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PROPHYLAXIS AGAINST INFECTIONS WITH LOW-DOSE INTRAVENOUS IMMUNOGLOBULINS (IVIG) IN CHRONIC LYMPHOCYTIC LEUKEMIA. RESULTS OF A CROSSOVER STUDY

Stefano Molica, Pellegrino Musto,° Federico Chiurazzi,# Giorgina Specchia,^ Maura Brugiatelli,@ Laura Cicoira,# Domenico Levato,* Francesco Nobile,@ Mario Carotenuto,° Vincenzo Liso,^ Bruno Rotoli#*

**Divisione di Ematologia, Azienda Ospedaliera "Pugliese-Ciaccio", Catanzaro; °Divisione di Ematologia, "Casa Sollievo della Sofferenza" IRCCS, S. Giovanni Rotondo; #Cattedra di Ematologia, II Policlinico, Università di Napoli; ^Cattedra di Ematologia, Università di Bari; @Divisione di Ematologia, Azienda ospedaliera, Reggio Calabria; Italy*

ABSTRACT

Background. **In a recently reported study, low doses of intravenous immunoglobulins (IVIG) were shown to be as effective as high doses in protecting chronic lymphocytic leukemia (CLL) patients against infections, although a control group was not included. With this background we started a crossover study of low-dose IVIG prophylaxis aimed at investigating its superiority over empirical treatment of infections.**

Materials and Methods. **Forty-two CLL patients with hypogammaglobulinemia (IgG < 600 mg/dL) and/or a history of at least one episode of severe infection in the 6 months preceding inclusion in the study were randomly allocated to receive either an infusion of 300 mg/kg IVIG every 4 weeks for 6 months or no treatment. Then they were switched to observation or IVIG for another 12 months; finally, they received IVIG or no therapy for 6 more months.**

Results. **A significantly lower incidence of infectious episodes was observed during IVIG prophylaxis in 30 patients who completed the 6-month period of either observation or IVIG therapy. The same applied to the 17 patients who completed 12 months of either observation or IVIG prophylaxis. Interestingly, the restoration of serum IgG levels obtained in 17 out of 25 patients (mean percent value of IgG increase, 41.8%) did not parallel a decrease in the number of infectious episodes.**

Conclusions. **A protective effect against infections is demonstrated for low-dose IVIG in the present study. A benefit was shown in patients who completed either 12 or 6 months of IVIG prophylaxis; however, even this low-dose treatment is not a cost effective way to prevent infection in CLL patients.**

Key words: intravenous immunoglobulins, chronic lymphocytic leukemia, infections, prophylaxis

Infection is the major cause of morbidity and mortality in B-cell chronic lymphocytic leukemia (CLL). It is generally due to bacteria and influenced by the degree of hypogammaglobulinemia;[1-3] furthermore, a defect in cell-mediated immunity appears to be a predisposing factor to infection, especially in patients treated with purine analogues.[4]

Regular intravenous immunoglobulin replacement therapy has been shown to reduce the incidence of serious bacterial infections in hypogammaglobulinemic patients with CLL.[5-7] However, immunoglobulin replacement is not recommended in every CLL patient for reasons of cost-effectiveness.[8] One way to improve the cost-effectiveness of immunoglobulin treatment is to limit its use to patients at high risk of developing life-threatening infections.[9-10] Another possibility would be to administer a lower immunoglobulin dose. A prospective random-

Correspondence: Dr. Stefano Molica, Divisione di Ematologia, Azienda Ospedaliera "Pugliese-Ciaccio", viale Pio X, 88100 Catanzaro, Italy. Tel. international +39.961.883001. Fax. international +39.961.743490.
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ized study of two intravenous immunoglobulin doses (500 mg/kg versus 250 mg/kg) every 4 weeks showed no differences in the rates of serious infections between the two treatment groups.[11]

Unfortunately, a control group of patients who did not receive IVIG therapy was not included in the Chapel *et al.* study[11] and these results, therefore, do not prove the superiority of low-dose IVIG over empirical treatment. In this context, the results of our crossover study based on low-dose IVIG replacement are timely. Interestingly, a benefit was demonstrated in patients who completed either 6 or 12 months of IVIG prophylaxis.

Materials and Methods

Forty-two B-cell CLL from 5 different hematological institutions were chosen this crossover study. Eligibility criteria included IgG levels below 600 mg/dL and/or a history of at least one serious infectious episode in the 6-month period preceding entry into the study (Table 1).[11] Prophylactic antibiotic treatment was not allowed during the study.

Patients were randomly allocated to receive an infusion of 300 mg/kg IVIG (Ig-Vena N, Sclavo, Siena, Italy) every 4 weeks for at least 6 months or no treatment. Then they were switched to observation or IVIG for another 12 months; finally, they received IVIG or no therapy for 6 more months. In this manner each patient acted as his own control and seasonal influences were reduced.

All patients gave informed consent before joining the study. Before each infusion an evaluation of infectious episodes was carried out as previously reported.[12] In brief, infections were graded as severe or trivial, with the latter including infectious episodes that did not require antibiotic therapy. Severe infections were further divided into major (usually necessitating intravenous antibiotic therapy and hospitalization, e.g. sepsis, pneumonia) and minor (requiring no intravenous antibiotic therapy or hospitalization, e.g. bronchitis, otitis, lower urinary tract infections).[11]

In 25 patients IgG determination was carried out on 2 to 5 occasions during the treatment, thus making it possible to evaluate whether IVIG replacement therapy could restore normal serum IgG levels.

Person-months of observation were calculated from the date of patient entry into the study to one of the following circumstances: patient death, patient lost to follow-up, termination of the study. The number of infections occurring during the treatment or observation period were compared by the chi-square test; an analysis was also carried out by the McNemar test for non-parametric data corrected for continuity.[13] Indeed this test is more appropriate when dealing with patient samples in which each patient is used as his own control.

Results

Clinical outcome

Patient characteristics are summarized in Table 1. As shown, there was an excess of patients in advanced clinical stage (i.e. Rai III - IV). During the study 32 patients received chemotherapy that consisted of intermittent chlorambucil (CLB) and prednisone (PDN) in 27 cases and a polychemotherapy regimen of vincristine, cyclophosphamide, low doses of adriamycin (i.e. 25 mg/m^2) and PDN in 5 cases.

Table 1. Patient characteristics.

Patient number		42
Sex (M/F)		30/12
Age (mean±SD)(yrs)		64 ± 11.5
Rai clinical stage	0	2 (4.7%)
	I - II	14 (33.3%)
	III - IV	36 (61.9%)
IgG levels (mg/dL)	< 500	16 (38%)
	≥ 500 < 650	13 (30.9%)
	> 650	13 (30.9%)
Polymorphonucleates (10^9/L)		3.5 ± 2.3
CD3 (%)		12.3 ± 8.8
Concomitant chemotherapy		32 (76.1 %)
Previous 6-mo. infection history		17 (40.4%)

Ten patients did not receive any antileukemic treatment while in the study.

There was a total of 368 patient-months during the observation phase and 376 patient-months during the IVIG therapy period. Seventeen patients concluded the full 12-month period of IVIG therapy and observation. A 6-month period of either observation or IVIG prophylaxis was completed by 30 patients. Seventeen patients did not complete the study. Two patients who experienced IVIG toxicity, represented by chills, fever and back pain, were withdrawn from the study after 2 and 22 months, respectively. Two patients were lost to follow-up after 2 and 18 months. Thirteen patients died. Death was related to disease progression in 5 cases, to a non-lymphoid second neoplasm (hepatocellular carcinoma, small cell lung carcinoma) in 2, and to non-infectious surgical complications in a patient who developed an occlusive intestinal syndrome. Five out of the 13 deaths could be attributed to infections (2 bacterial pneumonias, 1 mycotic pneumonia, 2 from sepsis). Four out of the 5 infectious deaths occurred during the observation phase.

Table 2. Type and site of infections during the study.

Type and site	*Empirical phase*	*IVIG therapy phase*
Major infections		
Sepsis	1	2
Bacterial pneumonia	5	3
Peritonitis	1	–
Mycotic pneumonia	1	–
Varicella	1	–
Minor infections		
Bronchitis	19	14
Bacterial skin infection	2	1
Bacterial stomatitis	2	–
Lower urinary tract infection	–	1
FUO	15	13
Herpes zoster	4	1
Trivial infections	11	6
Patients with no infections	10*	22*
Patient-months	368	376

* $p < 0.02$ (chi-square test).

Incidence and site of infection

Table 2, which refers to the entire series of CLL patients included in the present study, depicts the severity and the sites of infections observed. As shown, the lower respiratory tract was the predominant site of infection, accounting for 8 out of 14 (57.1%) severe infections. A significantly lower incidence of infectious episodes during IVIG prophylaxis was observed in the 30 patients who completed the 6-month period of either observation or IVIG therapy (Table 3). Twenty of these patients (66.6%) remained free of infection throughout the period in which they were receiving IVIG, while 9 out of the 30 patients (30%) suffered no infection during the observation phase ($p < 0.01$). Overall there were 25 serious infectious episodes (major plus minor) in 321 patient-months in the observation period (0.93 per year), while infections were observed in 292 patient-months in the IVIG prophylaxis phase (0.45 per year). Similar data were obtained for the 17 patients who completed the full 12-month period of either observation or IVIG prophylaxis (Table 3). Interestingly, when this group was analyzed statistically by methods applicable to studies in which each patient is used as his own control (the Mc Nemar test), a clear benefit in terms of lower rate of infections was registered in the IVIG prophylaxis period in comparison to the observation phase ($p < 0.01$). Again, this benefit was independent of the duration of the study (6 or 12 months). Finally, IgG determinations were obtained in 25 patients on 2 to 5 occasions during treatment. Seventeen out of the 25 patients displayed an increase of IgG level that ranged from 4.4% to 83.3% (mean value, 41.8%), while 8 showed stable IgG values during IVIG therapy. The number of patients who remained free of serious infections was not statistically different in these groups (58.8% versus 62.5%; p = NS).

Discussion

The frequent occurrence of hypogammaglobulinemia in CLL has led to trials of immunoglobulin administration,[5-6] the most important one being the large multicenter randomized study of the International Cooperative Group.

Table 3. Infection by etiology and severity in patients who completed 6 and 12 months of either IVIG or empirical therapy.

	6-month period (n=30)		*12-month period (n=17)*	
	Empirical	*IVIG*	*Empirical*	*IVIG*
Bacterial				
Major	4	2	2	1
Minor	18	8	16	7
Mycotic				
Major	1	–	–	–
Viral				
Minor	2	1	4	1
Trivial	12	4	6	1
Patients with no infections	9	20*	6	13**
Patient-months	321	292	206	215

*$p < 0.01$; **$p < 0.02$.

What emerged from this study was that in patients assigned to receive IVIG (400 mg/kg) at 3-week intervals for 1 year, moderately severe bacterial infections were reduced by 50%, while minor and severe bacterial, viral and fungal infections remained unchanged.[7]

Despite these promising results, several questions regarding the role of IVIG therapy in CLL still remain open. The cost-effectiveness of IVIG in patients with CLL was recently addressed by Weeks *et al.*[8] An expenditure of $6 million was necessary to achieve one quality-adjusted life-year (QUALY), without any increase in life expectancy.[8] In this context, the results of a randomized double-blind study specifically designed to compare low (250 mg/kg)-versus high (500 mg/kg)-dose IVIG given every 4 weeks for 1 year are of interest. Rates of serious infections in the two groups of patients were similar, thus suggesting that many CLL patients may be adequately protected by lower doses of IVIG given monthly on an outpatient basis.[11] Nevertheless, it is unlikely that IVIG may be a cost-effective way to prevent infection in CLL, since a cost lower than $70,000 per QUALY would be required for this.

Unfortunately, a control group of patients who did not receive IVIG prophylaxis was not included in the Chapel *et al.*[11] study, which therefore did not demonstrate the superiority of low-dose IVIG over empirical treatment. This is not the case of our crossover study, which provides information that are lacking in the literature.

It is not clear how long IVIG prophylaxis should be given in order to observe a marked benefit in terms of a reduced infection rate. According to the experience of the Cooperative Group for the study of immunoglobulin in CLL,[7] the greatest benefit was noted in patients who completed the full 1-year course of prophylaxis. This observation may lead physicians who treat CLL patients to include only the ones whose life expectancy is 1 year or more in infection prophylaxis programs with IVIG. Such a policy tends to exclude many patients with advanced CLL who are more likely to develop life-threating infections. Our results clearly show that a benefit in terms of reduced rate of infections could be demonstrated in patients who completed either the 12- or the 6-month course of IVIG prophylaxis. Therefore a short life expectancy (less than 1 year) should not be used as a criterion to exclude patients from IVIG infection prophylaxis.

The ultimate benefit of IVIG would be that of improving the quality of life and increasing survival. The short follow-up time of our patient series does not make it possible to carry out any effective survival analysis. It should be stressed, however, that 4 out of the 5 infectious deaths were registered during the observation phase, suggesting that IVIG prophylaxis may have some role in affecting the overall survival of CLL patients.

Adverse effects due to the infusion of IVIG were negligible. Twenty-two untransfused patients who were negative at entry were regularly monitored for anti-HCV antibodies at 6-month intervals. Four of them were found to be positive for anti-HCV antibodies while receiving IVIG therapy. Molecular studies aimed at investigating the presence of HCV-RNA were not carried out; however, anti-HCV antibodies disappeared when immunoglobulin administration was stopped, indicating passive transmission due

Table 4. IVIG studies in CLL.

Reference	*patient no.*	*Pts in advanced stage**	*Type of study*	*Dose IVIG/ schedule*	*Study duration (months)*	*Infection rate during IVIG administration*
Cooperative Group (7)	81	32 (39.5%)	Controlled, randomized double-blind	400 mg/kg/21 days	12	Decreased
Jurlander et al. (17)	15	8 (53.3%)	not controlled, pilot	10 g/28 days	12 (mean time)	Decreased
Chapel et al. (11)	34	15 (44.1%)	Controlled, randomized double-blind	250 mg/kg versus 500 mg/kg/28 days	12	Decreased
Sklenar et al. (21)	31	2 (6.4%)	dose-finding	100 to 800 mg/kg/21 days	4.5	Decreased
Griffiths et al. (15)	10	3 (30%)	Controlled, randomized double-blind	400 mg/kg/21 days	12	Decreased
Boughton et al. (23)	42	15 (35.7%)	randomized	18 g/21 days	12	Decreased
Present study	30	25 (83.3%)	randomized, crossover	300 mg/kg/28 days	6 or 12	Decreased

**Binet stage C or Rai III - IV.*

to infusion of IVIG.[15]

Although the therapeutic effect of immunoglobulins is evident, their mechanism of action is not fully understood. It seems that correction of existing hypogammaglobulinemia is not a good index of effectiveness; it is possible that an immunomodulatory effect contributes to the observed benefit of immunoglobulins in CLL. As recently suggested by Blasczyk *et al.*,[16] the immunomodulating effects of immunoglobulin therapy might be due, at least in part, to contaminating soluble CD4 and HLA molecules present in some commercial immunoglobulin preparations. In addition, we were unable to show any significant changes in the mean number of antibiotic prescriptions during the empirical versus the IVIG therapy phase. At present, the policy of administering antibiotics as soon as signs of infection are detected may represent a bias for this evaluation in our study as well as in those of other authors.[17]

The results of the present study, and those of others (Table 4), are biased by the small number of patients included. On the other hand, in order to get definitive evidence that low doses of IVIG are superior to empirical treatment in protecting against infections, it was estimated that over 400 patients would be required in each treatment group; this is really unachievable.[11] Interestingly, in comparison to other similar studies, our series included a greater number of patients in advanced clinical stage (Table 4) who could possibly take advantage of IVIG prophylaxis. The changing spectrum of infections in CLL patients receiving purine analogues should also be considered before starting IVIG therapy.[19-22] Studies comparing the efficacy of IVIG therapy with oral prophylactic antibiotics might end the controversies concerning the cost-effectivess of immunoglobulin in CLL.

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