

Letter to the Editor

Longitudinal decline in lung function in patients with primary immunoglobulin deficiencies

To the Editor:

Common variable immunodeficiency (CVID) and X-linked agammaglobulinemia (XLA) are 2 primary immunoglobulin deficiency (PID) disorders in which immunoglobulin replacement is indicated.¹ Despite treatment, sinopulmonary infection remains a major cause of morbidity and early mortality in these patients.² Lung function declines with normal aging, and accelerated decline is a major risk factor for adverse outcomes in healthy people, smokers, and patients with bronchiectasis.³⁻⁵ The rate of decline of lung function in patients with PID treated with intravenous immunoglobulin (IVIG) therapy is currently unknown but is likely a prognostic indicator. The aim of this study was to ascertain the rate of decline in FEV₁ and forced vital capacity (FVC) in patients with XLA and CVID receiving IVIG. Our secondary aim was to identify clinical variables predictive of lung function decline.

We undertook a retrospective study in a tertiary hospital in Melbourne, Australia. All patients age 18 years or older who satisfied stringent diagnostic criteria for CVID or XLA¹ and who were receiving IVIG therapy during the years 2008 to 2009 were identified. For each patient, all available lung function tests (LFTs) were collected, including weight and height at first LFT and age at diagnosis. Factors likely to influence decline in lung function were also recorded, including hospital admissions, pack-years of smoking (20 cigarettes per day for 1 year = 1 pack-year), *Pseudomonas aeruginosa* airway colonization, the presence of bronchiectasis on chest imaging, and duration of IVIG therapy. Immunoglobulin dose was calculated as grams per kilogram of body weight (g/kg) per month. Serum IgG measurements were taken before infusions, and a weighted mean level was calculated for each patient. Continuous variables were summarized and reported as mean $\pm$ SD or median (interquartile range) and categorical variables as number (proportion). Outcome variables FEV₁ and FVC were assessed for normality and found to be well approximated by a normal distribution. We used linear regression to estimate slopes and SEs of FEV₁ and FVC for each patient. We calculated decline in lung function by using predicted normal values from Knudson et al.⁶

We performed weighted linear regression analyses to examine the association of clinical factors with change in lung function with weights derived by using the inverse variance method⁷ and presented results as parameter estimates (PEs) with SEs. A 2-sided *P* value of .05 was considered statistically significant. Analyses were performed with SAS 9.1 (SAS Institute, Cary, NC). The study was approved by the Alfred Hospital Ethics Committee (Project 156/08).

Thirty-seven patients (21 male; 57%) were included in the study, and 375 LFTs were collected, with 10.2 ± 8.6 pulmonary function tests per patient (range, 2-34) spanning a follow-up period of 7.6 ± 5.6 years. Demographic data are presented in Table I. The mean baseline FEV₁ for the whole group was 2.83 ± 1.28 L (82% $\pm$ 25% predicted), and those for the CVID group and XLA group, 2.77 ± 1.16 L (82% $\pm$ 24% predicted) and 3.48 ± 1.39 L (81% $\pm$ 29% predicted), respectively. The mean FVC was 3.85 ± 1.35 L (88% $\pm$ 21% predicted). The average annual FEV₁ decline for all patients with PID was 45 ± 6 mL/y. The

TABLE I. Demographic characteristics of study group

Clinical variable	Total	CVID	XLA
Subjects (n)	37	29 (78%)	8 (22%)
Age (y)	48.34 $\pm$ 15.97	50.61 $\pm$ 16.63	40.09 $\pm$ 10.29
Male (n)	21 (57%)	13 (44%)	8 (100%)
Weight (kg)	66.84 $\pm$ 16.09	67.70 $\pm$ 17.64	63.68 $\pm$ 8.52
Height (cm)	167.48 $\pm$ 9.75	166.04 $\pm$ 9.98	172.67 $\pm$ 7.15
BMI (kg/m ²)	23.86 $\pm$ 5.87	24.55 $\pm$ 6.33	21.36 $\pm$ 2.75
IVIG dose/mo (g/kg/mo)	0.45 $\pm$ 0.12	0.43 $\pm$ 0.12	0.51 $\pm$ 0.10
IgG trough level (g/L)	7.73 $\pm$ 1.41	7.71 $\pm$ 1.48	7.79 $\pm$ 1.21
Hospital admissions	22 (59%)	15 (52%)	7 (87%)
Age at diagnosis (y)	34.72 $\pm$ 22.4	43.53 $\pm$ 16.75	3.87 $\pm$ 4.42
Pack years of smoking	0 (0-5)	0 (0-2)	3.5 (0-22.5)
Bronchodilator responsiveness	11 (30%)	8 (27%)	3 (37%)
Bronchiectasis	17 (46%)	12 (41%)	5 (63%)
<i>Pseudomonas</i> colonization (n)	5 (13%)	5 (17%)	0 (0%)
FEV ₁ predicted (%) at start	81.73 $\pm$ 25.09	81.86 $\pm$ 24.35	81.26 $\pm$ 29.40
FVC predicted (%) at start	87.83 $\pm$ 20.50	86.07 $\pm$ 21.28	94.19 $\pm$ 17.04

BMI, Body mass index.

Data are expressed as mean $\pm$ SD, median (interquartile range), or number (proportion).

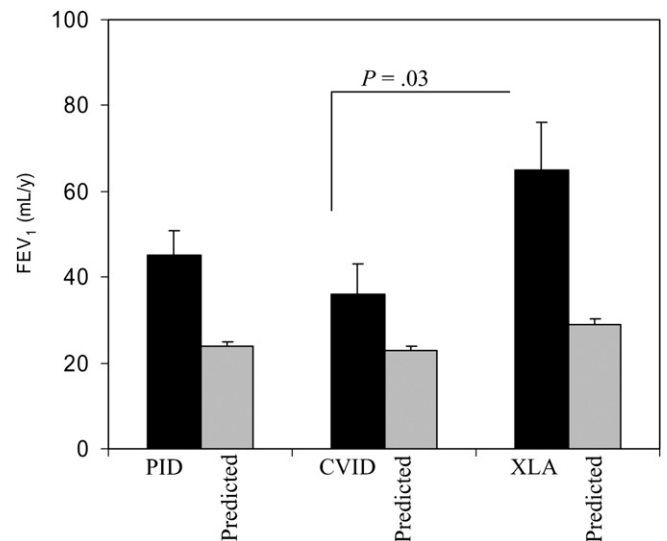


FIG 1. Average decline in FEV₁ (mL/y) for PID (total group), CVID, and XLA groups. Error bars represent estimates (SEs). Lung function tests were measured in an accredited laboratory performing tests according to American Thoracic Society criteria. Predicted decline is taken from predicted normal values at each time point for each patient.

XLA group was found to have a more rapid decline in FEV₁ (65 ± 11 mL/y) compared with the CVID group (36 ± 7 mL/y; *P* = .034; Fig 1). The decline in FVC (mean $\pm$ SE) was 43 ± 9.0 mL, higher in XLA (58 ± 20 mL/y) compared with CVID (39 ± 10 mL/y). However, the difference between groups was not significant (*P* = .39; Fig 2).

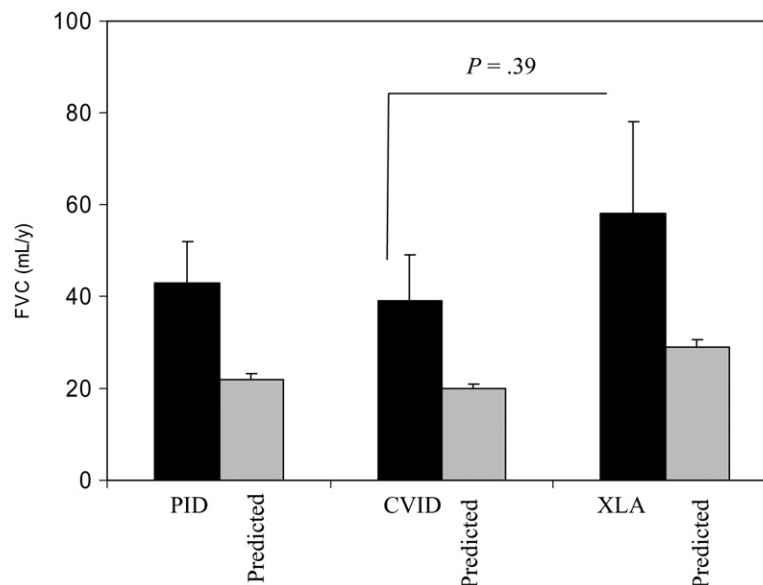


FIG 2. Average decline in FVC (mL/y) for PID (total group), CVID, and XLA groups. Error bars represent estimates (SEs). Predicted decline is taken from predicted normal values at each time point for each patient.

TABLE II. Factors associated with decline in FEV₁ (univariate analysis)

Variable	PE	SE	P value
IVIG dose (g/kg)	−0.121	0.039	.004
Age at diagnosis (y)	0.001	0.0002	.005
IVIG dose/mo (g/kg/mo)	−0.138	0.052	.01
IVIG dose (g)	−0.002	0.001	.03
CVID	0.028	0.013	.03
Pack-years of smoking	−0.002	0.001	.06
IgG trough level (g/L)	−0.004	0.006	.49

PEs describe the effect on FEV₁ decline in liters per year.

Univariate analysis identified 3 variables associated with decline in lung function (Table II). These were as follows:

1. Increased IVIG dose per kilogram was inversely associated with lung function decline (PE [SE] = −0.121 [0.039]; $P = .004$), indicating that higher dose per kilogram appeared to be protective of lung function. The related variables IVIG dose per month (g/kg/mo) and IVIG dose (g) were also inversely associated with lung function decline (Table II).
2. Diagnosis of XLA compared with CVID was associated with a more rapid decline in lung function (PE [SE] = 0.028 [0.013]; $P = .034$).
3. Younger age at diagnosis (PE [SE] = 0.001 [0.0002]; $P = .005$).

Trough IgG level did not have a statistically significant association with FEV₁ decline ($P = .485$) or FVC decline ($P = .69$). Similar significant associations with the IVIG dose/kg/mo and IVIG dose (g) were observed for FVC and FEV₁.

The normal rate of decline in FEV₁ (and 95% CI) in healthy nonsmoking men in a population similar to ours is reported to be 19.6 mL (17.1–22.1), and for women, 17.6 mL (13.8–21.4).⁵ The average decline of FEV₁ in our group of 45 mL per year

exceeds that associated with heavy smoking.⁵ Although smoking was recorded as a variable, the average duration of smoking was small (3.5 pack-years), so the decline in lung function associated with smoking just failed to reach statistical significance ($P = .06$).

Previous longitudinal reports of LFT in PID have used predicted normal values to indicate little change in LFT despite radiographic progression.⁸ However cross-sectional data used to derive predicted normal equations overestimate lung function decline by as much as 35 mL/y in the under 50 years age group compared with longitudinal studies^{4,9} indicating that predicted normal values are inappropriate to monitor longitudinal LFT changes.

In this study, higher monthly IVIG dose (g/kg) is significantly linked with decreased lung function decline (0.45 ± 0.12 [g/kg]; PE, −0.121 [0.039]; $P = .004$). This means that a 1 g per kg dose increase in IVIG was associated in these patients with a reduction in the decline of FEV₁ by 121 mL per year. Although such a dose is well beyond a practical therapeutic range, our findings suggest that IVIG dose might be targeted to reduce lung function decline. This approach is supported by a recent publication from Lucas et al¹⁰ reporting that infection frequency was found to be unrelated to trough IgG levels. Taken together, these results indicate that maintaining a higher dose of IVIG, independent of trough level, may be associated with superior outcomes in PID. Obviously this hypothesis should be tested in prospective trials, but such an approach differs from currently recommended algorithms.¹

One of the limitations of the study is the small number of patients. We were careful to ensure that this group met current definitions of XLA and CVID.¹ The strength of this cohort lies in this diagnostic rigor and the large number of respiratory function tests performed. Larger cohorts of patients with PID are now available through international registries, and such data will enable measurement of lung function decline and provide a basis for comparison of treatment outcomes.² This database also reveals reduced life expectancy in patients with PID, consistent with reduced lung function.

To our knowledge, this is the first study to report longitudinal rate of decline in lung function in well characterized patients with

PID. Our findings suggest that studies of the outcomes of immunoglobulin therapy in PID might use change in lung function as an indicator of treatment efficacy. Our study also supports higher doses of IVIG as protective of lung function decline.

Yan Chen, MB, BS^a

Rob G. Stirling, MB, BS, FRACP^{a,b}

Eldho Paul, MSc^c

Fiona Hore-Lacy, BSc (Hons)^a

Bruce R. Thompson, BAppSci, CRFS, PhD^{a,b}

Jo A. Douglass, MD, FRACP^{a,b}

From ^athe Department of Allergy, Immunology and Respiratory Medicine (AIRmed), Alfred Hospital; and the Departments of ^bMedicine and ^cEpidemiology and Preventive Medicine, Monash University, Melbourne, Australia. E-mail: j.douglass@alfred.org.au.

F. Hore-Lacy is part-funded by an Australian Society of Clinical Immunology and Allergy (ASCIA) research grant.

Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.

REFERENCES

1. Orange JS, Hossny EM, Weiler CR, Ballou M, Berger M, Bonilla FA, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 2006;117:S525-53.
2. Gathmann B, Grimbacher B, Beute J, Dudoit Y, Mahlaoui N, Fischer A, et al. The European internet-based patient and research database for primary immunodeficiencies: results 2006-2008. *Clin Exp Immunol* 2009;157(suppl 1):3-11.
3. Loebinger MR, Wells AU, Hansell DM, Cinyanganya N, Devaraj A, Meister M, et al. Mortality in bronchiectasis: a long-term study assessing the factors influencing survival. *Eur Respir J* 2009;34:843-9.
4. Kerstjens HA, Rijcken B, Schouten JP, Postma DS. Decline of FEV1 by age and smoking status: facts, figures and fallacies. *Thorax* 1997;52:820-7.
5. Kohansal R, Martinez-Camblor P, Agustí A, Buist AS, Mannino DM, Soriano JB. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham Offspring cohort. *Am J Respir Crit Care Med* 2009;180:3-10.
6. Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Respir Dis* 1983;127:725-34.
7. Senn S, Stevens L, Chaturvedi N. Repeated measures in clinical trials: simple strategies for analysis using summary measures. *Stat Med* 2000;19:861-77.
8. Haidopoulou K, Calder A, Jones A, Jaffe A, Sonnappa S. Bronchiectasis secondary to primary immunodeficiency in children: longitudinal changes in structure and function. *Pediatr Pulmonol* 2009;44:669-75.
9. Van Pelt W, Borsboom GJ, Rijcken B, Schouten JP, van Zomeren BC, Quanjer PH. Discrepancies between longitudinal and cross-sectional change in ventilatory function in 12 years of follow-up. *Am J Respir Crit Care Med* 1994;149:1218-26.
10. Lucas M, Lee M, Lortan J, Lopez-Granados E, Misbah S, Chapel H. Infection outcomes in patients with common variable immunodeficiency disorders: relationship to immunoglobulin therapy over 22 years. *J Allergy Clin Immunol* 2010;125:1354-60.

doi:10.1016/j.jaci.2011.03.041