

Original article

Intravenous immunoglobulin replacement prevents severe and lower respiratory tract infections, but not upper respiratory tract and non-respiratory infections in common variable immune deficiency

Background: Although the dose of 400 mg/kg body weight intravenous immunoglobulins (IVIG) every 3–4 weeks is now standard for treating patients with common variable immune deficiency, studies demonstrating its long-term benefits over low 200 mg/kg dose and its effects on infectious subsets (upper vs lower respiratory vs non-respiratory infections) are rare.

Methods: All patients from a single center with the diagnosis of common variable immune deficiency and whose clinical chart was available during three successive therapeutic periods [a pre-IVIG replacement period, a low-dose (200 mg/kg every 3 weeks) and a standard-dose replacement period (400 mg/kg every 3 weeks)] were screened retrospectively.

Results: Seven patients followed up for a total of 116 patient-years over the three defined periods of observation were recruited. When compared with low-dose therapy, standard-dose intravenous immunoglobulin therapy raised trough IgG levels from 4.3 to 6.5 g/l and significantly decreased the overall frequency of infections, with marked effects on lower respiratory tract and severe infection number. In contrast, non-respiratory and upper respiratory infections were, in comparison, resistant to therapy.

Conclusions: Overall, these data support the use of standard-dose 400 mg/kg intravenous immunoglobulin therapy, despite the high cost, to raise trough IgG levels to 5–7 g/l, but underlines that some categories of infectious events (non-respiratory, upper respiratory) may need parallel surgical or pharmacological approaches to be optimally prevented or treated.

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Common variable immune deficiency (CVID) is a heterogeneous, idiopathic immune deficiency characterized by an inability of the immune system to mount an efficient antibody response to infectious pathogens (1). Various defects of antigen presenting cells (2), B (3) or T cells have been described, from quantitative deficits to deficient production of cytokines by CD4⁺ or CD8⁺ T cells (4), defects in T-cell signaling and proliferation (5), and defaults in T/B cognate interactions (6, 7). In this respect, a subset of patients with CVID was found unable to express the 'inducible costimulator' ICOS on their activated T cells, because of a homozygous deletion in the ICOS gene, with subsequent reduction in the number of naive, switched and memory B cells (8). However, no common genetic or molecular deficits have yet been identified to explain this immune deficiency syndrome. Immune defects become generally manifest in the second decade or later by a decrease in total serum levels of IgG

and IgG subclasses, IgA and less frequently of IgM, and variable decrease in CD3⁺ or CD19⁺ lymphocyte number. Clinical expression is characterized by recurrent infections of the respiratory tract by mainly encapsulated bacteria, less frequently by opportunistic pathogens, either of the upper airways (sinusitis, otitis media, pharyngitis) or of the lower airways (pneumonia, bronchitis), as well as of the gastrointestinal tract, urinary tract or central nervous system when untreated (9). Chronic infections of lower airways may lead to bronchiectasis and severe limitations of respiratory functions (10).

Treatment is mainly based on replacement with intravenous immunoglobulins (IVIG), after a period of intramuscular injections of immunoglobulins, which proved painful and of limited efficacy (11). Although long-term follow-up analyses are rare, but strongly desirable with regard to the cost of the therapy, the

currently recommended IVIG dosage is 400 mg/kg every 3–4 weeks contrary to earlier recommendations of 200 mg/kg (12). The aim of this retrospective study was to demonstrate on a large period of observation in a single center that recurrent infections and, in particular, severe infections and lower respiratory tract infections were better controlled by standard-dose (SD) (400 mg/kg) than by low-dose (LD) (200 mg/kg) IVIG. This was in contrast to upper respiratory tract and non-respiratory infections which were non-significantly limited by IVIG therapy.

Patients and methods

Patients

Recruited patients had to fulfill the following criteria: (i) a diagnosis and history of CVID, (ii) a follow-up history over three phases, including a historical pre-IVIG replacement period (of at least 1 year), a low-dose IVIG (200 mg/kg every 3 weeks) and a standard-dose IVIG (400 mg/kg every 3 weeks) replacement period (of at least 1 year each). According to these criteria, seven patients from Lausanne outpatient clinic were enrolled into the study. Study protocol was reviewed by the Ethical Review Board of the Faculty of Medicine, Lausanne, Switzerland. Diagnosis of CVID was based on the presence of a history of recurrent bacterial infections of (mainly) the respiratory tract (>5 /year), decreased serum immunoglobulin levels (serum IgG < 5.0 g/l, IgA < 0.5 g/l), variable T-cell proliferative defects in the presence of antigens or mitogens, and absent or insufficient specific antibody response to recall vaccination (13). Other causes of secondary hypogammaglobulinemia such as non-Hodgkin's lymphoma, myeloma, nephrotic syndrome, exsudative gastroenteropathy, chronic immunosuppression, or catabolic states caused by malnutrition were excluded. Patients clinical and immunological data were retrospectively collected over three distinct periods: (i) IVIG pre-replacement period, (ii) IVIG 200 mg/kg replacement period and (iii) IVIG 400 mg/kg replacement period.

Immunological markers

Serum immunoglobulins were analyzed by nephelometry (Dade Behring, Marburg, Germany), lymphocytes subsets by cytofluorimetry using an Epics Coulter cytofluorimeter (Epics Profile II, Coulter, Miami, FL, USA).

Infections

All infections reported in patients' records were collected during the pre-replacement and the two-dosage replacement periods. The diagnosis of infections was based on clinical history and physical examinations, on microbiological documentation and, when available, on radiographic evidences. Lung infections including pneumonias, bronchopneumonias, bronchitis, abscesses and super-infected bronchiectasis were defined as lower respiratory tract infections, and infections of the ear–nose–throat sphere as upper respiratory tract infections (mainly sinusitis, otitis, pharyngitis). They were reported as severe when resulting in hospital admission: septicemia, meningitis, pyelonephritis, cellulitis or pneumonia, as well as sinusitis or otitis when both surgical drainage and antibiotic therapy were required to cure the infection. Antibiotic therapy was

administered whenever judged necessary according to microbial recommendations and good clinical practice. Chest physiotherapy was prescribed systematically in patients with evidence of infectious exacerbations on a background of bronchiectasis.

Treatment

According to inclusion criteria, after a period without IVIG replacement (pre-replacement period, including intramuscular immunoglobulin injections in two patients), all seven patients were initially treated with IVIG (Sandoglobulin, Novartis, Switzerland) at the dose of 200 mg/kg [low-dose (LD)], then 400 mg/kg [standard-dose (SD)] from 1994, in each case every 3 weeks. Because they developed various manifestations of intolerance such as flush, fever or chills during IVIG infusion, three patients were substituted during this third period with Endobulin, Immuno, Austria at the same dosage. When necessary, patients received additional replacements, including intravenous iron, vitamins A, D, E, K or calcium.

Statistical analysis

Data were analyzed by non-parametric ANOVA tests using an Instat 3.0 software, with $P < 0.05$ as limit of significance.

Results

Seven patients (five females, two males) were followed for a period of 14 ± 6.1 years (mean $\pm$ SD, range 6–23 years), representing overall 115.6 cumulative years of observation [pre-replacement period 41.3 years (per patient mean $\pm$ SD, 5.9 ± 2.3), LD-IVIG period 37.2 cumulative years (5.3 ± 5.0 years), SD-IVIG period 37.1 years (5.3 ± 2.0)]. Mean age at diagnosis was 42.6 ± 19 years (range 24–70 years), whereas age at first occurrence of recurrent infections was 25.7 ± 20.6 years (6–67 years). This represented a mean symptomatic delay prior to diagnosis of 16.9 ± 19.8 years (range 3–59 years), further prolonged by a 5.9 ± 2.3 years of delay before initiating IVIG therapy. Serum IgG levels at diagnosis were generally decreased (mean $\pm$ SD, 3.53 g/l ± 1.12), as were all IgG subclasses (IgG₁, IgG₂, IgG₃, IgG₄), serum IgM, IgA and spontaneous anti-staphylococcal and anti-streptococcal antibodies (Table 1). CD3⁺ T cells were moderately decreased with a decrease in CD4⁺ T cells in all patients. There was no marked decrease ($> 50\%$ of the lower value of the normal range) in monocytes and natural killer (NK) cells, except in one patient for each subset. CD19⁺ B cells were markedly decreased in one patient (21 cells/mm³), moderately in three patients (116–188 cells/mm³) and normal in three patients (201–784 cells/mm³).

The number of infections per patient-year (all causes confounded) decreased from a median of 5.0 during the pre-replacement period to 2.79 (44% decrease, ratio of medians) during the LD-IVIG period ($P = 0.002$), and to 1.53 during the SD-IVIG period (45% decrease, $P = 0.02$) [overall decrease between pre-treatment and

Table 1. Immunological characteristics of patients at diagnosis*

Immune parameters	Units	Mean	SD	Range	Normal range
IgG	g/l	3.53	1.12	2.22–5.01	8.20–17.00
IgG1	g/l	2.27	0.65	1.53–3.18	4.90–11.4
IgG2	g/l	0.98	0.41	0.49–1.38	1.50–6.40
IgG3	g/l	0.14	0.05	0.07–0.20	0.20–1.10
IgG4	g/l	0.09	0.03	0.06–0.14	0.08–1.40
IgM	g/l	0.23	0.08	0.07–0.32	0.50–3.60
IgA	g/l	0.07	0.01	0.07–0.08	0.85–4.90
Anti-staphylolysin Ab	UI/ml	0.01	0.01	0.00–0.03	0.25–2.00
Anti-streptolysin Ab	UI/ml	4.29	2.81	1–7	20–250
Anti-pneumolysin Ab	UI/ml	0.36	0.17	<0.03–0.50	0.12–2.00
Total lymphocytes	(cells/mm ³)	1749	344.1	1134–2310	1925–3175
CD3 ⁺	(cells/mm ³)	1089	150.8	958–1402	1350–2350
CD4 ⁺	(cells/mm ³)	572	81.1	456–675	825–1575
CD8 ⁺	(cells/mm ³)	502	126.1	333–692	475–1025
CD14 ⁺	(cells/mm ³)	344	97.2	158–454	340–480
CD16 ⁺	(cells/mm ³)	188	73.8	85–329	132–455
CD19 ⁺	(cells/mm ³)	253	247.2	21–784	200–400

*Diagnosis date was defined as the earliest time-point of the pre-replacement period. This explains differences in mean IgG levels at diagnosis and median IgG trough values during the pre-replacement period (cf. Fig. 1).

SD-IVIG: 69% ($P = 0.0006$)] (Fig. 1A). This was mainly because of a significant limitation in respiratory tract infections under therapy from a median of 4.4–1.87 during the LD-IVIG (58% decrease, $P = 0.0023$) and to 0.83 during the SD-IVIG (55% decrease, $P = 0.0012$) periods [overall decrease: 81% ($P = 0.0006$)] (Fig. 1B). Whereas most frequently reported recurrent infections regarded the respiratory tract (95% of all infections) during the pre-IVIG replacement period (52% lower respiratory tract *vs* 48% upper respiratory tract infections), this proportion regressed progressively to 74% (48% lower respiratory tract *vs* 52% upper respiratory tract infections) during the LD-IVIG replacement period, to reach 55% of all infections (29% lower respiratory *vs* 71% upper respiratory tract infections) during the SD-IVIG replacement period. This corresponded paradoxically to a relative resistance of upper respiratory tract and non-respiratory infections, in contrast to lower respiratory tract infections ($P < 0.01$). Indeed, upper respiratory tract infections per patient-year decreased from a median of 1.56 during the pre-IVIG replacement period to 0.53 during the LD-IVIG. There was no further improvement under SD-IVIG (median 0.40) (pre-IVIG *vs* LD-IVIG *vs* SD-IVIG, $P = 0.2$). Similarly, non-respiratory tract infections were of low frequency (absolute number per period: pre-IVIG $n = 16$, LD-IVIG $n = 24$, SD-IVIG $n = 23$), but were left unaffected from a median of 0.56 infections per patient-year during the pre-replacement period to 0.61 during the LD-IVIG period and to 0.48 during the SD-IVIG period ($P = 0.6$) (Table 2). These non-respiratory infections included gastrointestinal tract infections (total number over the three periods: $n = 14$) (fistulas, abscesses, diverticulitis, duodenitis, appendicitis), urinary tract infections ($n = 15$) (pyelonephritis, lower urinary tract infections), non-IVIG replacement

related viral hepatitis B and C ($n = 2$), conjunctivitis ($n = 10$), genital tract infections ($n = 15$) (epididymitis, prostatitis, vaginitis, cervicitis, vulvitis, annexitis), infectious arthritis ($n = 2$) and skin infections ($n = 5$) (cellulitis, abscesses). Interestingly, although IVIG replacement with 200 mg/kg tended to decrease the frequency of severe infections when compared with the pre-IVIG replacement period from 2.67 to 1.6 (Fig. 1C), this difference was not significant (40% decrease, $P = 0.2$). In contrast, SD-IVIG therapy efficiently controlled severe infections by reducing them further to 0.17 per patient-year (90% decrease, $P = 0.03$), corresponding to an overall limitation of 94% in comparison with pre-replacement period ($P = 0.002$).

As patients were initially not substituted for a per patient mean period of 5.9 ± 2.3 years (mean $\pm$ SD) after diagnosis, a further decrease in trough IgG levels during the pre-replacement period was observed from 3.53 g/l (mean level at diagnosis) to 1.13 g/l (median trough levels; mean 1.10 g/l) (Fig. 1D). As expected, IgG trough levels significantly increased during both LD- and SD-IVIG periods to reach median values of 4.28 g/l ($P = 0.0012$) and 6.48 g/l, respectively ($P = 0.008$). Biochemical (serum calcium, potassium, albumin) and hematological (hemoglobin, WBC) markers were not influenced by the increase in IVIG dose, as well as secondary events, which were dependent on the brand of immunoglobulin preparation and not on their dosage (data not shown).

Discussion

Though the number of patients followed in this study was small, the long-term clinical follow-up of 116 patient-

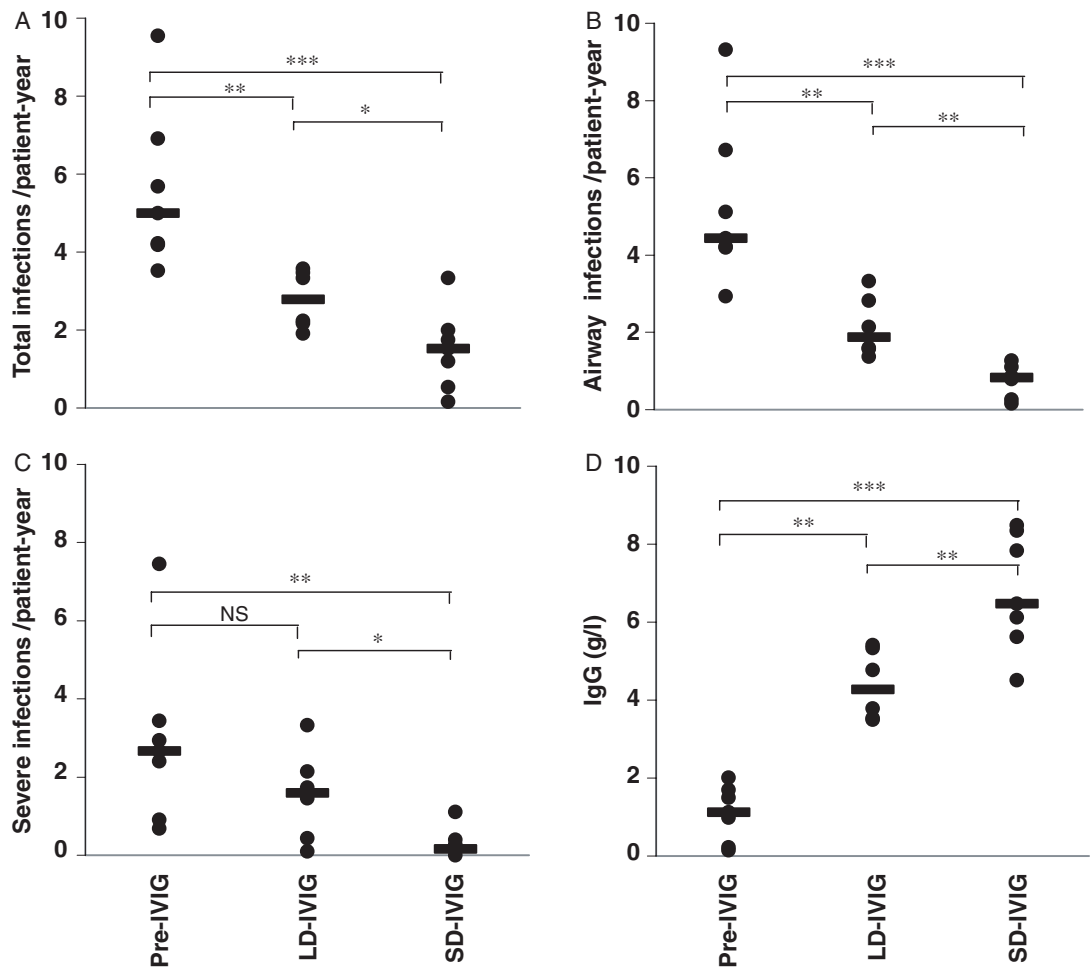


Figure 1. Standard-dose IVIG therapy decreases the number of infections in patients with CVID. Patients ($n = 7$) with CVID were followed before intravenous therapy with immunoglobulin (pre-replacement, pre-IVIG), during low-dose therapy (LD-IVIG, 200 mg/kg every 3 weeks) and during standard-dose therapy (SD-IVIG, 400 mg/kg every 3 weeks). (A) Total number of infections (all causes confounded); (B) upper and lower airway infections; (C) severe infections. Data are expressed in panel (A–C) as mean number of infections per patient-year for each patient (dots) during the considered period. (D) IgG trough levels in serum. Data are expressed in panel D as mean IgG trough levels during the three periods of observation. Thick bars: medians of individual data. NS, non-significant; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Table 2. Non-respiratory tract infections*

	Total	Gastrointestinal tract	Urinary tract	Viral hepatitis	Conjunctivitis	Genital tract	Arthritis	Skin
Pre-IVIG	16	4	5	0	2	4	0	1
LD	24	5	5	0	3	8	1	2
SD	23	5	5	2	5	3	1	2
Total	63	14	15	2	10	15	2	5

*Expressed as absolute number of episodes per period of treatment. Pre-IVIG: pre-IVIG replacement period; LD: 200 mg/kg, SD: 400 mg/kg IVIG replacement periods.

years over three periods (pre-replacement, LD- and SD-IVIG replacement) compensates this relative weakness to allow the clear conclusion that treatment with SD-IVIG leads to a significantly better control of total

infections, but more importantly of respiratory and severe recurrent infections in patients with CVID. We point out also that time to diagnosis is still excessively long in patients with humoral immune deficiency, as shown by others previously (9). This is highly regretful, as established structural defects are by no means reversible by IVIG therapy, which explains that early diagnosis and initiation of therapy were the strongest predictors of chronic pulmonary disease (10). The increase in IVIG dosage (and correspondingly in trough IgG levels) had a particularly powerful limiting effect on the risk of respiratory tract infections of all range of severity, what partially explains its effect on severe infections, in majority from the respiratory tract (93%). However, severe infections of urinary or gastrointestinal origin as well as the occurrence of sepsis were drastically reduced in

parallel. This contrasted with the relative resistance of non-respiratory infections (from gastrointestinal, genital, urinary, cutaneous or ocular origins), the frequency of which was unaffected by SD-IVIG. Similarly, although lower respiratory tract infections were further limited by SD-IVIG, upper respiratory tract infections represented the majority of respiratory infections (71%) during the third observation period and were not further limited by IVIG increase to standard dose. This relative resistance may indicate interference with local factors impinging on humoral defenses, such as various anatomical constraints, remodeling or impaired drainage. In terms of therapeutic management, this indicates that clinicians should not solely rely on IVIG substitution in preventing or treating non-respiratory or upper respiratory infections in patients with CVID, but that active prophylactic or other therapeutic approaches (surgical or pharmacological) may need to be taken in resistant cases.

There is an overall consensus that standard-dose IVIG (≥ 400 mg/kg/month) is superior to lower dosages. However, dose comparison studies in patients with humoral immunodeficiency provided variable results, in part related to short-term observation periods. From the study by Roifman et al. (14) maintenance of trough levels of at least 5 g/l was generally recommended as an arbitrary limit of efficacy in preventing recurrent infections. Although in this latter study the incidence of infections did not differ greatly in the high- vs low-dose treatment phases (600 mg/kg/month vs 200 mg/kg/month), the frequency of acute infections was indeed reduced when serum IgG was 5 g/l or more. Pulmonary function worsened on the low-dose regimen and improved on the standard-dose regimen. Comparing patients with 100 vs 400 mg/kg/month, Ochs et al. (15) did not demonstrate benefits of the standard-dose treatment on the number of infections, antibiotic use or number of days of absence from work or school. In a double-blind, crossover study of 6-month follow-up, Pruzanski et al. (16) compared three dosages of IVIG: 200, 400 and 600 mg/kg/month. No differences in the severity of infections, in the morbidity scores (infection/infusion) and in the duration of infection-free intervals were apparent, even with the highest dosage. In a retrospective study in children followed up from 1965 to 1990, Liese et al. (17), in contrast, demonstrated that high-dose IVIG (400 mg/kg every 3 weeks) significantly enhanced trough IgG levels, decreased the number of pneumonias and days spent in hospital compared with patients receiving 200 mg/kg IVIG or intramuscular immunoglobulins (< 100 mg/kg every 3 weeks). Severe

clinical conditions (bacterial meningitis, chronic pulmonary disease and bronchiectasis) occurred in the intramuscular group, but not in either of the IVIG groups. These data (in a pediatric cohort) are consistent with results we obtained, and that furthermore clearly demonstrate improved protection of standard-dose IVIG (400 mg/kg every 3 weeks) not only on the overall risk of infections, but more specifically on lower respiratory tract infections and on severe infections in comparison with low-dose IVIG (200 mg/kg every 3 weeks). These data also strengthen the observation that increasing the trough IgG levels above 5 g/l, from median trough level of 4.3 to 6.5 g/l, had a significant protective effect. The question whether further increase in IVIG dosage from 300 to 600 mg/kg/month may improve protection has been addressed in a recent randomized prospective, double-blind, crossover study by Eijkout et al. (18). Trough IgG levels increased from 6.3 to 9.4 g/l, and the mean number of infections per patient decreased from 3.5 to 2.5 ($P = 0.004$), regardless of infection severity. There was, however, no significant further decrease in respiratory infections. Though we applied a markedly different methodological approach, the excellent protection we obtained with median trough levels of 6.5 g/l questions the necessity to raise them as high as 9.4 g/l (18). Therapy with IVIG is indeed particularly expensive. In this regard, an improvement in the cost-benefit ratio with increasing dosages of IVIG should absolutely be demonstrated before recommending target trough IgG levels > 9 g/l. In the absence of significant effect on duration of hospital admission, on days of absence from work and on medication (antibiotic) score, Eijkout et al. (18) in their prospective study did not come to that conclusion, quite reasonably, and considered such extreme objectives to be reserved to selected cases with high infection rates. Taking into account our own results, and especially the relative resistance of upper respiratory tract and non-respiratory infections to SD-IVIG, we fully share this clinical judgment. In conclusion, our observations strongly support early diagnosis and referral of patients to specialized centers, and early initiation of therapy at optimal IVIG dosages (trough IgG target level of 5–7 g/l), to further improve humoral immune deficient patients' clinical course. Moreover, our longitudinal observation suggests that non-respiratory and upper respiratory infectious events may not be prevented as well by IVIG alone even at standard dose and may need parallel surgical or pharmacological approaches to be optimally cured.

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