory common variable immunodeficiency disorders need higher doses and that subcutaneous immunoglobulin may be more efficient than intravenous immunoglobulin at increasing IgG levels.

TO THE EDITOR:

To assess the pharmacological efficiency of immunoglobulin in replacement therapy, Gouilleux-Gruart et al¹ proposed an efficiency index to measure the increase in plasma IgG level per unit dose of immunoglobulin.¹ That index was calculated as serum IgG increment/dose per kilogram per week and was calculated in different clinical phenotypes of patients with common variable immunodeficiency disorder (CVID), as well as in relation to FcRn genotypes.¹⁻³

We have updated the equation to take into account the different time intervals used to determine serum IgG increments on treatment. For patients on subcutaneous immunoglobulin (SCIG), the preinfusion serum IgG (trough level/steady state) may be measured at day 4 or 7 postinfusion, whereas for those using intravenous immunoglobulin (IVIG), it is measured at day 7, 14, 21, or 28. Because immunoglobulin efficiency is a ratio between the IgG increment from baseline (pretreatment) and the dose of therapeutic immunoglobulin, both levels should be expressed in terms of time intervals. The revised ratio is changed and therefore renamed as follows:

Mean daily IgG increment/mean daily dose ratio = IgG increment (g/L) per day/immunoglobulin dose (g/kg) per week, also referred to as the IgG increment:dose ratio.

We used the previous data on patients with CVID for which log regression analysis was used,² as well as new data from Oxford and Paris, including patients with other primary antibody failures. A total of 450 patients receiving immunoglobulin replacement (Table I) were analyzed for each year or period in which the trough IgG level was stable²; 1567 patient-years were analyzed.

For patients with CVID, the daily IgG increment/dose ratio indices were studied in relation to clinical phenotypes.² The data confirm that those with at least 1 complex phenotype had significantly lower ratios ($P < 10^{-6}$).^{1,2} Those patients with enteropathy ($P = .00006$), autoimmune cytopenia ($P = .002$), or polyclonal lymphoproliferation ($P = .000003$) had significantly lower ratios than did those without.

Patients with bronchiectasis had similar daily IgG increment/dose ratios compared with those without, as reported previously¹ but in contrast to the log regression analysis in the original data.² However, the original study contained only 24% of patient periods receiving SCIG, whereas the new set contained 46% of SCIG periods; given that SCIG is more efficient,¹ this may explain the lack of difference here. Importantly, the original data compared patients without bronchiectasis with those with any bronchiectasis. More recently, Litzman³ compared mild or no bronchiectasis with generalized damage and found lower levels of FcRN mRNA levels in patients with generalized bronchiectasis as well as decreased efficiency (using the previous formula), emphasizing the importance of grading bronchiectasis. In this study, patients with splenomegaly also had significantly reduced daily IgG increment/dose ratios compared with those without ($P = .00002$).

Those receiving immunoglobulin via the subcutaneous route had significantly higher ratios than did those receiving IVIG, as in the original findings.¹ A total of 129 of 450 received replacement immunoglobulin via the subcutaneous route and had a mean increment/dose ratio of 8.63 (392 patient periods), compared with 359 of 450 (1256 patient periods) on IVIG with a significantly lower mean ratio of 3.30 ($P < 10^{-6}$). To see whether there was a difference if the infusion interval was changed without a change in the route of administration, 2 or more separate but stable periods were examined in 67 individual patients who had such interval changes; 50 (75%) had a clear decrease (>1.5) in the ratio with increasing infusion intervals despite the same route of administration. In 38 of these 50 patients, this change was not associated with onset of an inflammatory condition or corticosteroid therapy. (See individual examples in Figures E1 and E2 in this article's Online Repository at www.jaci-inpractice.org.) There was a significant decrease in the ratio in IVIG users when the infusion interval was increased ($P < 10^{-6}$) as well as for SCIG ($P = .001$) (Table II) when taken together.

Measurements of serum IgG level using the area under the curve suggested that the bioavailability of SCIG is lower than that of IVIG, and thus, to meet Food and Drug Administration bioequivalence noninferiority requirements, higher total SCIG dosing has been required for licensing trials in the United States, though not in Europe. Such licensing studies require repeated blood sampling for evaluation of serum total IgG level before the infusion and 30 minutes and 1, 4, 10, 14, and 21 to 28 days after the infusion so that the area under the curve from preinfusion to 21 days postinfusion (AUC_{0-21d}), maximum concentration (C_{max}), minimum concentration (C_{min}), elimination half-life, incremental recovery, and *in vivo* recovery could be calculated.⁴⁻⁶ Our report, using preinfusion IgG levels, is based on clinical practice rather than clinical trials, in which repeated venipuncture for sampling is not appropriate, and these values cannot be calculated. In addition, unlike these reports, our data are corrected for baseline (residual) IgG production. We suggest the ratio as a practical measure in terms of clinical management because venipuncture is still needed to obtain the blood samples until a pinprick method is developed and daily measurements become available/routine.

TABLE I. Mean daily IgG increment/dose ratio according to type of primary antibody deficiency

Disease	Mean daily IgG increment/dose ratio index	No. of patients
CVID	4.65	372
Infections only	5.32	236
Inflammatory (complex)	3.50	136
XLA	3.75	33
Good's syndrome	4.26	14
IgG subclass deficiency with associated IgA deficiency	4.81	6
Secondary antibody deficiency	5.28	6
Specific antibody deficiency	4.96	5

TABLE II. Mean daily IgG increment/dose ratio indexes for various infusion interval lengths*

Infusion interval (d)	New daily IgG increment/dose ratio index	No. of patient periods	P value
Intravenous administration			10 ⁻⁶
7	5.80	77	
10	4.89	1	
14	3.82	532	
21	2.80	472	
28	2.02	162	
Subcutaneous administration			.001
3.5	8.58	3	
7	8.77	372	
10	4.04	12	

*Data are arranged according to route of immunoglobulin administration. *P* values are for the comparison of the mean daily IgG increment/dose ratio indexes across the different infusion intervals for each route of administration using the Kruskal-Wallis test.

Since the advent of SCIG, several authors have reported that lower total SCIG doses (given by weekly infusions) are required to achieve equivalent trough/steady-state serum IgG levels to those during preceding IVIG therapy.⁷ In a direct comparison using the same product in 2 continents, Orange et al⁸ showed that 1:1 dosing increased serum IgG concentrations compared with previous IVIG therapy, thus confirming the results of the original trial.⁹

In a global analysis, mean daily IgG increment/dose ratio changed in patients receiving corticosteroids for inflammation; the mean ratio was 3.77 for those periods on corticosteroids compared with 4.86 for those periods without (*P* = .001). It was therefore important to know whether the difference in efficiencies between those with infections-only CVID versus complex CVIDs was due to corticosteroid therapy; however, the difference between clinical phenotypes remained when periods on corticosteroids were excluded.

Data on albumin levels in patients with CVID enteropathy showed that in those receiving either ciclosporin or methotrexate for intestinal inflammation, daily IgG increment/dose ratios rose when intestinal symptoms (and therefore IgG loss via the gut) were decreased. We confirm the lower daily IgG increment/dose ratio in those patients (*n* = 20) with low serum albumin levels

(<36 g/L), in patients receiving IVIG (*P* < 10⁻⁶), and now in those on SCIG (*P* = .01).¹⁰

When the data were analyzed according to disease type, daily IgG increment/dose ratios in patients with X-linked agammaglobulinaemia (XLA) looked similar to those in patients with CVID in distribution. The mean ratio was lower for XLA (3.75 vs 4.65) (Table I) (*P* = .11) but not significantly. This may be due to 60% of the patients with XLA (vs 37% of those with CVID) having bronchiectasis as in other series and 92% receiving IVIG. There appears to be no correlation between residual IgG levels and increment/dose ratios in patients with either CVID or XLA (see Figure E3 in this article's Online Repository at www.jaci-inpractice.org).

Given that trough IgG required to prevent breakthrough bacterial infections has been shown to vary between individual patients with CVID,² it was important to see whether daily IgG increment/dose ratio varied between individual patients too. The ratios for individuals with CVID or XLA were variable (data not shown); such variation was seen in the other groups of primary antibody deficiencies (PADS) (Table I) though there were insufficient patients to determine the exact distribution and extended studies are needed to resolve this question.

The data showing that daily IgG increment/dose ratio decreases as the infusion interval increases confirms that smaller doses at reduced intervals result not only in a more stable steady state, thus avoiding an infection-susceptible period when the serum IgG level falls below an individual's protection level,² but is also more efficient use of a scarce resource. This is in line with clinical experience that IVIG is more efficient if given in smaller doses more frequently rather than larger doses monthly.^{5,11,12}

We suggest that the new daily IgG increment/dose ratio formula is an improvement because it takes into account the infusion interval as well as the immunoglobulin dose/Kg per week. The data confirm the higher ratio in those using SCIG in comparison with IVIG users¹ in terms of supply of IgG to the circulation. Also, the mean daily increment/mean daily dose ratio is reduced in those CVID phenotypes with inflammation, explaining why this group requires more immunoglobulin to prevent breakthrough bacterial infections, as previously reported.² Whether this is due to higher consumption of IgG, reduced recirculation due to fewer FcRn numbers,¹⁰ or protein loss is not known, in some patients the ratio is corrected by corticosteroid therapy, suggesting that protein loss into extra-vascular tissues is at least a possibility.

^aNuffield Department of Medicine, University of Oxford, Oxford, United Kingdom

^bDepartment of Biostatistics, University of California at Los Angeles, Los Angeles, Calif

^cDepartment of Clinical Immunology, Hôpital Saint-Louis, AP-HP and Univ Paris Diderot, Sorbonne Paris Cité, EA3963, and CEREDIH, Paris, France

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Corresponding author: Helen Chapel, MD, MA, Level 7 Nuffield Department of Medicine, Oxford University Hospital, Headley Way, Oxford OX3 9DU, United Kingdom. E-mail: helen.chapel@ndm.ox.ac.uk.

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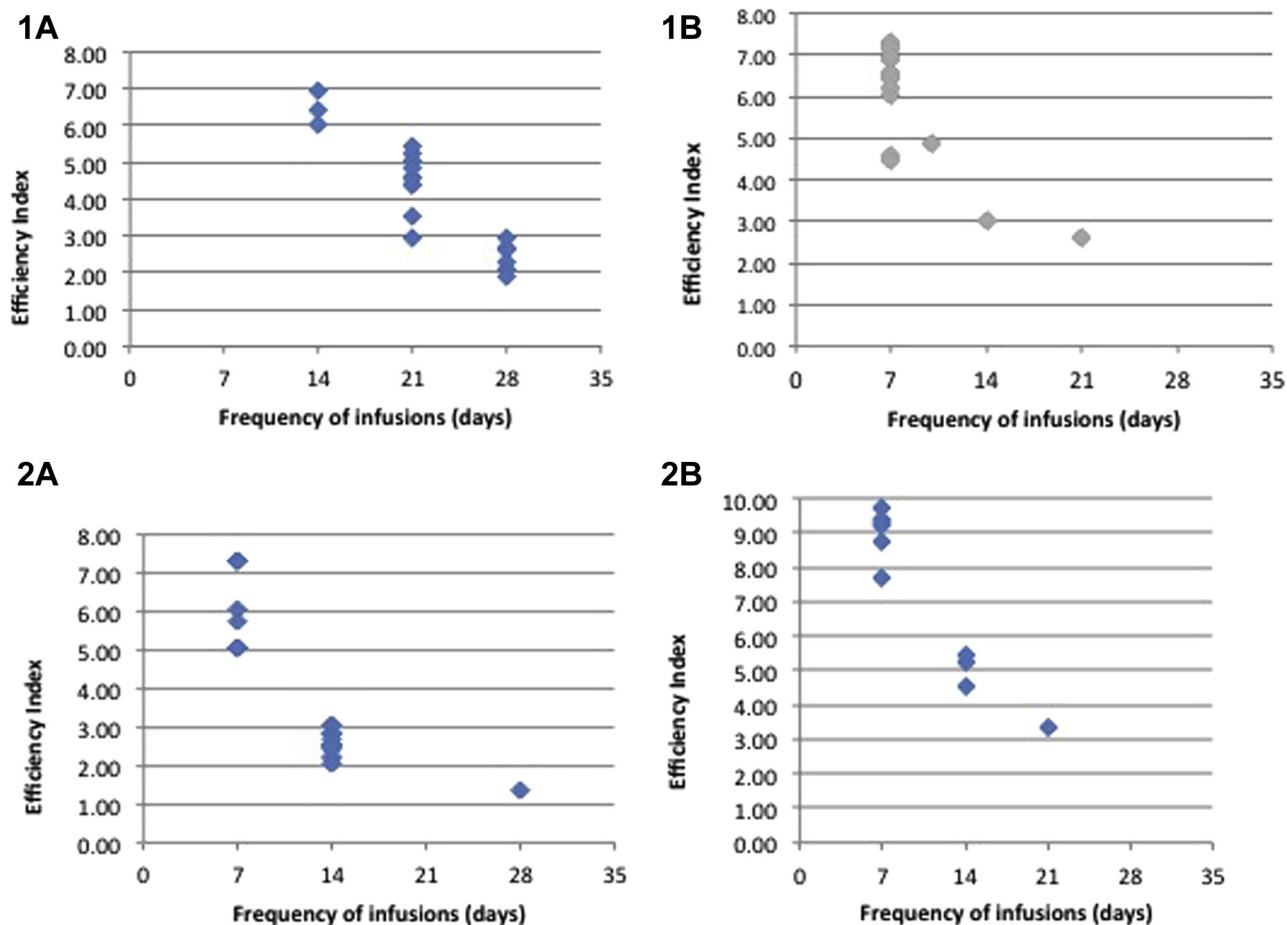


FIGURE E1. Examples of individual patients with CVID receiving IVIG over varying time intervals. 1A. No bronchiectasis. 1B. Bronchiectasis. 2. Patients with CVID receiving IVIG or SCIG over varying time intervals. 2A. No bronchiectasis. 2B. Bronchiectasis.

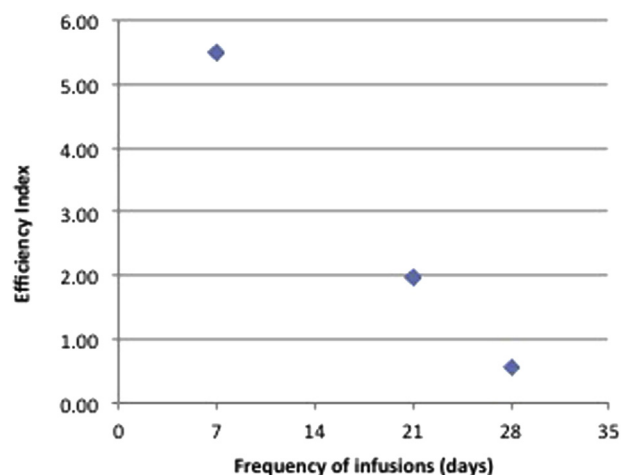


FIGURE E2. Patient with Good's syndrome (without bronchiectasis) receiving IVIG (2.1 g/kg/mo) every 28 days (for immunomodulation of cytopenia), IVIG (0.5 g/kg/mo) every 21 days, or SCIG (0.5 g/kg/mo) every 7 days (for replacement).

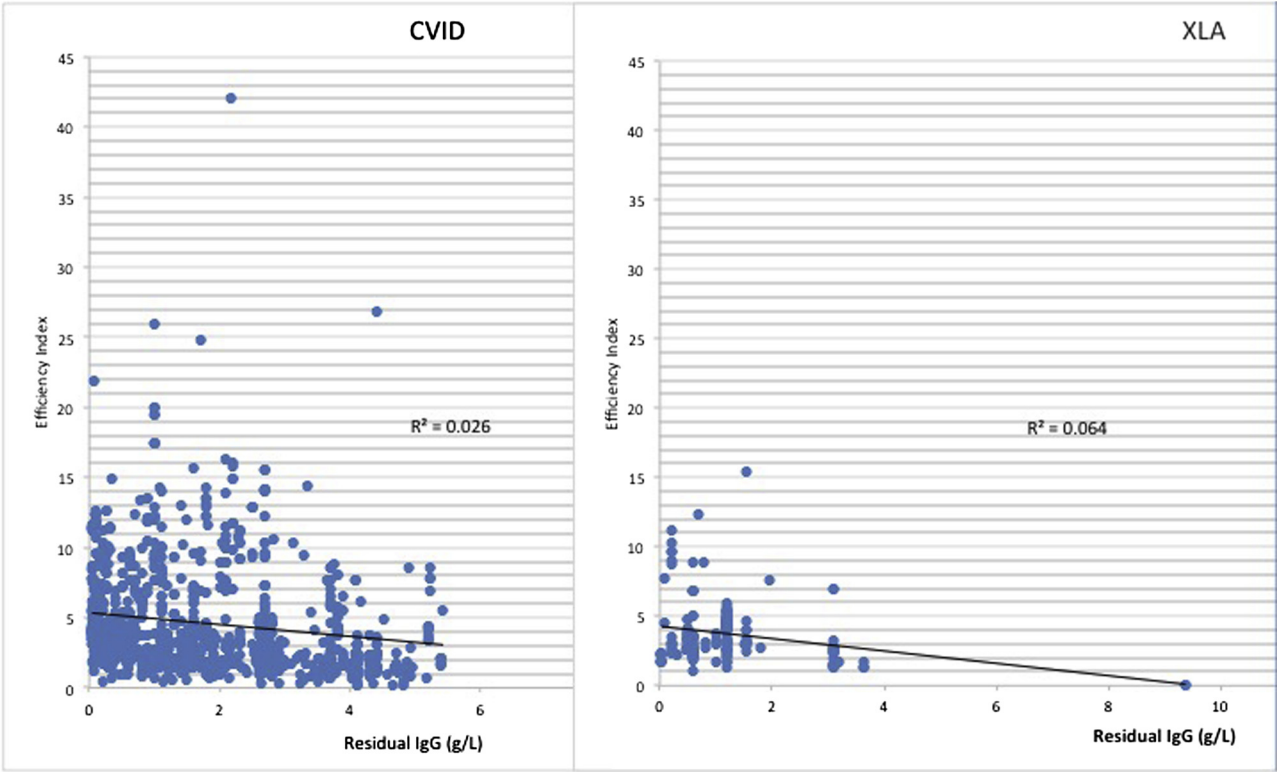


FIGURE E3. Daily IgG increment/dose ratio (immunoglobulin efficiency) versus residual (initial) IgG level in patients with CVID or XLA.

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