Crossover Study of Immunoglobulin Replacement Therapy in Patients With Low-Grade B-Cell Tumors

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A randomized crossover study of prophylactic immunoglobulin (IgG) therapy was performed in patients with chronic lymphocytic leukemia (CLL) or non-Hodgkin’s lymphoma (NHL). Twelve patients with hypogammaglobulinemia or a history of recurrent infections received infusions of IgG or placebo intravenously (IV) every 3 weeks for 1 year. They were then switched to the alternative prepa-

ration for another year. The number of serious bacterial infections was significantly less ($P = .001$; Mainland’s cross-over method) in the months in which patients received IgG. Serious bacterial infections showed a trend to be associated with an IgG level <8.4 g/L ($P = .048$; Fisher’s exact test).

MATERIALS AND METHODS

Patients. Patients with CLL or low-grade non-Hodgkin’s lymphoma (NHL) were eligible for the study if they had hypogammaglobulinemia (serum IgG level <3.5 g/L, $n = 9$) or one or more serious infections during the course of the disease (regardless of current IgG level, $n = 3$).

The patients entered into the study were selected following perusal of 72 patient notes. Eight patients with CLL and four patients with low-grade NHL entered the study; the first year of study in the patients with CLL formed part of an international multicenter study involving 84 patients. The lymphoproliferative disorder had been diagnosed from 1 to 8 years previously. Patients with CLL were staged according to the Rai classification at diagnosis and on entry to the first and second years of the study. Two patients were stage 0 on entry, three were stage II, and three were stage IV; these stages were essentially unchanged during the study period. Two of the four patients with NHL had progressive disease. The median age at the onset of the study was 63 years (range 47 to 72 years). No patient was on prophylactic antibiotics. Patients were selected regardless of the type of therapy used to treat the underlying disease; two patients had received no treatment during the previous year, eight patients had received chlorambucil with or without prednisolone, and two patients had received chlorambucil followed by cyclophosphamide and vincristine plus prednisolone (CVP). Patients with high- or intermediated-grade NHL were excluded from the study. Approval was given by the Central Oxford Ethics Committee, and written informed consent was obtained from each patient. Compliance was excellent, and no patient missed an infusion visit.

Protocol and evaluation. The study was conducted from December 1984 to July 1987. Patients were entered sequentially between December 1984 and August 1985. The patients were allocated randomly to receive an infusion of either 0.4 g/kg IVIgG (Gammagard, Hyland Therapeutic Division, Baxter Healthcare, Glenoaks, CA), or an equivalent volume of saline every 3 weeks for the first 12 months as an outpatient; they were then changed to the alternative preparation for 12 months more. The nature of each infusion was known only to the pharmacist. Each infusion took ~2.5 hours and was observed for side effects.

The patients were monitored carefully for infections. This included daily diaries of symptoms kept by the patients themselves and three weekly follow-up sheets completed at every infusion visit. Three weekly measurements were made of C-reactive protein, liver function tests, full blood count and microbiologic culture of sputum or urine as appropriate; IgG levels were also measured, but the results were withheld from the trial staff to preserve blinding. Infections were investigated and treated appropriately when they arose and were documented on trial forms. Each infection was
graded according to severity as follows: Major episodes were life-threatening infections requiring hospitalization and often IV antibiotics; moderate episodes were other infections requiring antibacterial therapy; trivial episodes were episodes in which no symptomatic or topical therapy was given. When major and moderate infections were grouped together, they were termed serious.

The infections were also classified, according to cause, as bacterial, viral, or fungal. Evaluation was made on clinical grounds in patients in whom microbiologic cultures were negative; the degree and duration of fever, response to antibiotics, CRP levels, and radiographic changes (if appropriate) were used for such evaluations.

Statistics. Analysis of the cross-over aspect of the design was performed using the sign method suggested by Mainland. To account for unequal times of observation for the two periods, rates of infection (for all infections and for the various subtypes of infection) for each patient for each therapy period were calculated. A comparison between the two periods determined which had the lower rate, thus creating a Bernoulli random variable. To determine whether any carryover effect occurred from one period to the next, Fisher’s exact test was used as suggested by Mainland.

RESULTS

Outcome of study. Five patients completed both years of the study. One patient was withdrawn during the second year (placebo) because of progression of his disease with bone marrow failure; he died 4 weeks later. Another patient was withdrawn during the second year (placebo) of the study after two infections but was followed for the remaining period. Two patients left the area (after 6 and 5.5 months, respectively). One patient died after four infusions in the second year (IgG); fungal infection was found at autopsy. In the case of two other patients, their physician refused the cross-over because of improvement in health during the first year (during which they received IgG); one patient was followed for 10 months of the second year, when he died; the other patient continued with IVIgG replacement therapy and is therefore excluded from the cross-over analysis. One hundred and ninety-one IVIgG infusions and 162 placebo infusions were administered to 12 patients during the study.

Infections. Six of the 12 patients were free of serious infection throughout the period in which they were receiving IVIgG; in contrast, only one patient of 11 suffered no infections while receiving placebo (Table 1). The severity of these infections is shown in Table 1.

When individual patients were considered, nine of 11 patients had fewer overall serious infections when they received IVIgG as compared with the period of saline infusions. When analyzed statistically by methods applicable to cross-over studies, the numbers of serious infections were significantly different between the two types of therapy (\(P = .033\); cross-over method of Mainland).

Classification of the serious infections by type of organism revealed that bacterial infections predominated overall and were less common in the periods in which IgG was given (Table 1). Ten patients had lower rates of serious bacterial infection when receiving IVIgG (\(P = .001\); Mainland’s crossover method). C-reactive protein levels were raised (>10 mg/dL) in all serious bacterial infections, and microbiologic cultures were positive in 10 of the 23.

The lower respiratory tract was the predominant site of infection; pneumonia accounted for nine of the 12 major infections (one fungal, eight bacterial). Other major infections included two pyresia of unknown origin (PUO) (one presumed viral and one bacterial) and one systemic chickenpox. The moderate infections in the saline phase included six bacterial chest infections, one urinary tract infection, one supplicative arthritis, one otitis media, one severe dental abscess, one supplicative wound infection, one oral thrush, and one PUO. Those in the immunoglobulin phase included three bacterial chest infections, one episode of influenza, two episodes of PUO (one believed to be viral although culture negative), and one pleurisy of presumed viral origin.

Serum IgG levels. Since this was a cross-over study, a significant carryover effect from one period of therapy to the next had to be excluded. In terms of overall infection rate five of six patients showed lower rates of infection on IVIgG therapy when they received IgG first, whereas five of five showed lower rates of infection on IVIgG therapy when they received placebo first (\(P = 1.00\), Fisher’s exact test), demonstrating that there was no IgG carryover effect. This was supported by the rapid decrease in IgG levels when patients switched from IgG to placebo therapy.

The preinfusion serum IgG levels in individual patients increased rapidly (within 12 weeks) to 6.0 g/L (almost within normal range) in 11 patients after infusions with this dose of IVIgG (0.4 g/kg/3 weeks); the other patient showed an increase, but these “trough” levels did not reach the normal range.

When infections were analyzed in relation to concurrent serum IgG levels, all serious infections tended to occur in periods when the IgG level was <6.4 g/L (\(P = .046\), Fisher’s exact test). The pre-study IgG level is probably an important factor in predicting infection; eight of nine patients with a serum IgG level of <6.4 g/L at entry had major bacterial infections while receiving saline; only one of these patients had such an infection while receiving IgG. Patients with a
serum IgG level of >6.4 g/L at entry had fewer infections in either phase.

Progress and treatment of lymphoproliferative disease. Chemotherapy did not appear to be associated with an increased incidence of infection. Neutropenia (ie, neutropenia) was associated with only two major infection episodes; both occurred in patients who were receiving saline infusions.

Adverse reactions. No serious adverse reactions occurred during the study.

DISCUSSION

Infections were predominantly bacterial and of a similar pattern to that which occurs in primary hypogammaglobulinemia. The number of major and moderate bacterial infections was significantly reduced ($P = .001$) with prophylactic IVIgG. Maintenance of the serum IgG level at 6.4 g/L correlated significantly with fewer infections, especially serious bacterial infections. In patients with primary hypogammaglobulinemia, although intramuscular (IM) IgG is partially effective in reducing infections, maintenance of the serum IgG at physiologic levels using higher doses of IVIgG is more effective. However, the optimum dose in patients with secondary hypogammaglobulinemia needs further evaluation.

The number of trivial infections was unchanged by IVIgG, presumably because most of these episodes were of viral origin. Serious fungal and viral infections, which reflect defective cell-mediated responses, were uncommon. Cell-mediated immunity is defective in approximately half of patients with CLL, as shown by recall skin tests, but this may be due to chemotherapy. Treatment is costly and should be restricted to selected patients, taking into account the type of infections and serum IgG levels. The type of infections is important; patients with recurrent viral or fungal infections will not necessarily benefit from IVIgG therapy. IgG levels may be helpful in predicting infections; 89% of patients with an IgG level <6.4 g/L developed major infections while receiving saline infusions. In our study, all three stage IV patients had major bacterial infections during the saline period but not during the IVIgG period; therefore, stage of disease should not preclude patients from receiving IVIgG therapy. Patients with neutropenia may be particularly at risk.

We conclude that patients of any age, with a stable disease, a history of recurrent bacterial infections, and hypogammaglobulinemia should benefit from long-term prophylaxis with IVIgG.

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REFERENCES

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