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Bronchiectasis and deteriorating lung function in agammaglobulinaemia despite immunoglobulin replacement therapy

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Summary

Immunoglobulin replacement therapy enhances survival and reduces infection risk in patients with agammaglobulinaemia. We hypothesized that despite regular immunoglobulin therapy, some patients will experience ongoing respiratory infections and develop progressive bronchiectasis with deteriorating lung function. One hundred and thirty-nine (70%) of 199 patients aged 1–80 years from nine cities in the United Kingdom with agammaglobulinaemia currently listed on the UK Primary Immune Deficiency (UKPID) registry were recruited into this retrospective case study and their clinical and laboratory features analysed; 94% were male, 78% of whom had Bruton tyrosine kinase (*BTK*) gene mutations. All patients were on immunoglobulin replacement therapy and 52% had commenced therapy by the time they were 2 years old. Sixty per cent were also taking prophylactic oral antibiotics; 56% of patients had radiological evidence of bronchiectasis, which developed between the ages of 7 and 45 years. Multivariate analysis showed that three factors were associated significantly with bronchiectasis: reaching 18 years old [relative risk (RR) = 14·2, 95% confidence interval (CI) = 2·7–74·6], history of pneumonia (RR = 3·9, 95% CI = 1·1–13·8) and intravenous immunoglobulin (IVIG) rather than subcutaneous immunoglobulin (SCIG) = (RR = 3·5, 95% CI = 1·2–10·1), while starting immunoglobulin replacement after reaching 2 years of age, gender and recent serum IgG concentration were not associated significantly. Independent of age, patients with bronchiectasis had significantly poorer lung function [predicted forced expiratory volume in 1 s 74% (50–91)] than those without this complication [92% (84–101)] ($P < 0·001$). We conclude that despite immunoglobulin replacement therapy, many patients with agammaglobulinaemia can develop chronic lung disease and progressive impairment of lung function.

Keywords: agammaglobulinaemia, bronchiectasis, IVIG, lung function, SCIG

Introduction

Agammaglobulinaemia is a group of inherited antibody immunodeficiency diseases which, unlike common variable immunodeficiency (CVID), usually present during the first few years of life. Males are affected more commonly than females, with mutations detected most commonly in the *BTK* gene on the X-chromosome [1]. Less frequently, mutations are found in genes coding for the immunoglobulin heavy mu chain (*IGHM*), pre-B cell and B cell receptor (*IGLL1*, *CD79A*, *CD79B*) and the scaffold protein B cell linker (BLNK) of both males and females [2–6]. Respiratory tract and other deep-seated infections caused particularly by encapsulated bacteria account for much of the morbidity and mortality [7,8].

Since the initial description of inherited agammaglobulinaemia by Ogden Bruton in 1952, the mainstay of treatment has been immunoglobulin (Ig) replacement therapy to reduce this infection risk [9]. With early diagnosis and Ig replacement therapy, clinicians currently expect that chronic lung damage and bronchiectasis might be prevented, more so than in other antibody deficiencies presenting more insidiously and later in life, e.g. CVID [10–13]. However, there is evidence that bronchiectasis can develop in more than half and progress in a third of the patients, despite carefully monitored Ig replacement [14–18].

Using data from the UK national Primary Immunodeficiency Network (UKPIN) registry, this study aimed to determine if Ig replacement therapy protects patients with agammaglobulinaemia developing recurrent respiratory infections, and in particular bronchiectasis with concomitant impairment of lung function. The findings of this study should help clinicians to advise their patients more accurately as to the natural history of agammaglobulinaemia and its potential complications, even with modern, well-monitored Ig therapy.

Methods

Patient definition and identification

Patients with agammaglobulinaemia excluding CVID were identified from large clinical immunology referral centres throughout the United Kingdom contributing patients to the national UK Primary Immune Deficiency (UKPID) registry [19]. The UKPID registry was established in 2009 and recruits patients prospectively after obtaining written consent. The registry currently contains 4460 patients with primary immunodeficiency diseases, 199 of whom are classified as having agammaglobulinaemia.

Data from nine UK cities with patients registered with agammaglobulinaemia were approached. The study had multi-centre ethical approval (04/MRE07/68). After requesting permission from Centre Principle Investigators, data were collated into a single SPSS database (IBM SPSS Statistics version 22.0) for analysis. Clinical information included demographics, past medical history of acute or recurrent respiratory tract infections. UKPID registry entries are updated on an annual basis by C. B., who visits each of the centres personally to ensure that subsequent morbidity and mortality, as well as the latest laboratory parameters, are recorded. For the purposes of this survey, registry entries were rechecked with source data by A. S., C. B. and centre investigators and missing data points filled. Lower respiratory tract infection (LRTI) was defined as respiratory symptoms associated with consolidation noted on chest X-ray. Bronchiectasis was diagnosed when radiological abnormalities were identified by high-resolution chest computerized tomography (CT) imaging. Date of diagnosis of bronchiectasis was recorded. Timing of the CT imaging depended on the clinician. Spirometry was not recorded routinely within the PIDUK registry database. For the purposes of this study, the patient's most recent forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) results were requested from individual site investigators. There is currently no UK-wide protocol for performing chest CT scans or pulmonary function tests. Frequency of monitoring of lung function among patients in the study is not known. Therapies, including Ig replacement and antibiotic prophylaxis, were also recorded. None of the patients were documented to have spent any time off infusions.

Laboratory investigations

Laboratory data included routine haematology [haemoglobin, white blood count (WBC), absolute neutrophil and lymphocyte counts and platelets] and immunology [lymphocyte subsets: absolute CD3, CD4, CD8, CD19, CD56 and serum immunoglobulin (Ig)] concentrations taken at diagnosis and on Ig replacement therapy. Immunoglobulin subclasses and vaccine antibody responses were not available for most patients in this cohort. Lymphocyte subsets were assessed using standard immunofluorescent staining and flow cytometry was performed in accredited regional clinical immunology laboratories. Serum immunoglobulin concentrations were measured by nephelometry. For patients on 3–4-weekly intravenous Ig replacement (IVIG), trough IgG concentrations were checked just prior to administering the next dose; for patients on weekly subcutaneous Ig therapy (SCIG), levels were checked at scheduled clinic visits which did not necessarily occur just prior to administration of next dose.

Statistical analysis

Analysis was conducted using the IBM SPSS Statistics version 22 program. Continuous variables are quoted as medians and interquartile ranges. Statistical differences between groups were determined by χ^2, Mann–Whitney or Kruskal–Wallis tests. Differences were considered statistically significant with a P-value $< 0{\cdot}05$. Multivariate analysis was calculated using binominal logistic and Cox regression.

Results

Demographics

One hundred and thirty-nine of 199 patients (70%) classified as having agammaglobulinaemia on the PIDUK registry were recruited from nine cities treating patients for primary immunodeficiency diseases within the United Kingdom. Twenty-seven per cent were from Manchester, 18% in London, 12% in Newcastle, 12% in Belfast and 11% in Glasgow, with smaller numbers of patients from Aberdeen, Cardiff, Leeds and Nottingham. Eighty per cent

Table 1. Demographic, clinical and laboratory parameters of 139 patients with agammaglobulinaemia

Parameter	Total cohort	No bronchiectasis	Bronchiectasis	*P*-value
Number	139	61	78	
Age (years)	27 (18–40)	20 (12–34)	34 (28–48)	0·001
Gender	94% male	91% male	93% male	0·5
Ethnicity	80% white European	82% white European	81% white European	1·0
Family history	54%	59%	53%	0·6
Age of onset of symptoms (years)	0 (0–1)	0 (0–1)	0 (0–2)	0·2
Age at diagnosis (years)	3 (1–14)	3 (1–4)	7 (1–43)	0·5
Bacterial infections	78%	69%	85%	0·05
Bronchiectasis (on chest CT scan)	56%	0%	100%	
Bacterial pneumonia	74%	60%	87%	0·001
Chronic sinusitis	70%	67%	71%	0·7
Otitis	38%	20%	50%	0·004
Conjunctivitis	23%	36%	18%	0·07
Died	2%	0%	4%	0·1
FEV_1 (% predicted for age)	84 (56–94)	92 (84–101)	74 (50–91)	0·001
FVC (% predicted for age)	89 (78–103)	96 (81–106)	89 (68–100)	0·2
Pretreatment IgM (g/l)	0·0 (0·0–0·05)	0·1(0·0–0·2)	0·1 (0·0–0·2)	0·9
Pretreatment IgG (g/l)	1·0 (0·1–2·8)	0·9 (0·1–2·6)	1·1 (0·0–2·9)	0·9
Pretreatment IgA (g/l)	0·0 (0·0–0·0)	0·0 (0·0–0·1)	0·0 (0·0–0·2)	0·9
CD19 (B cells) (cells/microlitre)	0 (0–6)	1 (0–42)	0 (0–2)	0·2
CD3 (T cells) (cells/microlitre)	1504 (1143–1980)	1470 (1195–1945)	1539 (1159–2049)	0·7
Neutrophils ($\times 10^9$/l)	4·5 (3·3–6·8)	4·3 (3·0–6·5)	4·9 (3·5–7·5)	0·06
Latest IgG (g/l)	10·1 (8·5–11·9)	9·7 (8·5–11·1)	10·8 (8·7–12·9)	0·02
Latest IgG $\geq$ 4·0 g/l	136 (98%)	59 (96%)	76 (98%)	0·6
Latest IgG $\geq$ 7·0 g/l	131 (94%)	55 (90%)	74 (95%)	0·5
Latest IgG $\geq$ 10·0 g/l	75 (54%)	28 (46%)	46 (59%)	0·2
Latest IgG $\geq$ 14·0 g/l	14 (10%)	0 (0%)	14 (18%)	0·001
IG replacement	IVIG 55%, SCIG 45%	IVIG 58%, SCIG 42%	IVIG 34%, SCIG 66%	0·008
Dose Ig (mg/kg/month)	538 (459–705)	510 (438–584)	598 (495–848)	0·006
Age Ig replacement commenced (years)	3 (1–6)	1 (0–3)	4 (2–8)	0·02
Ig, started when $\geq$ 2 years old	72 (52%)	20 (32%)	52 (67%)	0·002
Prophylactic antibiotics	60%	54%	64%	0·3

Continuous variables are displayed as median (interquartile range) Ig = immunoglobulin replacement; IVIG = intravenous immunoglobulin; SCIG = subcutaneous immunoglobulin; CT = computerized tomography; FEV1 – forced expiratory volume in 1 s; FCV = forced vital capacity. Subgroups with and without bronchiectasis are compared using χ^2 test for discrete variables and Mann–Whitney *U*-test for continuous variables.

were white European. Only nine (6%) were female. A *BTK* gene mutation was found in 109 (78%) of the 130 males. Two males had *IGHM* mutations. No specific genetic cause was available in the remainder. The median age of the cohort was 27 (range = 1–80) years. Eighty-five per cent of patients' symptoms commenced by age 3 years. The median age of diagnosis was 3 years (93% by age 5 years). The median [interquartile range (IQR)] duration of follow-up was 21 (IQR = 13–32) years, with an overall follow-up for the total cohort of 2922 years. Three patients (2%) had died (Table 1).

Clinical and laboratory correlates with infectious complications: bacterial respiratory tract infections and bronchiectasis

Seventy-eight per cent of patients had suffered from bacterial infections: 74% from pneumonia, 70% chronic sinusitis, 38% otitis and 23% conjunctivitis. Fifty-six per cent had bronchiectasis (Table 2). Bronchiectasis was associated with a history of bacterial infection at any site [relative risk (RR) = 1·0–6·3, 95% confidence interval (CI) = 2·6], particularly with pneumonia (RR = 4·6, 95% CI = 1·8–11·8) and otitis (RR = 4·2, 95% CI = 1·6–11·0), but not sinusitis (RR = 1·4, 95% CI = 0·6–3·1) or conjunctivitis (RR = 0·4, 95% CI = 0·2–1·1) (Table 1, Fig. 1). Patients with bronchiectasis were significantly older (RR = 34, 95% CI = 28–48 years) than those without this complication (RR =20, 95% CI = 12–34 years) ($P < 0·001$) (Table 1) and there was a linear increase in the proportion of patients with bronchiectasis from 18 to 60 years of age ($r = 0·81$, $P < 0·001$) (Fig. 2a). Spirometry was available on 73 patients (52%). Twenty of the remaining patients (14%) were too young to perform lung function tests. Patients with bronchiectasis ($n = 46$) had significantly lower FEV_1 (RR = 74%, 95% CI = 50–91) than those without this

Table 2. Clinical and laboratory features of patients receiving immunoglobulin replacement intravenously and subcutaneously

	IVIG	SCIG	*P*-value
Number (%)	73	63	
Age (years)	34 (23–47)	22 (13–32)	0·001
Males (%)	96%	93%	0·7
White European (%)	85%	75%	0·2
IgG on Ig replacement (g/l)	10·8 (9·2–12·3)	9·4 (8·0–11·2)	0·004
Prophylactic antibiotics (%)	69%	48%	0·02
Bacterial sepsis (%)	81%	76%	0·5
Bronchiectasis (%)	68%	44%	0·02
LRTI (%)	75%	74%	1·0
Otitis (%)	42%	35%	0·5
Sinusitis (%)	74%	67%	0·5
Conjunctivitis (%)	19%	29%	0·3

Immunoglobulin replacement therapy: IVIG = intravenous immunoglobulin; SCIG = subcutaneous immunoglobulin; LRTI = history of bacterial lower respiratory tract infections; Ig = immunoglobulin. Continuous variables represent medians/interquartile ranges. Mann–Whitney *U*-test was used for continuous variables and χ^2 test for discrete variables to compare groups with and without complications.

complication ($n = 24$) (RR = 92%, 95% CI = 84–101, $P < 0·001$). Fifty-five per cent of patients (25 of 46) with bronchiectasis had an FEV_1 of < 70% compared with 8% (two of 24 patients) without bronchiectasis, ($P < 0·001$). Using Cox regression multivariate analysis, the association between FEV_1 and bronchiectasis (RR = 3·2, 95% CI = 1·8–5·4) was independent of age. FVC was not significantly different between the two groups (RR = 89%, 95% CI = 68–100 *versus* RR = 96%, 95% CI = 81–106, $P = 0·2$).

The most common bacteria isolated from respiratory secretions was *Haemophilus influenzae* (46% of total isolates), followed by *Streptococcus pneumoniae* (18%), *Staphylococcus aureus* (12%) and *Mycoplasma pneumoniae* (8%). There was no association between a particular bacterial species and bronchiectasis. Extra-respiratory tract infections, in order of frequency, were septic arthritis, osteomyelitis, skin infections, meningitis, septicaemia and gastroenteritis. Only one patient was reported to have echovirus encephalitis.

All but one patient had low or absent B cells and normal CD56 natural killer (NK) cells. Absolute T cell numbers (CD3, CD4 and CD8) were within the normal range in all patients. None of the patients had evidence of a persistent neutropenia (absolute neutrophil count $< 1·0 \times 10^9$/l).

Treatment

Fifty-two per cent of patients had started on Ig replacement therapy by age 2 years. The current median (IQR) Ig dose was equivalent to 538 (459–705) mg/kg/month. Fifty-five per cent were on intravenous (i.v.) therapy, while 45% were having the therapy administered subcutaneously (s.c.). Patients on IVIG therapy were significantly older (median age = 34 years) than those on SCIG (median age = 22 years, $P < 0·001$) (Table 2). A significantly greater proportion of patients on IVIG than on SCIG had bronchiectasis, and this association remained significant after adjusting for patient's age [3·5 (1·2–10·1), $P = 0·02$].

Patients with bronchiectasis started on Ig therapy at a significantly older age than those without this complication (Table 1, Fig. 2b). However, using binominal regression multivariate analysis the three key variables associated with bronchiectasis were: (i) reaching adulthood (> 18 years) [14·2 (2·7–74·6)], (ii) history of previous pneumonia [3·9 (1·1–13·8)] and (iii) treatment with IVIG rather than SCIG [3·5 (1·2–10·1)]. Factors that were not significant in this multivariate analysis were having started Ig supplementation after age 2 years, gender and recent serum IgG concentration. Regarding serum IgG concentration, patients with bronchiectasis were more likely to have been prescribed larger doses of Ig [equivalent to 598 (498–848) mg/kg/month] than those without this complication [equivalent

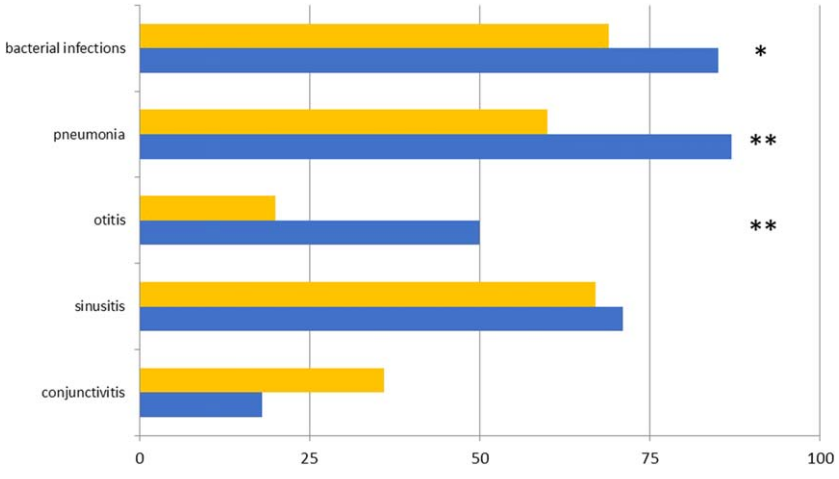

Fig. 1. Association between bronchiectasis and other respiratory tract infections. Orange = patients with no bronchiectasis, blue = patients with bronchiectasis. *$P < 0·05$; **$P < 0·005$; χ^2 test. [Colour figure can be viewed at wileyonlinelibrary.com]

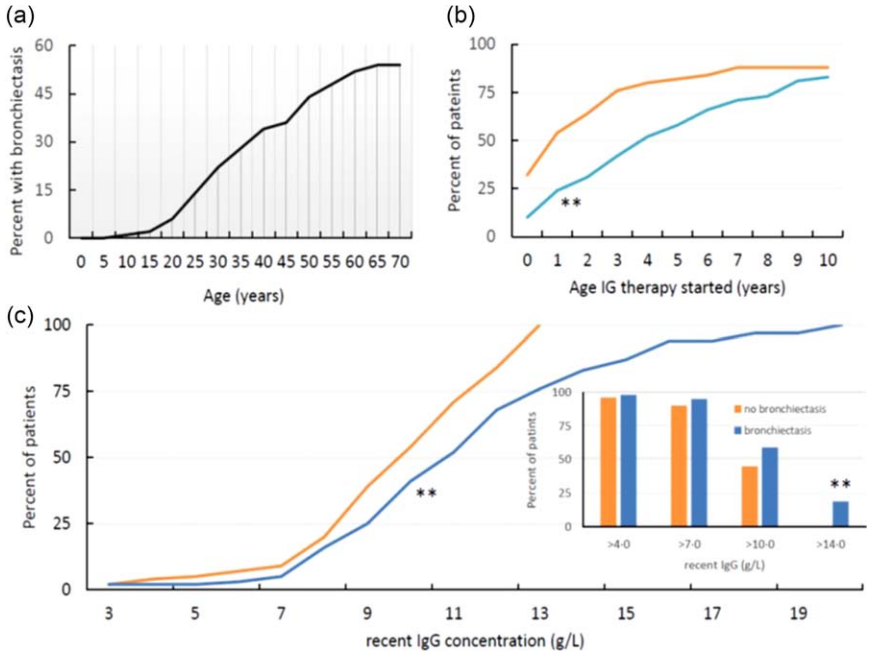

Fig. 2. Factors associated with bronchiectasis. (a) Current age of patients with bronchiectasis. (b) Age at which patients with (blue) and without (orange) bronchiectasis commenced immunoglobulin (Ig) replacement therapy. (c) Recent serum IgG concentration in patients with (blue) and without (orange) bronchiectasis. Insert: percentage of patients with serum IgG concentrations $> 4{\cdot}0$, $> 7{\cdot}0$, $> 10{\cdot}0$ and $> 14{\cdot}0$ g/l. $^{**}P < 0{\cdot}005$ using Breslow or χ^2 statistics. [Colour figure can be viewed at wileyonlinelibrary.com]

to 511 (436–584), $P < 0{\cdot}01$] and subsequently had significantly higher serum IgG concentrations [10·8 (8·7–12·9) *versus* 9·7 (8·5–11·1) g/l, $P < 0{\cdot}03$] (Table 1, Fig. 2c), with nearly one in five patients with bronchiectasis having an IgG concentration above 14·0 g/l. Eighty-three per cent of patients in the cohort had been on immunoglobulin replacement therapy for more than 7 years (range = 0–43 years) prior to their diagnosis with bronchiectasis. There was no significant association between history of pneumonia or otitis and recent serum IgG concentrations above 4·0, 7·0, 10·0 or 14·0 g/l.

Sixty per cent of patients had been prescribed prophylactic antibiotics (Table 1). Although the use of prophylactic antibiotic use did not increase significantly with age or with history of respiratory infections (pneumonia, otitis or bronchiectasis), their use was associated with poorer lung function [FEV_1 = 75 (49–93) *versus* FEV_1 = 90 (83–93), $P = 0{\cdot}004$]. These patients were also more likely to be on a higher dose of Ig replacement therapy [FEV_1 = 580 (508–788) *versus* FEV_1 = 497 (428–582) equivalent mg/kg/month, $P = 0{\cdot}002$] and have higher serum IgG concentrations [FEV_1 = 11·1 (9·3–12·4) *versus* FEV_1 = 9·4 (8·4–10·4) g/l, $P = 0{\cdot}003$].

Patients recruited from London were significantly older than those from other UK cities. All patients recruited from Newcastle upon Tyne and Belfast were white European, in contrast to 64–73% of patients from London, Manchester and Glasgow ($P < 0{\cdot}005$). There were no significant regional differences in age of commencement of Ig therapy, dose of Ig therapy, use of prophylactic antibiotics, serum IgG concentration or prevalence of bronchiectasis. However, London and Glasgow centres prescribed IVIG rather than SCIG more frequently than other centres ($P < 0{\cdot}005$) (Table 3).

Table 3. Demographics, clinical features and treatment of patients with agammaglobulinaemia from major UK cities

	London	Manchester	Newcastle	Belfast	Glasgow	*P* value
Number (%)	24	44	17	17	15	
Age (years)	39 (28–53)	22 (13–37)	29 (14–36)	22 (18–27)	22 (12–34)	0·002
White European (%)	71%	64%	100%	100%	73%	0·004
Bronchiectasis (%)	87%	46%	53%	44%	38%	0·01
Age bronchiectasis diagnosed (years)	19 (16–29)	16 (14–35)	23 (20–23)	–	18 (18–18)	0·8
Age Ig commenced (years)	4 (1–6)	3 (0–5)	7 (1–7)	2 (0–12)	2 (2–6)	0·8
Percentage on SCIG	21%	62%	47%	60%	20%	0·004
Dose of Ig (mg/kg/month equivalent)	661 (461–1048)	511 (436–559)	612 (460–612)	584 (443–869)	518 (492–815)	0·2
Latest IgG (g/l)	11·1 (9·4–13·4)	10·2 (8·4–11·8)	9·3 (8·4–10·5)	8·5 (7·4–12·4)	10·8 (10–11·4)	0·054
Prophylactic antibiotics	59%	70%	47%	42%	50%	0·3

Numbers for continuous variables represent medians/interquartile ranges. Kruskal–Wallis test was used for continuous variables and χ^2 test for discrete variables to compare groups. Ig = immunoglobulin replacement therapy; SCIG = subcutaneous immunoglobulin.

Discussion

In contrast to the relatively large number of retrospective case studies on CVID, there are only a few previously published studies with more than 100 agammaglobulinemia patients [20,21]. This is the largest study of patients with agammaglobinaemia focusing on chronic lung disease and lung function. Since Sweinberg *et al.* [22] suggested in 1991 that Ig replacement could prevent chronic lung damage, the perceived dogma of many patients and clinicians is that optimal Ig therapy, good compliance and close monitoring can prevent lung disease [23,24]. This retrospective case study shows that more than half the patients with agammaglobulinaemia in our UK registry developed radiological evidence of bronchiectasis and poor lung function. Furthermore, these measures of lung disease occurred many years after starting Ig replacement therapy. Three independent factors were associated with risk of bronchiectasis: attaining adulthood, history of previous pneumonia and treatment with IVIG rather than SCIG therapy. Gender, age at starting Ig therapy and species of bacterial pathogen isolated from respiratory secretions were not significant risk factors after adjusting for age.

A major difference between our study and the small study of 22 patients [10 with X-linked agammaglobulinaemia (XLA)] performed by Sweinberg *et al.* is that during the last 25 years, high-resolution chest CT scans rather than chest X-rays have become the standard, and a much more sensitive test for bronchiectasis. This is likely to explain, at least partly, the higher prevalence of bronchiectasis in our study [24,25]. An important question not addressed here is whether the observed radiological evidence of bronchiectasis and the poorer lung function corresponds to deterioration in patients' quality of life. Bryan *et al.* [26], in their survey of 15 patients with agammaglobinaemia from the North of England, suggested that there may well be a significant impact on patients' respiratory and overall quality of life. Larger studies are required to understand more fully the overall burden of disease.

There is ongoing debate as to the optimal serum IgG concentration in patients with agammaglobulinaemia [27–29], with some clinicians suggesting that a trough (IgG) of > 4 g/l is adequate, while others recommend an IgG of > 10 g/l to prevent the development of subclinical lung damage. We found no significant association between the proportion of patients with bronchiectasis, pneumonia, otitis or poor lung function and serum IgG cut-off concentrations of 4·0, 7·0 or 10·0 g/l. Nineteen per cent of patients, all with bronchiectasis, had an IgG concentration $\geq$ 14·0 g/l, suggesting that in a subset of patients with bronchiectasis high-dose Ig supplementation is used to try to prevent further deterioration. In this regard, patients with poorer lung function were on more treatment, both in terms of dose of Ig supplementation and use of prophylactic antibiotics. Whether or not this escalation in therapy is beneficial is not possible to determine from this study.

There were some regional differences, particularly in the age of the patients, with the longer-established London centres having older patients with a higher prevalence of bronchiectasis. This may also explain the preferential use of IVIG in London compared with most other regional centres, as the use of SCIG has been largely introduced into the United Kingdom during the last 20 years. Serum IgG concentrations were significantly lower in patients on SCIG than IVIG but, after taking the age of the patient into account, IVIG rather than SCIG was associated with an increased risk of bronchiectasis. This is a novel finding, as no previously published studies have directly compared the efficacy of IVIG and SCIG in preventing lung disease. Independent studies from other countries are required to determine if this finding can be generalized as, if confirmed, it may lead to SCIG being recommended as the preferred route of treatment for patients with agammaglobulinaemia in the future.

There are a number of limitations of this study. The retrospective nature is inevitable, as a prospective study to look at the natural history of these patients is difficult. As the UKPID registry has only been collecting data since 2009, deaths prior to that time would not have been recorded and therefore the study may well underestimate the severity of the clinical course. It may be that, followed-up for longer, most of these patients will eventually develop chronic lung damage and respiratory impairment. Alternatively, with more patient-friendly infusion modalities [30], and more precise and regular monitoring, fewer patients would develop these pulmonary complications. The criteria used by clinicians in each centre to order CT scans were not recorded, and may have affected the timing of diagnosis of bronchiectasis. Quality of life data and smoking history were not collected as part of our survey or the UKPID registry. It would be useful for registries to consider collecting smoking history and 'patient experience' as part of future routine data collection, particularly in view of the potential impact and co-founding effects of smoking on lung function. Lung function data are currently not recorded routinely as part of the UKPID registry, and had to be requested directly from the centre investigators. Recording of lung function data by the UKPID and other registries could potentially provide an additional useful outcome measure, particularly as deterioration in lung function is a recognized important complication of agammaglobulinaemia.

In conclusion, this study suggests that, even with Ig replacement therapy, many patients with agammaglobulinaemia develop chronic lung disease and reduced lung function. Patients at higher risk are those who have reached adulthood, have a previous history of pneumonia and are on IVIG rather than SCIG therapy. It is important for clinicians to counsel their patients appropriately to avoid unrealistic expectations and promote careful long-term

monitoring of lung disease, particularly in those with higher risks.

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Author contributions

P. D. A. conceived of and led the study. Each regional centre lead was in charge of recruiting patients with agammaglobulinaemia onto the UKPID registry, which was maintained and updated by C. B.; A. S. collated all the data into the centralized database. All authors contributed to the writing of the manuscript and approved the final version.

References

1 Vetrie D, Vorechovský I, Sideras P *et al.* The gene involved in X-linked agammaglobulinaemia is a member of the SRC family of protein-tyrosine kinases. Nature 1993; **361**:226–33.
2 Conley ME, Dobbs AK, Farmer DM *et al.* Primary B cell immunodeficiencies: comparisons and contrasts. Annu Rev Immunol 2009; **27**:199–227.
3 Yel L, Minegishi Y, Coustan-Smith E *et al.* Mutations in the mu heavy-chain gene in patients with agammaglobulinemia. N Engl J Med 1996; **335**:1486–93.
4 Minegishi Y, Coustan-Smith E, Wang YH *et al.* Mutations in the human lambda5/14.1 gene result in B cell deficiency and agammaglobulinemia. J Exp Med 1998; **187**:71–7.
5 Minegishi Y, Rohrer J, Coustan-Smith E *et al.* An essential role for BLNK in human B cell development. Science 1999; **286**: 1954–7.
6 Minegishi Y, Coustan-Smith E, Rapalus L *et al.* Mutations in Igalpha (CD79a) result in a complete block in B-cell development. J Clin Invest 1999; **104**:1115–21.
7 Costa-Carvalho BT, Wandalsen GF, Pulici G *et al.* Pulmonary complications in patients with antibody deficiency. Allergol Immunopathol (Madr) 2011; **39**:128–32.
8 Reisi M, Azizi G, Kiaee F *et al.* Evaluation of pulmonary complications in patients with primary immunodeficiency disorders. Eur Ann Allergy Clin Immunol 2017; **49**:122–8.
9 Bruton OC. Agammaglobulinemia. Pediatrics 1952; **9**:722.
10 Aghamohammadi A, Allahverdi A, Abolhassani H *et al.* Comparison of pulmonary diseases in common variable immunodeficiency and X-linked agammaglobulinaemia. Respirology 2010; **15**:289–95.
11 Brent J, Guzman D, Bangs C *et al.* Clinical and laboratory correlates of lung disease and cancer in adults with idiopathic hypogammaglobulinaemia. Clin Exp Immunol 2016; **184**:73–82.
12 Gathmann B, Mahlaoui N, Gérard L *et al.* Clinical picture and treatment of 2212 patients with common variable immunodeficiency. J Allergy Clin Immunol 2014; **134**:116–26.
13 Verma N, Grimbacher B, Hurst JR. Lung disease in primary antibody deficiency. Lancet Respir Med 2015; **3**:651–60.
14 Gregersen S, Aaløkken TM, Mynarek G *et al.* Development of pulmonary abnormalities in patients with common variable immunodeficiency: associations with clinical and immunologic factors. Ann Allergy Asthma Immunol 2010; **104**:503–10.
15 Curtin JJ, Webster AD, Farrant J, Katz D. Bronchiectasis in hypogammaglobulinaemia–a computed tomography assessment. Clin Radiol 1991; **44**:82–4.
16 Kainulainen L, Varpula M, Liippo K *et al.* Pulmonary abnormalities in patients with primary hypogammaglobulinemia. J Allergy Clin Immunol 1999; **104**:1031–6.
17 Collins HD, Dudley HR. Agammaglobulinemia and bronchiectasis; a report of two cases in adults, with autopsy findings. N Engl J Med 1955; **252**:255–9.
18 Janssen WJ, Mohamed Hoesein F, Van de Ven AA *et al.* IgG trough levels and progression of pulmonary disease in pediatric and adult common variable immunodeficiency disorder patients. J Allergy Clin Immunol 2017; **140**: 303–6.e4.
19 Edgar JD, Buckland M, Guzman D *et al.* The United Kingdom Primary Immune Deficiency (UKPID) Registry: report of the first 4 years' activity 2008–2012. Clin Exp Immunol 2014; **175**: 68–78.
20 Chen X-F, Wang W-F, Zhang Y-D *et al.* Clinical characteristics and genetic profiles of 174 patients with X-linked agammaglobulinemia: report from Shanghai, China (2000–2015). Medicine (Baltimore) 2016; **95**:e4544.
21 Tóth B, Volokha A, Mihas A *et al.* Genetic and demographic features of X-linked agammaglobulinemia in Eastern and Central Europe: a cohort study. Mol Immunol 2009; **46**:2140–6.
22 Sweinberg SK, Wodell RA, Grodofsky MP *et al.* Retrospective analysis of the incidence of pulmonary disease in hypogammaglobulinemia. J Allergy Clin Immunol 1991; **88**:96–104.
23 Lucas M, Lee M, Lortan J *et al.* Infection outcomes in patients with common variable immunodeficiency disorders: relationship to immunoglobulin therapy over 22 years. J Allergy Clin Immunol 2010; **125**:1354–60.
24 Maglione PJ, Overbey JR, Radigan L *et al.* Pulmonary radiologic findings in common variable immunodeficiency: clinical and immunological correlations. Ann Allergy Asthma Immunol 2014; **113**:452–9.
25 Maarschalk-Ellerbroek LJ, de Jong PA, van Montfrans JM *et al.* CT screening for pulmonary pathology in common variable immunodeficiency disorders and the correlation with clinical and immunological parameters. J Clin Immunol 2014; **34**:642–54.
26 Bryan BA, Battersby A, Shillitoe BM *et al.* Respiratory health and related quality of life in patients with congenital agammaglobulinemia in the northern region of the UK. J Clin Immunol 2016; **36**:472–9.
27 Suri D, Bhattad S, Sharma A *et al.* Serial serum immunoglobulin G (IgG) trough levels in patients with X-linked

agammaglobulinemia on replacement therapy with intravenous immunoglobulin: its correlation with infections in Indian children. J Clin Immunol 2017; **37**:311–8.

28 Quinti I, Soresina A, Guerra A *et al*. Effectiveness of immunoglobulin replacement therapy on clinical outcome in patients with primary antibody deficiencies: results from a multicenter prospective cohort study. J Clin Immunol 2011; **31**:315–22.

29 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; **137**:21–30.

30 Espanol T, Prevot J, Drabwell J *et al*. Improving current immunoglobulin therapy for patients with primary immunodeficiency: quality of life and views on treatment. Patient Prefer Adherence 2014; **8**:621–9.