Effectiveness of Immunoglobulin Replacement Therapy on Clinical Outcome in Patients with Primary Antibody Deficiencies: Results from a Multicenter Prospective Cohort Study

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Abstract A 5-years multicenter prospective study on 201 patients with common variable immunodeficiencies and 101 patients with X-linked agammaglobulinemia over a cumulative follow-up period of 1,365 patient-years was conducted to identify prognostic markers and risk factors for associated clinical co-morbidities, the effects of long-term immunoglobulin treatment and the IgG trough level to be maintained over time required to minimise infection risk. Overall, 21% of the patients with common variable immunodeficiencies and 24% of patients with X-linked agammaglobulinemia remained infection free during the study. A reduction of pneumonia episodes has been observed after initiation of Ig replacement. During the observation time, pneumonia incidence remained low and constant over time. Patients with pneumonia did not have significant lower IgG trough levels than patients without

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pneumonia, with the exception of patients whose IgG trough levels were persistently <400 mg/dL. In X-linked agammaglobulinemia, the only co-morbidity risk factor identified for pneumonia by the final multivariable model was the presence of bronchiectasis. In common variable immunodeficiencies, our data allowed us to identify a clinical phenotype characterised by a high pneumonia risk: patients with low IgG and IgA levels at diagnosis; patients who had IgA level <7 mg/dL and who had bronchiectasis. The effect of therapy with immunoglobulins at replacement dosage for non-infectious co-morbidities (autoimmunity, lymphocytic hyperplasia and enteropathy) remains to be established. A unique general protective trough IgG level in antibody deficiency patients will remain undefined because of the major role played by the progression of lung disease in X-linked agammaglobulinemia and in a subset of patients with common variable immunodeficiencies.

Introduction

Survival of patients with primary antibody deficiencies has increased due to improved detection of infectious diseases, availability of Ig replacement therapy and antimicrobial agents. IgG replacement therapy has been stated as beneficial [1], although the optimal IgG trough level to be maintained over time in order to minimise infectious risk is not established. Consequently, there is a wide variation in treatment practices [2–7]. A summary of guidelines on the management of primary antibody deficiency with replacement therapy suggested achieving trough IgG serum levels of at least 5 g/L and ideally of 6.5–10 g/L [8]. More recently, a study on a cohort of common variable immunodeficiencies (CVIDs) and X-linked agammaglobulinemia (XLA) English patients [9] and a meta-analysis on the impact of trough IgG on pneumonia incidence [10] provided evidence that patients might remain infection free and the pneumonia risk can be progressively reduced by higher trough IgG levels in order to reach a "biologic" level that is unique for each patient [11]. Severe infections are the main cause of morbidity and mortality in XLA patients [12]. Clinical phenotypes of CVIDs patients are more heterogeneous and patients are susceptible to a wide range of co-morbidities other than infections [13]. Therefore, the suggested protective high trough IgG level might not be considered a general goal and only large prospective multi-centre studies might help to identify CVIDs subgroups of patients at high infection risk. We have carried out a prospective study with the aim to identify prognostic

markers and risk factors for associated clinical complications in a cohort of 302 patients with primary antibody deficiencies over a cumulative follow-up period of 1,365 patient-years.

Methods

Patients and Study Design In year 2001, a total of 302 patients diagnosed according to the ESID/PAGID criteria for XLA and CVIDs [14] and registered in the Italian Primary Immunodeficiency Network (IPINET) database have been included in this prospective study. One hundred and one patients had a definitive diagnosis of XLA based on <2% of peripheral B cells and mutations of the *Btk* gene; 201 patients had a diagnosis of CVIDs based on a marked decrease (at least 2 standard deviation (SD) below the mean for age) in serum IgG and IgA, onset age >2 years, poor response to vaccines and exclusion of other causes of hypogammaglobulinemia. Data has been prospectively collected for 5 years according to the study protocol and inserted in an internet-based patient database on a yearly basis. Detailed information with personal data, pedigree, date of diagnosis, immunological data and clinical manifestations, route and dosage of immunoglobulin replacement from the time of enrolment were collected in a structured questionnaire filled by one physician per centre on a yearly basis. All data were processed in a database and sent to the Interuniversity Computing Center (CINECA) responsible for processing and analysing the data. For each patient, full blood counts, lymphocyte subsets, chemistries, serum immunoglobulin levels were performed four times per year. Chest and sinus computerised tomography (CT) scans were performed every 4 years, gastrointestinal endoscopy with biopsy every 2 years or when indicated (Supplemental Table I). Retrospective data related to diagnosis was also available (study design: Supplemental Figure 1). All patients were on intravenous or subcutaneous immunoglobulins according to the national guidelines (www.aieop.org). All participants provided written informed consent. The study protocol was approved by the Institutional Review Board at Università Sapienza of Rome.

Measurements Disease-associated clinical co-morbidities such as X-ray defined pneumonia, acute sinusitis, meningitis, sepsis, bronchiectasis confirmed by CT, histologicailly defined chronic lymphatic hyperplasia, chronic diarrhoea, splenomegaly confirmed by ultrasound, autoimmunity were recorded. The diagnosis of chronic lung disease was based on clinical findings, pulmonary function tests and chest thin-section CT examinations. The diagnosis of chronic sinusitis was based on clinical findings and confirmed with the CT scan of sinonasal cavities, performed in a period free of

acute symptoms [15]. The diagnosis of pneumonia was made according to guidelines from The Infectious Disease Society of America [16].

Statistical Analysis Parametric and non-parametric data is presented as mean±SD or range, as indicated. For comparison of clinical and biomarker changes between groups, the Student *T* test and Mann–Whitney test were used for parametric or non-parametric datasets. Multiple proportional hazards analysis was performed to determine independent predictors of any clinical condition studied, after selecting relevant significant variables by univariate analysis. Analyses were performed separately for each outcome. The risk for each clinical condition was calculated by Cox proportional hazards models with the given clinical condition as the dichotomous outcome. The time-to-event variable was the time from enrolment in the prospective study to the first episode of that clinical condition. Subjects who did not develop that condition were censored at the time of their last follow-up or death. Because of the many clinical and immunological variables we considered in the univariate analyses (Supplemental Table I), some of which were highly correlated; we evaluated each of these variables as a potential confounder. In the final multivariable models, we included those factors known to be of clinical importance or that seemed to confound the relationship between risk factors and the outcome variable. To detect a possible level of protection of different Ig isotypes we used a receiver operating characteristic (ROC) curve, that is a graphical plot of the sensitivity vs. (1−specificity) for a binary classifier system as its discrimination threshold is varied. We used SAS, JMP8 version (SAS Institute, Cary, North Carolina), for all statistical analyses. Results were expressed as hazard ratios (HR) with 95% CIs and *p* values. A *p* value of <0.05 was taken as the threshold of statistical significance.

Results

Patients Characteristics

The prospective study included 201 CVIDs (97 females, 104 males) and 101 XLA patients. CVIDs patients were followed up for a cumulative period of 778 patient-years (mean time 3.8 years follow-up per patient) and XLA for 587 patient-years (mean time 5.8 years). At diagnosis, the mean age was 28.7±18.4 years for CVIDs (range, 3–68) and 4.9±6.2 years for XLA (range, 16 days–40.9 years). At the end of the study, mean age was 40.5±18.9 years for CVIDs and 21±5 years for XLA.

At diagnosis immunoglobulins levels (Supplemental Tables II and III) were: IgG 252.1±133.2 mg/dL (CVIDs) and 139.6±103 mg/dL (XLA); IgA 18.6±24.3 mg/dL (CVIDs) and 7±6.1 mg/dL (XLA); IgM 32.6±47.4 mg/dL (CVIDs) and 13.8±12.9 mg/dL (XLA). In CVIDs, IgG, IgA, IgM levels did not differ between females and males.

The delta IgG (mean IgG trough levels at the end of the study period minus the IgG level at diagnosis) was 415.2± 197.8 mg/dL in patients with CVID and 577.9±208.7 mg/dL in patients with XLA (Supplemental Tables II and III). The trough IgG levels at the time of the study were slightly correlated with the Ig replacement dose in XLA patients without chronic diarrhoea ($r=0.12$; $p=0.047$), and in CVID patients without chronic diarrhoea and without chronic lymphatic hyperplasia ($r=0.22$; $p<0.0001$; data not shown).

Is There a Direct Relationship Between Ig Level and Reduced Infections?

Overall, 79% of the patients with CVIDs and 76% of patients with XLA had major infectious complications (at least one episode of pneumonia and/or acute sinusitis or had a condition of chronic lung disease with bronchiectasis). As shown in Table I, CVIDs patients who experienced infections had lower IgA (17±26 mg/dL) and IgM (34± 77 mg/dL) serum levels than patients who did not have infections (IgA: 34±36 mg/dL; IgM: 42±43 mg/dL) ($p<0.001$). IgG trough levels and the monthly mean IgG dose administered were stable over time in most of our patients. However, in some of them, in particular those with enteropathy (manuscript in preparation), increasing the Ig dosage did not result in an adequate increase in IgG trough levels. In other patients raising the IgG trough level did not prevent episodes of pneumonia. The monthly mean Ig dose administered was lower in CVIDs patients without infections (350±116 mg/kg/month) in comparison to patients who had infections (398±167 mg/kg/month). XLA patients without or with infections received higher doses than CVID patients (594±176 and 608±273 mg/kg/month, respectively; Table I).

Acute Infections

Pneumonia A significant reduction in the prevalence of pneumonia, the main XLA- and CVIDs-associated acute infection [17–21], has been observed after initiation of immunoglobulin replacement therapy in XLA (from 38.5% to 25.7%, $p=0.037$) and CVIDs patients (from 39.4% to 22.3%, $p<0.0001$). During the prospective study the incidence of pneumonia remained relatively constant both in XLA (range 0.03–0.11 episodes/patient/year) and in CVIDs (range 0.06–0.10 episodes patient-year). It has been previously suggested that the total number of infectious

Table I Mean IgG, IgA, IgM (±SD) (mg/dL) serum levels and mean (±SD) monthly IgG dosage administered (milligrams per kilogram per month) in "infectious" and "non infectious" CVID and XLA patients and in patients with none, one or more than one episode of pneumonia during the 5 years of the prospective study

	"Non infectious"	"Infectious"	No pneumonia	1 episode of pneumonia	>1 episodes of pneumonia
CVID					
Number of patients	42	159	160	25	16
IgG	622±179	667±176	652±159	725±211	594±226*
IgA	34±36	17±26*	23±31	14±24*	6±8*
IgM	42±43	34±77*	34±61	48±120	23±35*
Monthly Ig replacement dose	350±116	398±167	375±156	463±193	415±88
XLA					
Number of patients	24	77	76	13	12
IgG	768±140	758±202	749±167	747±158	753±172
IgA	6±6	5.6±9	6±9	3±2	4±6
IgM	8±7	6.2±7	6±6	6±5	4±5
Monthly Ig replacement dose	594±176	608±273	589±190	550±110	712±278

* $p<0.0001$

episodes per patient is lower in patients who receive high-dose immunoglobulin replacement therapy [4, 5, 7, 9, 10]. Overall, in the 5 years of observation, episodes of pneumonia developed in 41/201 CVIDs patients and in 25/101 XLA patients (Fig. 1). Patients with pneumonia did not have significant lower IgG trough levels than patients without pneumonia. When patients were grouped into IgG trough level intervals, only the group with persistently IgG trough<400 mg/dL had an increased risk to have pneumonia (HR 5.1; $p<0.0009$; Table II). In CVID, lower IgG levels at diagnosis (<250 vs >250 mg/dL; HR, 1.2; $p=0.04$) and higher delta IgG (a difference >430 mg/dL between the IgG trough level at the end of the study period and the IgG level at diagnosis; HR, 1.5; $p=0.006$) were significantly associated with the subsequent occurrence of pneumonia (IgG at diagnosis: 209.9±123.5 mg/dL, pneumonia group; 263.4±133.8 mg/dL, no pneumonia group; and delta IgG: 493.7±220.4 mg/dL, pneumonia group; 394.1±186.6 mg/dL, no pneumonia group).

CVIDs patients with more than one episode of pneumonia (16/41) during the 5 years of observation had lower mean values of IgA (6±8 mg/dL), and IgM (23±35 mg/dL) in comparison with patients who had only one episode (IgA 14±24, and IgM 48±120 mg/dL; $p<000.1$) and with patients without pneumonia (IgA 23±31, and IgM 34±61 mg/dL; $p<0.0001$; Table I).

Since pre-existing co-morbidity factors may obscure the effects of Ig replacement therapy, we performed a multivariate analysis. The major co-morbidity risk factor identified for pneumonia was the presence of bronchiectasis (HR, 3; $p=0.007$ for CVIDs; HR, 3.52; $p=0.004$ for XLA; Table II).

Within the CVIDs cohort (Table II), a significant increase in the risk of pneumonia (HR, 5.1; $p=0.0009$) was found only in those patients who did not reach an IgG trough level>400 mg/dL. Using ROC curves we did not identify a statistically valid cut-off value of IgG, when we only analysed data collected during the prospective study where IgG levels were higher. When data collected at diagnosis before Ig replacement were included in the analysis, a pneumonia cutoff value of 408 mg/dL was found, albeit with a low sensitivity (62%) and a low specificity (75%). This also showed that even so, not everyone gets pneumonia and other risk factors such as bronchiectasis and low IgA played a major role. Within the XLA cohort, episodes of pneumonia occurred in patients over a wide range of IgG trough levels (Fig. 1), with a slight increase in the hazard risk for patients who did not reach an IgG trough levels>500 mg/dL ($p=0.049$; Table II). It has been recently suggested that IgG levels should be kept at high levels [10] in order to prevent pneumonia. However, in our XLA cohort, only 1 episode of pneumonia was observed when IgG trough levels were kept higher than 1,000 mg/dL. This might suggest that very high IgG trough levels might be protective, even if we couldn't statistically confirm this hypothesis due to the low number of observations that falls into this trough IgG interval.

In CVID patients, serum IgA levels were lower in patients who had pneumonia (11.3±18.6 mg/dL) than in patients who never developed pneumonia (24.1±31.8 mg/dL) ($p=0.02$; Fig. 2). Using ROC analysis, the statistically chosen cut-off value for IgA levels was 7 mg/dL, with a sensitivity of 84% and a specificity of 48%. In patients with IgA lower than 7 mg/dL there was an increase risk of pneumonia (HR, 2.6; $p=0.03$), independently of other risk factors.
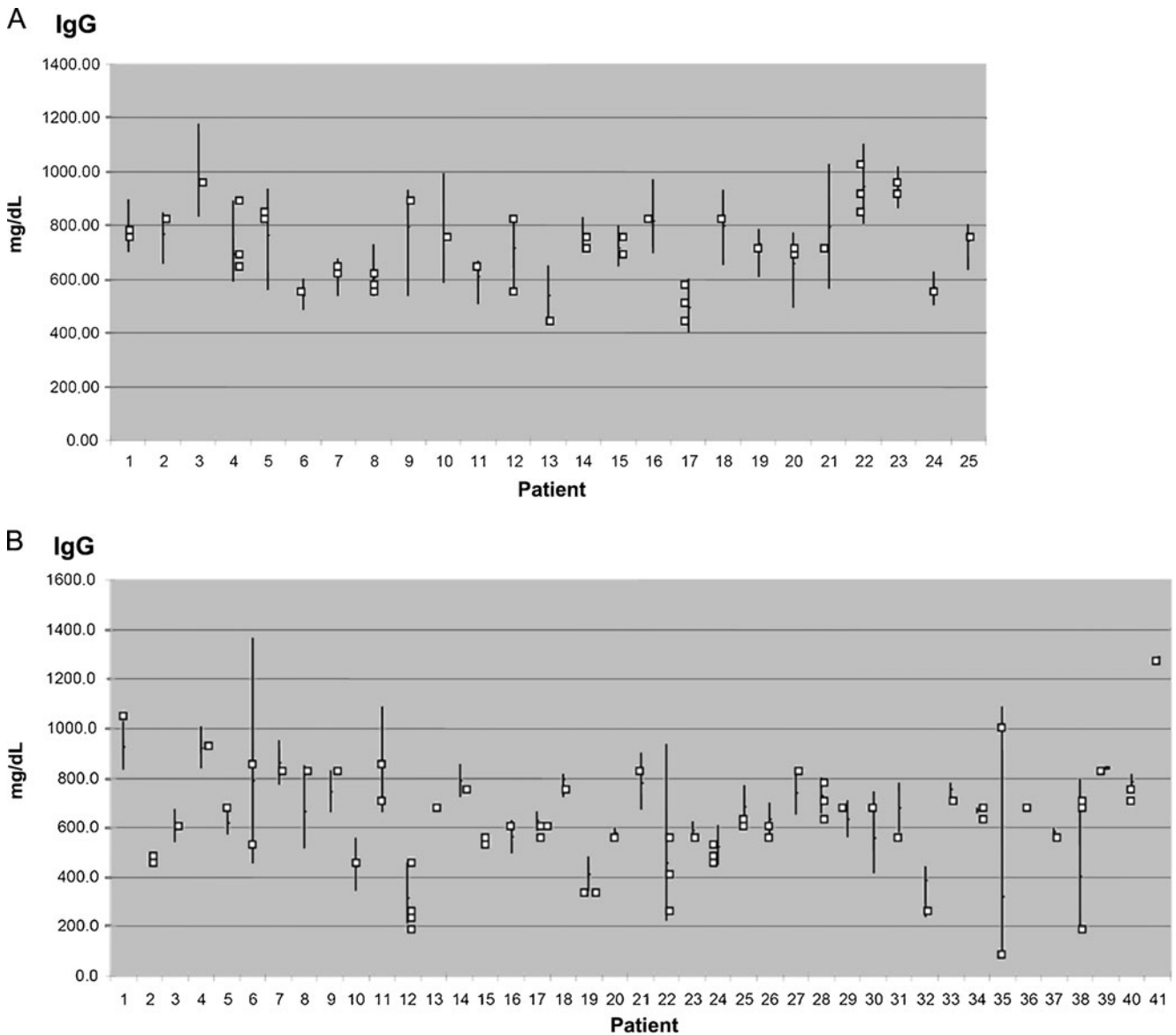
Fig. 1 IgG level (milligrams per deciliter, mg/dL; *white squares*) at the time of each distinct episode of pneumonia in the 25 XLA patients (*panel A*) and in 41 CVIDs patients (*panel B*) who had pneumonias during the prospective study. *Black lines* indicate the range with geometric means of IgG trough level (milligrams per deciliter) of each patient during the study time

Acute Sinusitis Data on acute sinusitis were only available for CVIDs patients. As expected, the multivariate analysis identified as risk factors for acute sinusitis only chronic sinusitis (HR 11.4, $p<0.0001$) and bronchiectasis (HR 1.6, $p=0.02$).

Invasive Bacterial Infections A drastic reduction in the incidence of invasive infections, bacterial sepsis and meningitis, has been observed after initiation of replacement therapy in both XLA from 6% to 2.4% (0.003 episodes patient-year) and CVIDs patients from 16.6% to 2.5% (0.0007 episodes patient-year).

Chronic Conditions

Bronchiectasis Over a 5-year observation period, bronchiectasis prevalence increased from 47.3% at the time of enrolment to 53.7% at the last year of follow-up in CVIDs patients and from 33% to 39% in XLA patients. No significant difference was observed in the mean IgG trough levels between patients who developed (648±171 mg/dL) or did not develop (650±147 mg/dL) bronchiectasis.

In CVIDs, by univariate analysis IgA and IgM levels, age, age of disease onset, pneumonia, acute and chronic

Table II Risk factors and hazard risks (HR) for CVIDs and XLA associated co-morbidities identified by multiple regression analysis

Clinical condition	Risk factor	HR	p
CVIDs			
Pneumonia	Basal IgG, <250 vs >250 mg/dL	1.2	0.04
	Delta IgG, >430 vs <430 mg/dL	1.5	0.006
	IgG trough, <400 mg/dL vs >400 mg/dL	5.1	0.0009
	IgA,<7 mg/dL vs >7 mg/dL	2.6	0.03
	Bronchiectasis	3	0.007
Acute sinusitis	Chronic sinusitis	11.4	<0.0001
	Bronchiectasis	1.6	0.02
Bronchiectasis	IgA,<7 mg/dL vs >7 mg/dL	2.4	0.04
	Age	1.5[a]	0.0007
Chronic sinusitis	IgA,<7 mg/dL vs >7 mg/dL	3.7	0.02
	Acute sinusitis	11.5	<0.0001
	Age	1.2[a]	0.01
Splenomegaly	IgA,<7 mg/dL vs >7 mg/dL	2.2	0.02
	Bronchiectasis	2.6	0.0003
XLA			
Pneumonia	Chronic lung disease	3.5	0.004
	IgG trough, <500 mg/dL vs >500 mg/dL	1.1	0.049
Bronchiectasis	Pneumonia	22.2	<0.0001
Chronic sinusitis	Bronchiectasis	3.8	0.005

Multiple proportional hazards analysis was performed to determine independent predictors of any clinical condition studied, after selecting relevant significant variables by univariate analysis

In the final multivariable models, those factors known to be of clinical importance or that seemed to confound the relationship between risk factors and the outcome variable were evaluated

[a] 10-years intervals)

sinusitis, splenomegaly showed an association with bronchiectasis. By multiple regression (Table II) only age (HR for 10-year intervals, 1.5; p=0.0007), and IgA serum levels <7 mg/dL (HR 2.4, p=0.04) were independently associated with bronchiectasis. In XLA, the finding of bronchiectasis was associated with chronic sinusitis, pneumonia, age and length of disease time by univariate analysis. By multiple regression (Table II), the only independent risk factor for the subsequent development of bronchiectasis was pneumonia (HR 22.2, p<0.0001). The presence of bronchiectasis was higher in patients older than 5 years at the time of diagnosis (p=0.001; high diagnosis delay) and in patients with an associated condition of chronic sinusitis (HR, 3.84; p=0.05). Differently from our previous observations [12, 19], the

length of time of disease was not a risk factor for bronchiectasis.

Splenomegaly In CVIDs, a spleen enlargement is a common finding in patients with granulomatous disease and/or chronic lymphatic hyperplasia [22]. However, its prevalence is much higher than that related to these CVIDs-associated conditions [17, 19]. In our CVIDs cohort, the prevalence of patients with splenomegaly (longitudinal diameter >12 cm, identified by ultrasound) increased during the observation period from 31% to 42.3%. Low IgA and IgM levels, age, age at onset, bronchiectasis, acute and chronic sinusitis, pneumonia, chronic lymphatic hyperplasia and autoimmunity were found to be associated with splenomegaly by univariate analysis. By multiple regres-

Fig. 2 Mean IgA levels (mg/dl) ± SD in CVID patients with or without pneumonias (*panel A*). IgA levels (mg/dl) in CVID patients with (*black*) or without pneumonias (*grey*). Patients are grouped in percentile intervals according to their IgG trough level. Each dot represents a single year of follow-up (*panel B*)
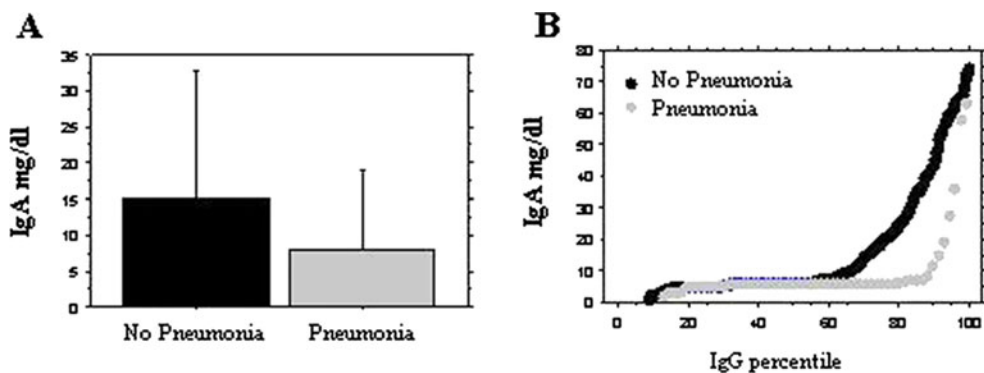
sion bronchiectasis (HR 2.6, $p=0.0003$) and low IgA levels ($p=0.004$) were independent risk factors for splenomegaly (Table II). By ROC analysis, the statistically chosen cut-off value for IgA levels was 7 mg/dl, (sensitivity 70.2%; specificity 61.1%). Patients with IgA<7 mg/dL had an increased risk of splenomegaly (HR 2.2, $p=0.02$).

Chronic Sinusitis In the CVIDs cohort, the prevalence of patients with chronic sinusitis, increased over time from 45.3% at enrolment to 52.2% in CVID and from 50% to 51% in XLA. In CVIDs, its occurrence was associated with IgA serum level of <7 mg/dL (HR 3.7, $p=0.02$), and with acute sinusitis (HR 11.5, $p<0.0001$; Table II). In XLA, chronic sinusitis was highly associated with bronchiectasis (HR, 3.8; $p=0.005$).

Discussion

The events that define the pathogenesis of an infection depend on a large range of variables related to specific infecting organisms and to the overall immunological state of the host. In primary antibody deficiencies, where the defect is the inability to produce an effective antibody response to pathogens, only IgG antibodies might be replaced by intravenous or subcutaneous administration. Evidence of immunoglobulin replacement efficacy has been demonstrated in small trials comparing high- and low-dose immunoglobulin doses and from several observational studies [1–8, 15, 17–19, 23]. Recently, a study by Chapel et al. [9] and a meta-analysis [10] on the impact of trough IgG on pneumonia incidence provided evidence that pneumonia risk can be progressively reduced by higher trough IgG levels up to a "biologic" level [11]. Replacement doses greater than 600 mg/kg/month and trough levels >1,000 mg/dL have been suggested. In this context, what do we learn from this "real life" observation of patients treated with lower doses, a common practice in many immunological centres?

Clinical phenotypes of CVIDs and XLA, the most common symptomatic primary antibody deficiencies requiring a long-life Ig substitution, are quite variable even within one disease or syndrome. Therefore, the suggested protective trough IgG level of 1,000 mg/dl might not be considered a general goal and only large prospective multi-centre studies might help to identify subgroups of patients at high infection risk. This prospective study identified prognostic markers and risk factors for associated clinical co-morbidities in a large cohort of patients with primary antibody deficiencies over a long cumulative follow-up period. After starting on replacement therapy a reduction in the incidence of severe acute infections was observed. Thereafter, this incidence remained low and constant over time. The trough IgG levels measured at the time of each episode of pneumonia were extremely variable

and were not lower in those patients who experienced one or more pneumonia episodes. In XLA, the only co-morbidity risk factor identified for pneumonia was the presence of bronchiectasis and bronchiectasis was the major risk factor for pneumonia. This means that in order to modify the XLA clinical course our efforts should be directed to the prevention of pneumonia. The same observation was only partially true for CVIDs in which bronchiectasis was the major risk factor for pneumonia, while age and low IgA levels but not pneumonia was the major risk factors for bronchiectasis. Moreover, our data allowed identifying a clinical phenotype characterised by a high pneumonia risk: patients who had low IgG and IgA levels at diagnosis; patients who had IgA level<7 mg/dL and who had bronchiectasis.

International guidelines on immunoglobulin replacement suggest a similar monthly IgG dose to be administered in XLA and CVIDs [1]. In our study, the mean IgG dose administered to XLA patients was higher than that administered to CVIDs. This choice might reflect a greater apprehension of physicians regarding the risk of severe infections in XLA. A similar variability was recently found by the Chapel's group [9]. In both XLA and CVIDs, we could not identify a unique IgG trough level and an optimal IgG replacement dose to prevent pneumonia, because of the major role played by the progression of lung disease as risk factor. However, when data from the prospective study were cumulated with retrospective data we found that in CVIDs, the hazard risk for pneumonia increased in those patients who did not reach an IgG trough level>400 mg/dL. This figure was not evident in the recent paper from Chapel et al. [9] as they did not have any IgG trough levels that were this low. This data does not indicate that the protective trough IgG level is 400 mg/dL, but it remarks a higher risk to develop pneumonia at low IgG levels. Our results prompted us to support the still controversial recommendation to start Ig replacement treatment, even before the development of a severe infection, when IgG are that low.

Low IgG and IgA at diagnosis and very low IgA level at the prospective study, reflecting a severe impaired isotype switching process, were major independent risk factors for lung complications, confirming that loss of function of memory B cells represents a major cause of CVIDs-infectious-associated clinical conditions, as demonstrated in CVIDs with bronchiestasis [24–26]. A classification of CVIDs based on memory B cell frequency has been proposed, but how this biomarker relates to CVIDs clinical phenotypes remains uncertain [27, 28]. While infections are the main cause of morbidity in all XLA patients, the same might not be true for all CVIDs. In fact, non infectious complications (autoimmunity, lymphocityc hyperplasia and enteropathy) are unique clinical phenotypes in subgroup of CVIDs patients who

might not develop infections and might have an unclear benefit from Ig replacement [13]. The effect of therapy with immunoglobulins at replacement dosage for non-infectious co-morbidities (autoimmunity, lymphocytic hyperplasia and enteropathy) remains to be established.

We conclude that a unique general protective trough IgG level in antibody deficiency patients will remain undefined because of the major role played by the progression of lung disease. Aside from Ig replacement, which greatly contributed to the reduction of invasive infections, a strategy to reduce lung damage should be approached. Our still ongoing study represents call for further prospective evaluations that should analyse the effectiveness of Ig replacement on the different clinical and immunological forms of antibody deficiencies.

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