科技资料

Long-Term Intravenous Immunoglobulin Treatment in Patients with AIDS-Related Complex

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21 figures and 20 tables, 1990

KARGER

Vox Sanguinis

Vol. 59, Supplement 1, 1990

S. Karger · Medical and Scientific Publishers
Basel · München · Paris · London · New York · New Delhi · Bangkok · Singapore · Tokyo · Sydney

Drug Dosage

The authors and the publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

Printed in Switzerland by Graphische Anstalt Schüler AG, Biel
ISBN 3-8055-5256-4

Contents

Introduction

In this supplement issue of *Vox Sanguinis*, we wish to report on the results of long-term treatment with intravenous immunoglobulin (IVIG) in patients with AIDS-related complex (ARC) and Walter-Reed stage 5 (WR5).

When the study was designed in 1986, the knowledge about the pathogenesis of HIV-1 infection was limited. It was known that AIDS represents the final stage of infection with the retrovirus HIV-1, that progress of the disease is characterized by marked decreases in T4 lymphocytes resulting in inadequate cellular immune responses, and that the ensuing opportunistic infections invariably lead to death.

The following facts suggested that IVIG might have an effect on the progression of the disease:

(1) Deficiencies of the humoral immune response as a result of perinatal HIV infection responded to IVIG replacement therapy in a manner similar to primary immune deficiencies [1, 2].

(2) Epidemiological findings and in vitro characteristics of HIV-1 infection indicated that virus proliferation took place in activated T4 lymphocytes; thus, prevention of T cell activation by prophylaxis of infection was assumed to interrupt or at least to delay the progression of the disease [3].

(3) Thrombocytopenia, a symptom frequently associated with HIV-1 infection, resembling an autoimmune phenomenon occurring in other disorders, was known to respond well to IVIG treatment. In fact, there were isolated reports of IVIG having a benefical effect where such symptoms were associated with ARC [4, 5].

(4) Hybridization experiments had revealed that only a minority of T4 lymphocytes was affected. This meant that their destruction was not necessarily due to the cytotoxic effects of the virus, and that autoimmune mechanisms might play a key role [6].

Following a workshop held in Berne, Switzerland, during which some 50 clinical scientists from all over the world discussed the possible role of immunoglobulins in the treatment of lymphoproliferative syndromes, mainly AIDS and ARC [7], representatives of both the University of Cologne, FRG, and the University of Berne, Switzerland, decided to form a collaborative study group. The group's goal was to prospectively study possible effects of IVIG in patients with HIV-1 infection. After intensive discussions, a protocol for a controlled, double-blind study in patients with ARC and WR5 was elaborated. It was anticipated that 30 patients from the cohort of outpatients who were regularly cared for at the 'Medizinische Klinik II und Poliklinik' and the 'Universitäts-Hautklinik' of the University Hospital of Cologne, FRG, could be recruited within a few months. Half of the patient group should receive IVIG (Sandoglobulin®), the other half a placebo, both manufactured and supplied by the Central Laboratory of the Swiss Red Cross Blood Transfusion Service, Berne, Switzerland. Details of patient evaluations and treatment schedules are reported in the paper of Schrappe-Bächer et al. [8, this issue p. 3].

The study was started in the second half of 1987 and kept the collaborative study group busy for more than two years. During this time, over one million data were collected and processed. The results of the clinical conditions of the patients before, during and after the treatment period are summarized in the paper by Schrappe-Bächer et al. [8, this issue p. 3]. In the second paper, Plum et al. [9, this issue p. 15] describe their findings on the major histocompatibility complex class I–III allotypes in the treated patients. The

virological parameters were monitored and evaluated by Mertens et al. [10, this issue p. 21]. Krueger et al. [11, this issue p. 30] present their results on cellular immunity. Lymphocyte proliferation studies, especially the responses to herpes simplex virus, tuberculin antigen and mitogens are summarized in the paper of Krickeberg et al. [12, this issue p. 38]. The aspect of the complement receptor 1 on erythrocytes is described by Spycher et al. [13, this issue p. 44]. Späth et al. [14, this issue p. 51] on the other hand, studied the complement profiles and the presence of circulating immune complexes in the patient population. Finally, Heitmann et al. [15, this issue p. 59] comment on the statistical evaluations of the study results.

Although sensational results did not appear during the study, we would like to emphasize that this was the first controlled, randomized, double-blind, longitudinal clinical study in which the influence of long-term IVIG treatment on clinical status and T4 cells was evaluated. The results indicate that the clinical status of patients with advanced HIV-1 infection can be improved by IVIG, although there is little or no influence on the underlying impaired immunity.

The papers on the following pages are a summary of a joint and intensive effort of the participants of the trial, i.e. the patients, the clinicians, the laboratory specialists and the sponsor. All of their contributions are gratefully acknowledged.

On behalf of the study group

B. A. Perret, P. Imbach and G. R. F. Krueger

References

1 Schaad UB, Morell A, Vogt M: Acquired immunodeficiency syndrome (AIDS) in pediatric patients. Helv Paediatr Acta 1985; 40:249–260.

2 Schaad UB, Gianella-Borradori A, Perret BA, Imbach P, Morell A: Intravenous immune globulin in symptomatic paediatric human immunodeficiency virus infection. Eur J Pediatr 1988;147:300–303.

3 McDougal ME, Mawle A, Cort SP, Nicholson JK, Cross GD, Scheppler-Cambell JA, Hicks D, Sligh J: Cellular tropism of the human retrovirus HTLV III/LAV. I. Role of T cell activation and expression of the T4 antigen. J Immunol 1985;135:3151–3162.

4 Zeitlhuber U, Haschka F, Püspök R, Lechner K, Knapp W, Imbach P: Hemophilia and thrombocytopenia in a patient with impaired cellular immunity. Blut 1984;48:393–395.

5 Silvermann BA, Rubinstein A: Serum lactate dehydrogenase levels in adults and children with acquired immune deficiency syndrome (AIDS) and AIDS-related complex: Possible indicator of B cell lymphoproliferation and disease activity. Am J Med 1985;78:728–736.

6 Harper ME, Marselle LM, Gallo RC, Wong-Staal F: Detection of rare HTLV-III-infected cells in primary tissue from AIDS patients by in situ hybridization (abstract). Int Conf on AIDS, Atlanta, April 1985, p 27.

7 Perret BA, Baumgartner C: Workshop on immunoglobulin therapy of lymphoproliferative syndromes, mainly AIDS-related complex, and AIDS. Vox Sang 1987;52:162–175.

8 Schrappe-Bächer M, Rasokat H, Bauer P, et al: High-dose intravenous immunoglobulins in HIV-1-infected adults with AIDS-related complex and Walter-Reed 5. Vox Sang 1990;59(suppl 1): 3–14.

9 Plum G, Siebel E, Bendick CH, et al: Major histocompatibility complex class I–III allotypes in patients with AIDS-related complex/Walter-Reed 5, disseminated Kaposi's sarcoma and in normal controls. Vox Sang 1990;59(suppl 1):15–20.

10 Mertens TH, Ramon A, Kruppenbacher JP, et al: Virological examinations of patients with AIDS-related complex/Walter-Reed 5 enrolled in a double-blind placebo-controlled study with intravenous gammaglobulin administration. Prognostic value of anti-p24 determination. Vox Sang 1990;59(suppl 1):21–29.

11 Krueger GRF, Ramon A, Degenhardt St, et al: Cellular immunologic parameters in HIV-positive patients with AIDS-related complex and intravenous immunoglobulin therapy. Vox Sang 1990; 59(suppl 1):30–37.

12 Krickeberg H, Mauff G, Mertens Th, et al: Lymphocyte proliferation in AIDS-related complex/Walter-Reed 5 patients: Response to herpes simplex virus and tuberculin antigen and mitogen during intravenous immunoglobulin treatment. Vox Sang 1990; 59(suppl 1):38–43.

13 Spycher MO, Späth PJ, The ARC-IVIG Study Group Cologne/Berne: Quantification of complement receptor 1 on erythrocytes: Follow-up of HIV-1-infected patients with AIDS-related complex/Walter-Reed 5 under treatment with intravenous immunoglobulin. Vox Sang 1990;59(suppl 1):44–50.

14 Späth PJ, Braun M, Meyer-Hänni L, et al: Complement levels and circulating immune complexes in a controlled, longitudinal, multicenter study of effects of intravenous immunoglobulin in adults with AIDS-related complex/Walter-Reed 5. Vox Sang 1990; 59(suppl 1):51–58.

15 Heitmann K, Stützer H, Bauer P: Comments on the statistical evaluation of the ARC-IVIG study. Vox Sang 1990;59(suppl 1): 59–60.

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Vox Sang 1990;59(suppl 1):3–14

0042–9007/90/0595–0003 $2.75/0

High-Dose Intravenous Immunoglobulins in HIV-1-Infected Adults with AIDS-Related Complex and Walter-Reed 5

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Abstract. The influence of high-dose intravenous immunoglobulins (HD-IVIG) on the clinical status and T4 cell count of adults with AIDS-related complex (ARC) and Walter-Reed 5 (WR5) was evaluated in a randomized double-blind longitudinal study. Inclusion criteria were: (1) T4 cells <400/μl and (2a) oral thrush or cutaneous anergy or (2b) two clinical ARC criteria (fever, diarrhea, weight loss, fatigue, night sweats). Thirty patients [28 males, 2 females, median age 41 (24–64) years] with ARC (n = 8), WR5 (n = 12) and both (n = 10) were stratified according to their T4 cell count (≥ vs. <300/μl). Fifteen patients received 0.4 g/kg body weight IVIG and 15 placebo (albumin 0.03%) every other week for 26 weeks with follow-up for another 26 weeks. The clinical status was defined as a score consisting of fever, diarrhea, night sweats, fatigue, weight loss, oral candidiasis and mucosal or cutaneous herpes simplex. Clinical examination and routine laboratory assessments were performed before initiation of the study and before each administration, lymphocyte phenotyping every 4 weeks and cutaneous reaction, serology and lymphocyte stimulation every 12 weeks. Both groups were comparable in initial clinical symptoms and laboratory values. Seven patients developed AIDS (treatment group: 3, placebo group: 4), 1 patient died by homicide. After 26 weeks, the clinical score (particularly fatigue and fever) was significantly improved in the treatment group, while the T4 cell count and other clinical and immunological parameters remained unaltered. This limited effect was still evident at termination of the study after 52 weeks. In conclusion, HD-IVIG can improve the clinical status of patients with advanced HIV-1 infection without obviously correcting the underlying impaired cellular immunity. The substitution of intact antibodies in the state of functional hypogammaglobulinemia is suggested as possible therapeutic mechanism.

Introduction

Advanced HIV-1 infection not yet complicated by opportunistic manifestations [AIDS-related complex (ARC), lesser AIDS, stage CDC IVA or Walter-Reed 5 (WR5)] is characterized by fever, diarrhea, weight loss, night sweats and fatigue [1–5]. Pathophysiological dysfunctions suggest quantitative and functional abnormalities of T4 helper cells [6], polyclonal B cell activation [7–9], impaired B cell function [10, 11], immunoglobulin subclass deficiencies [8] and autoimmune phenomena [12]. While in pediatric AIDS the B cell defect is of major clinical importance [13–15], the significance of functional hypogammaglobulinemia in adults remains to be elucidated. Recurrent bacterial infections [16–

19] and reactivation of latent virus infections [20–24] may exert an additional pathogenic effect on the immune system.

Parenteral administration of immunoglobulins is used for antibody substitution in primary and secondary immunodeficiency [25–27]. In addition, it may serve as an immunomodulatory measure in idiopathic thrombopenic purpura and other autoimmune disorders [28–33]. Pathophysiological concepts include an inhibition of Fc-receptor-mediated removal of antigen-antibody complexes [34, 35], a decrease in autoantibody production [36–39], a restitution of selective antibody defects [40] and an accelerated catabolism of autoantibodies [41].

In HIV-1-infected children, high-dose intravenous immunoglobulins (HD-IVIG) are known as an effective therapeutic principle in reducing the frequency of episodes of bacterial infections, fever and diarrhea [14, 15, 42–45]. In adults, only few studies were done [44, 46–48] showing encouraging results on the clinical course but without thorough evidence of restitution of cellular immunity.

On this basis, we conducted a randomized and stratified double-blind trial on adults with ARC and WR5 to gain further information on the effect of IVIG on clinical status and immunological parameters.

Patients and Methods

The patients were selected according to the inclusion criteria listed in table 1. HIV-1 infection was proven by two independent positive HIV-1 antibody ELISA tests confirmed by indirect immunofluorescence or Western blot. Exclusion criteria were: (1) drug addiction; (2) AIDS according to the CDC criteria [49]; (3) thrombocytopenia $<100 \times 10^3$ cells/μl.

Randomization and stratification were done according to T4 cells ≥ or <300/μl.

The patients were 24–64 years old (median 41 years), 28 males and 2 females. 28 patients were male homosexuals, 1 patient was infected by heterosexual transmission, 1 by blood products.

The experimental (group A) and control group (group B) consisted of 15 patients each. Both, the treatment and observation periods lasted 6 months; at the end of the treatment period (day 183; fig. 1), both groups were blindly evaluated according to their clinical score and absolute T4 cell number in order to decide about early discontinuation.

The discontinuation criteria for individual participation in the study were defined as: (1) patient's intention (none); (2) insufficient compliance (1 case); (3) progress to AIDS (7 cases); (4) development of disorders representing a well-recognized indication for immunoglobulin therapy such as thrombocytopenia $<50 \times 10^3$/μl or life-threatening infections (none). The administration of two additional immunoglobulin doses of 0.4 g/kg body weight were allowed without discontinuating the study.

The general criteria for study discontinuation were defined as: (1) 6 or more cases of AIDS developing during the study with a prevalence of 1:5 or 0:6 in one group (to be checked blindly after the 6th AIDS case) and (2) decision of the study group.

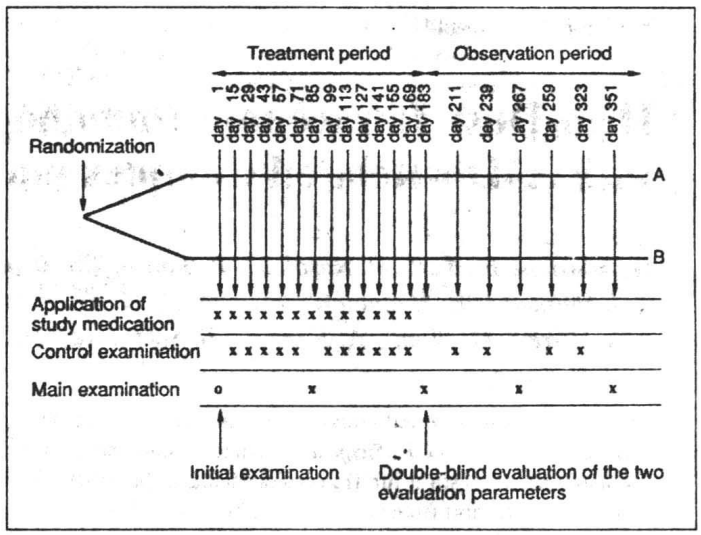

Fig. 1. Study design. A = IVIG group; B = placebo group.

Table 1. Inclusion criteria (all 3 criteria had to be fulfilled)

(1) Proven HIV-1 infection
(2) Clinical status:
  (a) WR5 defined as [5]: T4 cells < or ≥ 400/μl
  and
  Cutaneous anergy or oral thrush
  or
  (b) ARC defined as [1, 3]: at least two clinical symptoms (2 weeks in the last 3 months):
  Fever (>38°C)
  Diarrhea (>5 movements/day)
  Weight loss (>5 kg)
  Fatigue (inability to work)
  Night sweats
  and
  Two of three laboratory criteria:
  T4 cell count <400 cells/μl
  T4/T8 ratio <1.0
  Hemoglobin <110 g/l or leukocytes <3,000/μl
(3) Written informed consent of the patient

Table 2. Score used to evaluate the clinical status

Symptoms	Points	
	0	2
Fever	<38°C	>38°C
Diarrhea	<5/day	>5/day
Weight loss	<5 kg	>5 kg
Fatigue	ability to work	inability to work
Night sweats	not present	present
Stomatitis	not present	present
Herpes infection	not present	present

Medication (fig. 1)

In the treatment group 0.4 g/kg body weight IVIG (Sandoglobulin®) prepared by the Central Laboratory of the Swiss Red Cross Blood Transfusion Service were administered. In the placebo group, an equivalent volume of 0.03% albumin solution exhibiting equal color and viscosity as IVIG was given. In both groups it was given intravenously 13 times, once every 2 weeks, from days 1–169.

Evaluation (fig. 1)

The clinical score and absolute T4 cell count were used to evaluate the therapeutic efficacy. The clinical score consisted of seven symptoms, as shown in table 2. Weight loss was reported in relation to the initial body weight before weight loss started. All other symptoms were evaluated as 2 points, when they were present on more than 7 days in the last 2 weeks. Herpes stomatitis was only counted as herpes infection and not additionally as stomatitis. The clinical score was assessed every 2 weeks, lymphocyte phenotyping every 4 weeks. The development of AIDS did not serve as an evaluation parameter because of its low probability of significant differences during the observation time in a small group of 30 patients.

Additionally, serum protein, gamma globulins, immunoglobulins (IgG, IgM, IgA), T4 and T8 percentages, T4/T8 ratio, skin testing, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), β_2-microglobulin, LDH, hemoglobin, leukocytes, neutrophils, platelets, haptoglobin, and further parameters described in the articles of Krueger et al. [50], Mertens et al. [51], Krickeberg et al. [52], Plum et al. [53], Spycher et al. [54] and Späth et al. [55] in the issue were assessed. Determination of lymphocyte subsets was done by use of monoclonal antibodies (OKT4 and OKT8, Ortho Diagnostic Systems, Neckargmünd, FRG) and cytometry (Ortho Spectrum III, Ortho Diagnostic Systems, Neckargmünd, FRG). For further references see Krueger et al. [50].

The clinical course was additionally described by the indices of Spitzer et al. [56] and Karnofsky and Burchenall [57]. For statistical methods, in particular models of extrapolation of censored data, see Heitman et al. [58] in this issue.

Results

Patients

Initially, only patients with ARC were included. After 8 months, 8 patients were enrolled, and the inclusion criteria were extended to WR5 in order to obtain 30 patients in an acceptable period of time. The patient characteristics of both groups are given in tables 3 and 4. No difference in initial stage (table 3) and proportion of patients enrolled by fulfilling the ARC and WR5 definition were observed, nor any difference in initial T4 cell counts, initial clinical score, clinical symptoms and criteria of WR5 (table 4).

Evaluation Parameters

The analysis of the areas under the curve (AUC) [58] over the treatment period showed a significant improvement ($p<0.05$) in the IVIG group (fig. 2–4), assuming models 1, 2 and 4, describing patients discontinuating the study

Table 3. Stage according to Walter-Reed and CDC classification at time of enrollment

	Total	Group A	Group B
Walter-Reed classification			
WR3	3	1	2
WR4	5	3	2
WR5	22	11	11
CDC classification			
IIB	3	1	2
IIIB	3	0	3
IVA	7	5	2
IVC2	17	9	8

Table 4. Comparability of groups A and B with regard to the basical characteristics

	Group A	Group B	Groups A + B
WR5 symptoms			
Oral candidiasis	7	8	15
Normergy	1	1	2
Hypergy	6	6	12
Anergy	8	7	15
Not done	0	1	1
Clincal symptoms			
Night sweats	6	8	14
Fever	3	2	5
Weight loss	6	3	9
Diarrhea	3	2	5
Fatigue	10	10	20
No symptoms	2	3	5
Inclusion criteria			
ARC	4	4	8
WR5	5	7	12
Both	6	4	10
Score			
10	0	0	0
9	0	0	0
8	1	0	1
7	1	0	1
6	0	3	3
5	3	0	3
4	2	0	2
3	3	2	5
2	4	8	12
1	0	1	1
0	1	1	2
T4 cell count			
≤100/μl	3	2	5
100 ≤ 200/μl	1	4	5
200 ≤ 300/μl	6	5	11
300 ≤ 400/μl	5	4	9

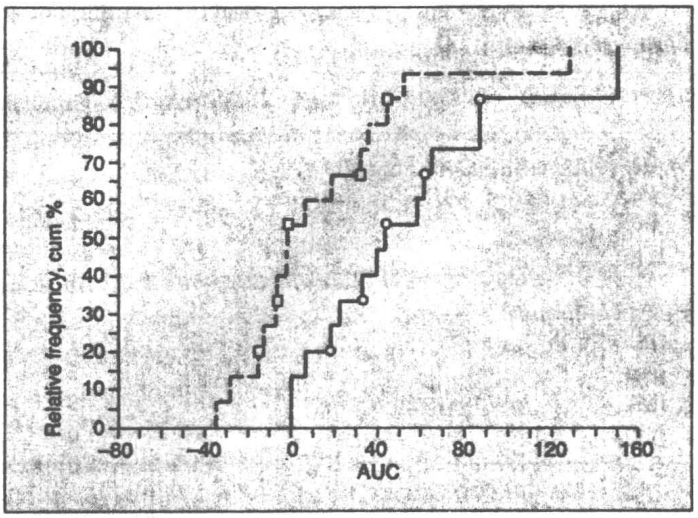

Fig. 2. AUC clinical score, empirical distribution function. – = Group A; — = group B.

[58]. Assuming model 3, this difference could not be established.

Additional univariate analyses done analogously for all seven components of the score detected no remarkable diferences for the variables diarrhea, night sweats, weight loss, oral candidiasis and mucosal or cutaneous herpes infection, but showed differences based on the variables fatigue and fever. Comparison of adjusted group means based on analyses of covariance confirmed these results.

The findings from the 6-month treatment period did not substantially change when the whole follow-up period of 1 year was considered, the early decrease of the clinical score dominating the analyses. Moreover, the late results have to be taken with care, since with increasing follow-up time the amount of missing information increases. Therefore, it has been expected that late results are more depending on the estimation procedure for the drop-outs.

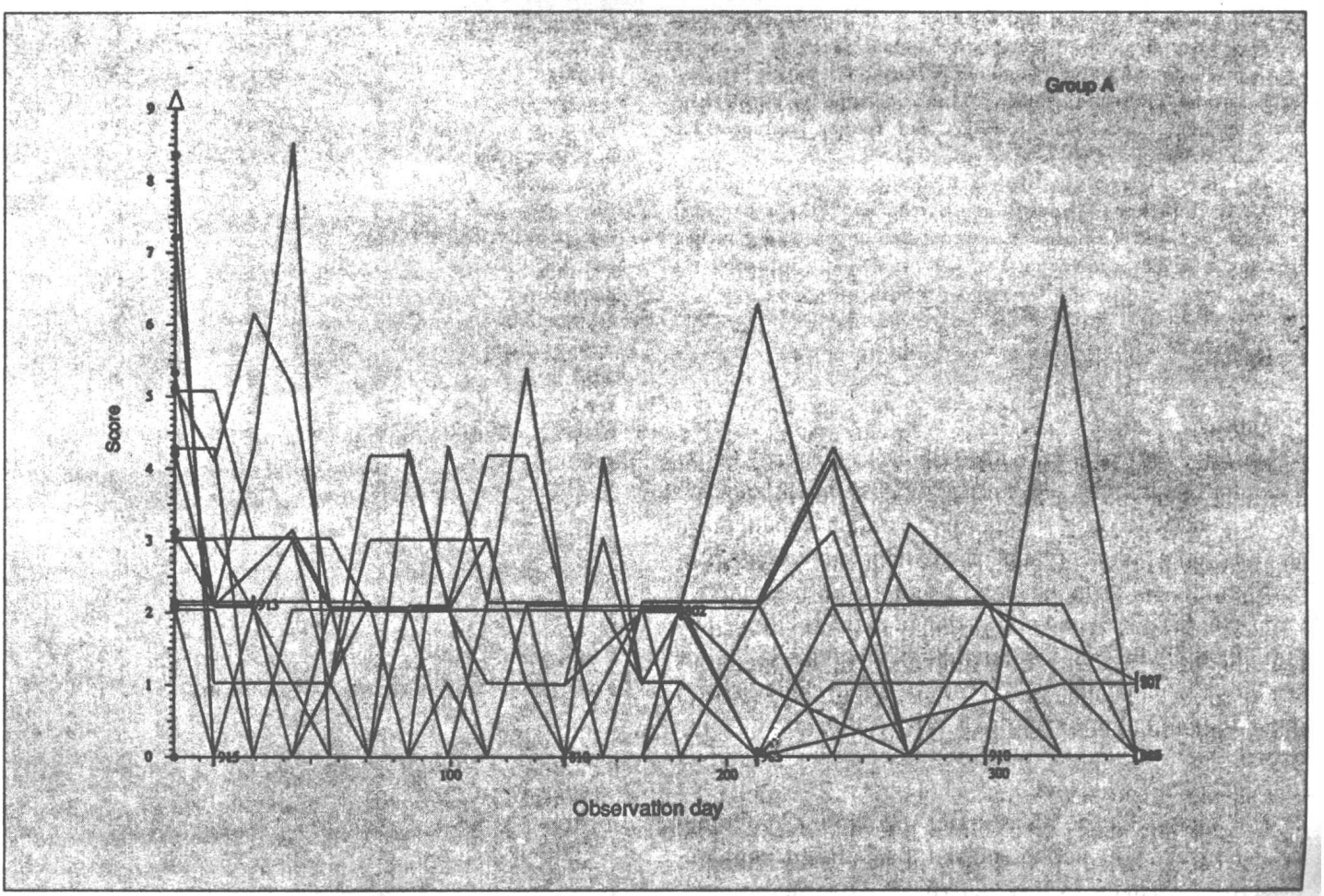

Fig. 3. Clinical scores of the IVIG group (group A). Each line represents a single patient.

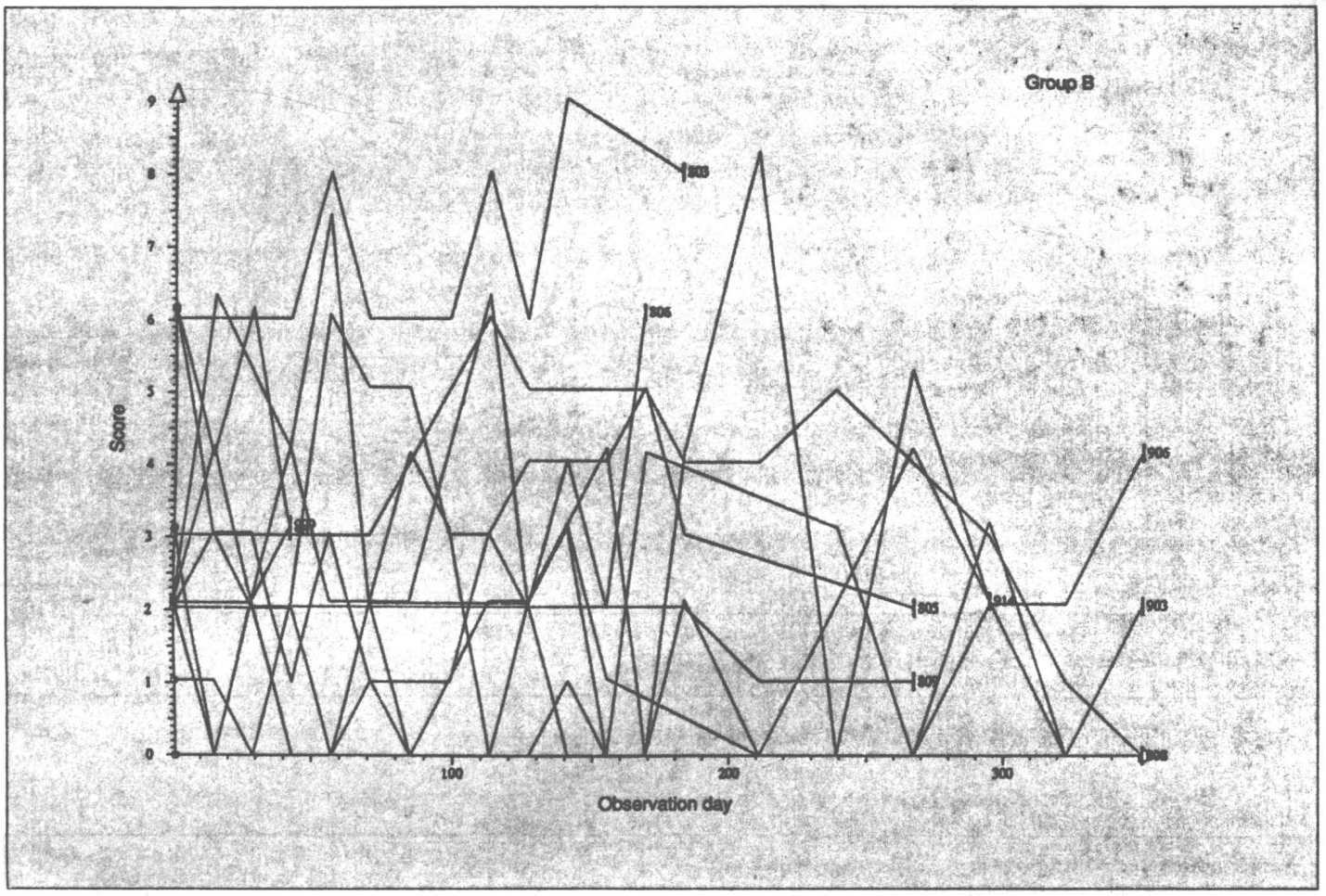

Fig. 4. Clinical scores of the placebo group (group B). Each line represents a single patient.

The AUC of the T4 cell counts showed no difference between the groups, neither after treatment nor after the observation period (fig. 5–7).

Development of AIDS and Individual Study Termination

Seven patients developed AIDS 26–217 (median 45) days after enrollment in the study; in 6 patients, opportunistic infections could be treated successfully. One patient died by homicide, 1 patient was excluded for noncompliance. The drop-outs showed no imbalance between the treatment and placebo group with regard to the parameters listed in table 5.

Other Parameters (table 6)

Total serum protein, gammaglobulins and immunoglobulins showed no difference between both groups, with the

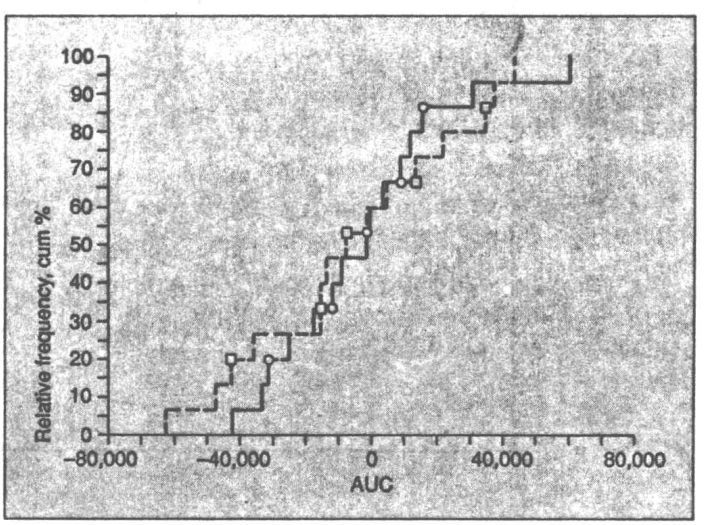

Fig. 5. AUC T4 cell count, empirical distribution function. – = Group A; — = group B.

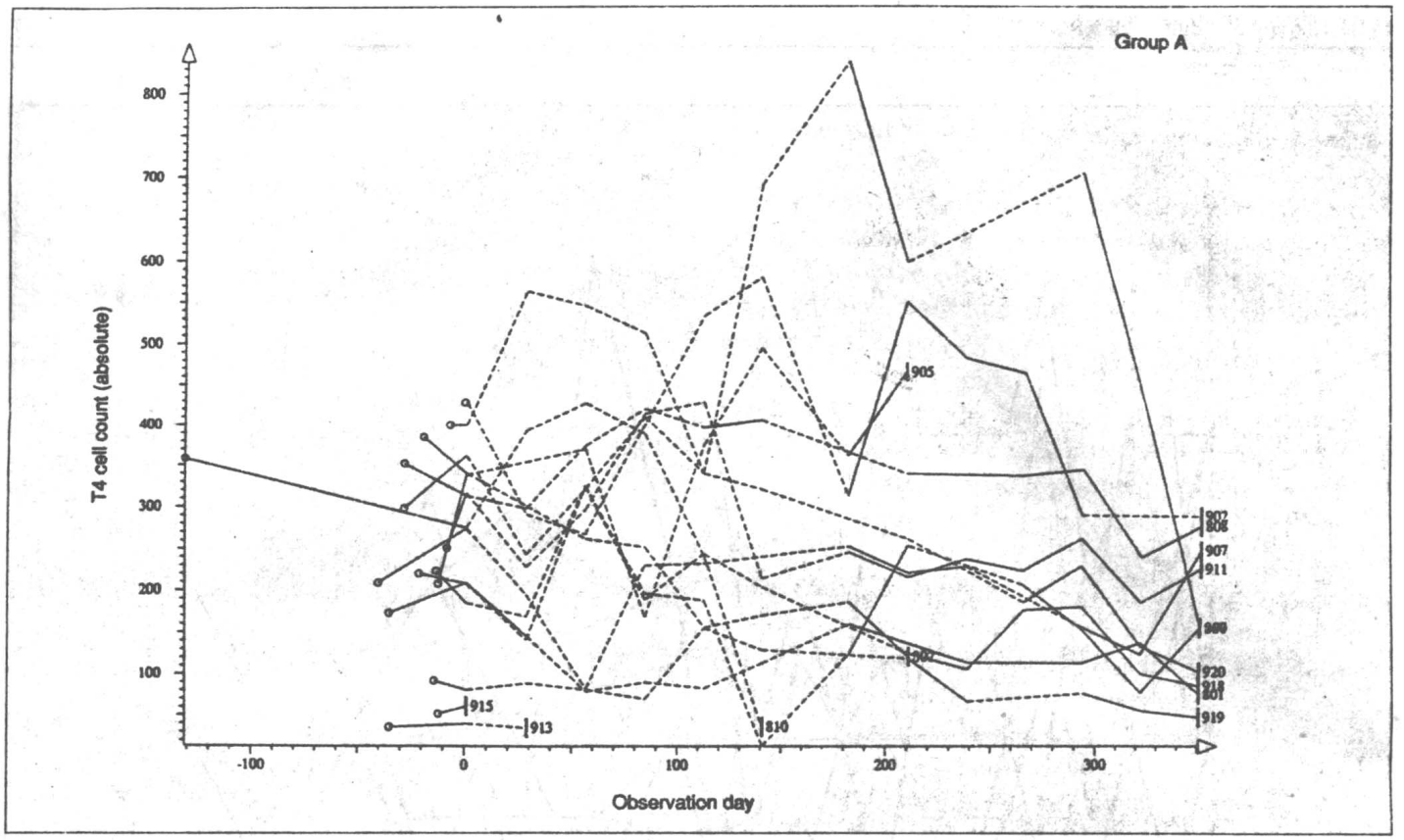

Fig. 6. T4 cell counts of the IVIG group (group A). Each line represents a single patient.

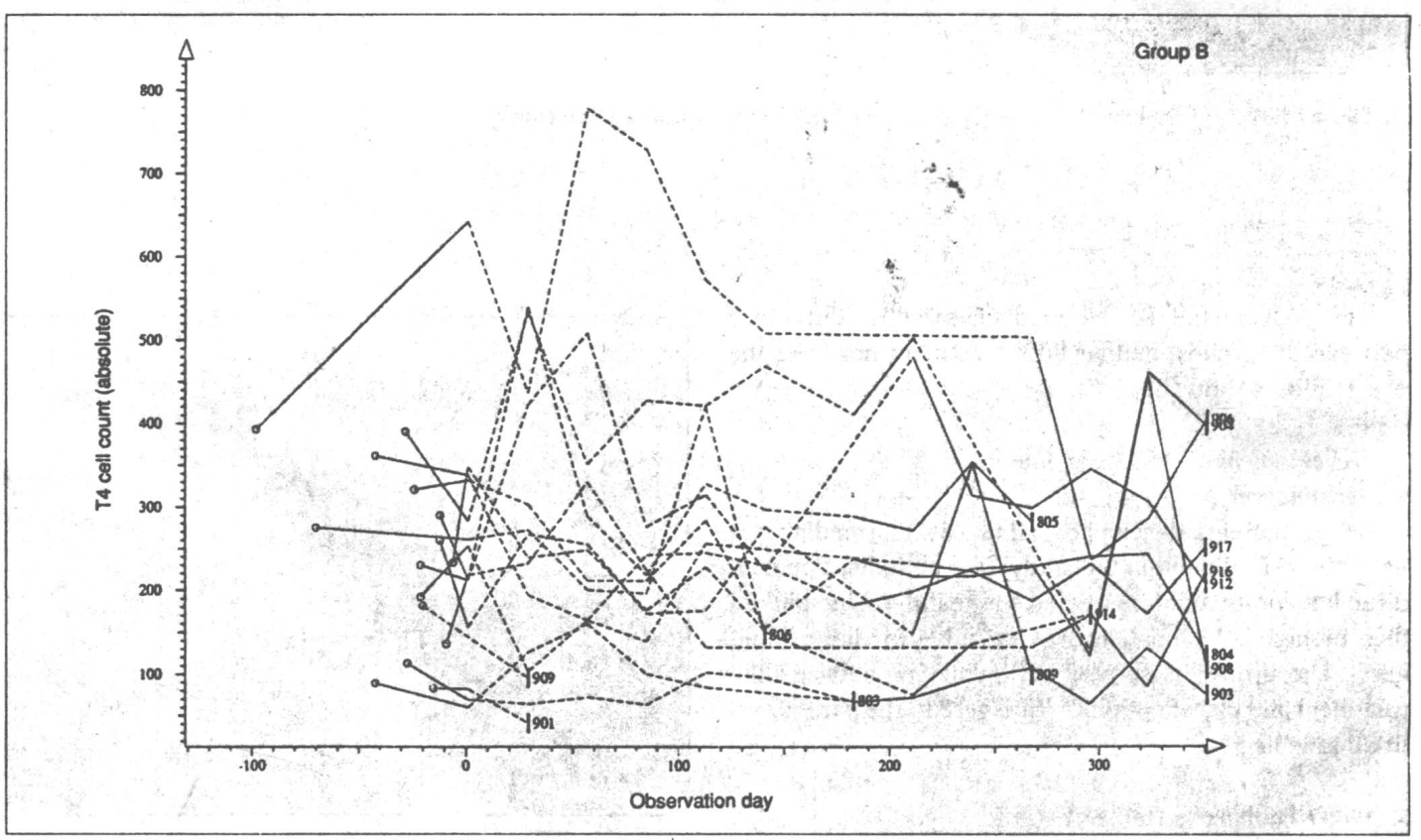

Fig. 7. T4 cell counts of the placebo group (group B). Each line represents a single patient.

Table 5. Patients discontinuating the study

	Total	Groups	
		A	B
Total number	9	5	4
Development of AIDS	7	3	4
Death for other cause	1	1	0
Absence of compliance	1	1	0
AIDS manifestations			
Pneumocystis carinii pneumonia	4	2	2
Toxoplasmosis	2	1	1
Kaposis sarcoma and wasting syndrome	1	0	1
Initial T4 cell counts			
0–≤100/μl	4	2	2
101–≤200/μl	1	0	1
201–≤300/μl	2	1	1
301–≤400/μl	2	2	0
Initial score			
6	2	0	2
5	1	1	0
3	1	1	0
2	4	2	2
0	1	1	0
Initial skin testing			
Normergy	1	1	0
Hypergy	3	2	1
Anergy	4	2	2
Not done	1	0	1
Inclusion criteria			
ARC	4	3	1
WR5	3	2	1
Both	2	0	2

exception of IgG which exhibited a slight increase during the treatment period, followed by a slight decrease in the observation period, reflecting immunoglobulin administration. Neither T cell subsets nor T4/T8 ratio and cutaneous reaction were influenced significantly. ESR, CRP, β_2-microglobulin, LDH, hemoglobin, leukocytes, lymphocytes, neutrophils, platelets and haptoglobin were equally distributed between both groups. Parameters describing protein catabolism, such as urea, and clinical parameters other than the clinical score (indices of Spitzer et al. and Karnofsky and Burchenall) were not influenced by IVIG therapy.

Discussion

Our double-blind randomized study on adults with advanced HIV-1 infection (ARC and WR5) was carried out in an attempt to evaluate the effect of HD-IVIG on the clinical course and HIV-1-associated immunological alterations. The effectiveness of the treatment was assessed by a clinical score and the absolute T4 cell count. The clinical score, which consisted of seven symptoms and preopportunistic conditions, revealed a significant improvement in the general status of the therapy group as compared to the placebo group. The T4 cell count and other immunological parameters failed to show any significant difference between the two groups.

An amelioration of the clinical course was obvious in terms of fever and fatigue, other symptoms remained unchanged. An influence of the initial score values was excluded by covariance analyses; the significant difference was observed regardless of the statistical model on the extrapolation of censored data, except the model based on the worst individual value assessed during study participation [58].

A clinical amelioration was reported by other authors as well [14, 42–45], although trials on adults are rare [46–48, 59]. All but two studies were uncontrolled; one study was announced as 'randomized', but did not provide any information about the control group [59], the other was conducted on four groups, showing a decrease in opportunistic infections in the treatment group [48].

The immunological results were disappointing with regard to the interpretation of the observed clinical benefit [50–55]. A slight, not significant increase in IgG levels during the treatment period followed by a decrease during the observation period can be regarded as the result of repeated immunoglobulin administrations [41]. The biological half-life of externally administered immunoglobulins varies between 13 and 32 days [28, 60]. In primary hypogammaglobulinemic patients, the administration of 0.3 g/kg body weight, every 2 weeks [26, 61] or 10 mg/kg body weight daily [41] results in a steady low-range IgG level.

Disturbances of B cell function [10, 11, 14] were indicated by polyclonal hypergammaglobulinemia, which may be related to chronic stimulation by the Epstein-Barr virus, loss of T4 cell control and a direct T-cell-independent B cell stimulation by HIV-1 antigens [7, 9]. Additionally, subclass deficiences of IgG2 [8, 62] and of IgG3 [63] seem to play a role in the humoral immune defect of HIV-1-infected patients.

Several studies report on recurrent bacterial infections in HIV-1-infected patients [16–19], but no prospective stud-

Table 6. Immunological, inflammation and hematological parameters

	Initial values			After treatment period			After observation period		
	groups A + B	group A	group B	groups A + B	group A	group B	groups A + B	group A	group B
Immunological parameters									
S. protein, g/dl	7.8 ± 0.7	7.6 ± 0.6	8.0 ± 0.6	8.2 ± 0.7	8.1 ± 0.8	8.2 ± 0.8	8.2 ± 0.6	8.0 ± 0.5	8.6 ± 0.6
n	30	15	15	22	12	10	17	9	8
γ-Globulin, %	23.0 ± 5.8	20.8 ± 5.3	25.2 ± 5.5	24.0 ± 7.5	22.0 ± 8.3	27.1 ± 5.3	25.2 ± 4.7	24.7 ± 4.7	25.6 ± 5.3
n	30	15	15	20	12	8	16	8	
IgG, mg/l	19,627 ± 66,157	17,531 ± 5,102	21,814 ± 6,533	22,584 ± 6,569	21,957 ± 6,166	23,337 ± 7,285	22,349 ± 7,226	19,934 ± 5,811	25,368 ± 8,041
n	30	15	15	22	12	10	18	10	8
IgM, mg/l	2,583 ± 1,023	2,414 ± 831	2,753 ± 1,189	2,749 ± 1,200	2,693 ± 1,040	2,817 ± 1,424	2,543 ± 1,098	2,593 ± 1,329	2,480 ± 805
n	30	15	15	22	12	10	18	10	8
IgA, mg/l	2,585 ± 1,433	2,573 ± 1,414	2,597 ± 1,501	2,191 ± 1,273	2,618 ± 1,525	1,679 ± 633	2,106 ± 978	2,333 ± 999	1.821 ± 934
n	30	15	15	22	12	10	18	10	8
T4 cells, %	19.6 ± 9.0	19.1 ± 9.0	20.0 ± 9.3	19.8 ± 9.2	18.4 ± 9.6	21.5 ± 8.9	15.6 ± 8.0	13.4 ± 9.0	18.2 ± 6.1
n	30	15	15	18	10	8	18	10	8
T4 cells, absolute	249 ± 133	255 ± 122	243 ± 149	267 ± 193	310 ± 227	209 ± 133	192 ± 107	167 ± 89	224 ± 126
n	30	15	15	14	8	6	18	10	8
T8 cells, %	58.9 ± 10.7	56.7 ± 12.7	59.0 ± 8.2	50.7 ± 12.3	49.5 ± 15.1	52.2 ± 8.2	48.6 ± 16.0	47.2 ± 18.4	50.2 ± 13.6
n	30	15	15	18	10	8	18	10	8
T4/T8 ratio	0.39 ± 0.22	0.38 ± 0.22	0.40 ± 0.21	0.42 ± 0.21	0.40 ± 0.22	0.43 ± 0.21	0.36 ± 0.20	0.34 ± 0.21	0.40 ± 0.20
n	30	15	15	18	10	8	18	10	8
CR, score	3 ± 4	3 ± 4	4 ± 4	8 ± 11	10 ± 14	7 ± 7	5 ± 7	3 ± 7	7 ± 8
n	29	15	14	21	11	10	9	5	4
Inflammation parameters									
ESR, 1st hour	14 ± 12	10 ± 10	18 ± 14	19 ± 18	19 ± 23	20 ± 11	19 ± 17	16 ± 13	22 ± 20
n	29	15	14	22	12	10	17	9	8
ESR, 2nd hour	35 ± 24	27 ± 21	44 ± 25	52 ± 56	54 ± 74	50 ± 23	44 ± 28	39 ± 24	50 ± 32
n	29	15	14	22	12	10	17	9	8
CRP, mg/l	3.25 ± 4.28	4.21 ± 5.48	2.29 ± 2.44	8.57 ± 19.63	5,58 ± 10.86	12.12 ± 27.00	2.82 ± 3.29	2.83 ± 3.29	5.15
n	30	15	15	22	12	10	3	2	1
β_2-Microglobulin, mg/dl	3.5 ± 0.8	3.6 ± 0.8	3.3 ± 0.8	3.2 ± 1.1	3.1 ± 1.4	3.3 ± 0.5	3.6 ± 1.3	4.0 ± 1.7	3.3 ± 0.9
n	20	9	11	16	9	7	14	7	7
LDH, µ/l	191 ± 34	189 ± 37	192 ± 33	177 ± 53	168 ± 63	190 ± 32	182 ± 30	174 ± 36	191 ± 20
n	29	14	15	20	12	8	17	9	8

Hematological parameters									
Hemoglobin, g/dl	14.9 ± 1.3	15.0 ± 1.4	14.8 ± 1.4	14.6 ± 1.5	14.8 ± 1.4	14.3 ± 1.5	15.0 ± 1.7	14.9 ± 1.7	15.0 ± 1.8
n	30	15	15	22	12	10	18	10	8
Leukocytes/mm^3	4,577 ± 1,082	4,747 ± 1,256	4,407 ± 887	4,159 ± 1,341	4,450 ± 1,599	3,810 ± 970	4,200 ± 1,205	3,980 ± 1,018	4,475 ± 1,427
n	30	15	15	22	12	10	18	10	8
Lymphocytes/ mm^3	1,282 ± 458	1,377 ± 475	1,146 ± 441	1,206 ± 541	1,424 ± 668	991 ± 381	1,176 ± 378	1,154 ± 358	1,253 ± 448
n	30	15	15	22	12	10	18	10	8
Neutrophils/mm^3	2,609 ± 641	2,706 ± 807	2,556 ± 529	2,454 ± 624	2,581 ± 801	2,324 ± 419	2,436 ± 672	2,348 ± 796	2,551 ± 537
n	30	15	15	22	12	10	18	10	8
Platelets, ×1,000/mm^3	194 ± 141	154 ± 31	235 ± 191	175 ± 48	154 ± 22	201 ± 59	153 ± 44	140 ± 46	168 ± 39
n	30	15	15	20	11	9	18	10	8
Haptoglobin, mg/dl	196 ± 93	208 ± 86	185 ± 101	213 ± 131	221 ± 141	201 ± 123	209 ± 88	235 ± 89	183 ± 83
n	27	13	14	18	11	7	16	8	8
Other parameters									
Urea, mg/dl	28.5 ± 8.9	29.6 ± 8.2	27.4 ± 9.7	31.1 ± 9.3	32.2 ± 7.3	29.7 ± 11.7	30.1 ± 8.5	34.2 ± 8.1	25.5 ± 6.5
n	30	15	15	20	11	9	17	9	8
Spitzer index	8 ± 2	8 ± 2	8 ± 3	8 ± 3	9 ± 1	8 ± 4	9 ± 1	8 ± 2	9 ± 1
n	30	15	15	22	12	10	17	9	8
Karnofsky index	82 ± 11	83 ± 10	81 ± 12	90 ± 10	89 ± 5	90 ± 14	91 ± 8	88 ± 8	95 ± 5
n	30	15	15	21	12	10	17	9	8

Values are expressed as mean ± SEM. Cr = Cutaneous reaction, n = number of assessments.

ies are available on the prognostic value with regard to the clinical course of HIV-1 infection. Latent herpes virus infections, which exert immunosuppressive effects themselves, are frequently reactivated under the conditions of cellular immunodefiency [20–24]. Recurrent bacterial infections and reactivated herpes virus infections both represent a stimulating factor to T4 cells, possibly leading to increased HIV-1 replication [64]. A reconstitution of humoral immunity and antibody-dependent cellular cytotoxicity by substitution of idiotypic antibodies could be followed by a better clearing of bacterial infections and viral reactivations resulting in a decreased number of fever episodes and improved general condition.

In children, HD-IVIG was shown to have a therapeutic effect on functional hypogammaglobulinemia [13–15, 42, 43]. This could explain its mode of action. A decrease of LDH levels was observed [44, 45], but otherwise no unequivocal changes of B cell parameters were found. In adult HIV-1-infected patients, an effect of parenteral immunoglobulins on the frequency of bacterial and (reactivated) herpes virus infections was not described, and in our study no significant influence on inflammation or B cell function was obvious.

Eventual alterations of T cell subsets, another possibility of interpreting the obvious influence of IVIG on the clinical course of HIV-1-infected patients, were examined in several trials [46, 47]; only in two studies an increase in T4 cells was observed [14, 44]. All other studies reported no influence on T cell subsets and T cell function. Schaad et al. [45] found a decrease in T4 cells. Two trials with high-dose immunoglobulins in patients with idiopathic thrombopenic purpura reported a decrease in T4 cells and T4/T8 ratio [65, 66]. In essence, however, the role of T4 cells in HD-IVIG remains speculative.

Although a limited effect of HD-IVIG on the clinical status of adult patients with ARC and WR5 could be observed, we do not recommend a general indication for patients in this stage, taking into consideration the high costs and limited availability.

References

1 Abrams DI: AIDS-related conditions. Clin Immunol Allergy 1986;6:581–599.

2 Centers for Disease Control: Classification system for human T-lymphotropic virus type III/lymphadenopathy-associated virus infections. MMWR 1986;35:334–339.

3 Ebbessen P, Biggar RJ, Melbye M: AIDS – A Basic Guide for Clinicians. Copenhagen, Munksgaards, 1984;p 234.

4 Goedert JJ, Biggar RJ, Winn DM: Determinants of retrovirus (HTLV III) antibody and immunodeficiency conditions in homosexual men. Lancet 1984;ii:711–716.

5 Redfield RR, Wright DC, Tramont EC: The Walter-Reed classification in the follow-up of HIV-infection. N Engl J Med 1986; 315:1355–1356.

6 Lane HC, Depper JM, Greene WC, et al: Quantitative analysis of immune function in patients with the acquired immunodeficiency syndrome. N Engl J Med 1985;313:79–84.

7 Pahwa S, Pahwa R, Good RA, et al: Stimulatory and inhibitory influences of human immunodeficiency virus on normal B lymphocytes. Proc Natl. Acad Sci USA 1986;83:9124–9128.

8 Reimer CB, Black CM, Holman RC, et al: Hypergammaglobulinemia associated with human immunodeficiency virus infection. Monogr Allergy 1988;23:83–96.

9 Yarchoan R, Redfield R, Broder S: Mechanisms of B cell activation in patients with acquired immunodeficiency syndrome and related disorders. J Clin Invest 1986;78:439–447.

10 Lane HC, Masur H, Edgar LC, et al: Abnormalities of B cell activation and immunoregulation in patients with the acquired immunodeficiency syndrome. N Engl J Med 1983;309:453–458.

11 Ochs HD, Junker AK, Collier AC, et al: Abnormal antibody responses in patients with persistent generalized lymphadenopathy. J Clin Immunol 1988;8:57–63.

12 Martinez AC, Marcos MAR, De La Hera A, et al: Immunological consequences of HIV infection: Advantage of being low responder casts doubts on vaccine development. Lancet 1988;i:454–457.

13 Bernstein LJ, Ochs HD, Wedgwood RJ, et al: Defective humoral immunity in pediatric acquired immune deficiency syndrome. J Pediatr 1985;107:352–357.

14 Calvelli TA, Rubinstein A: Intravenous gammaglobulin in infant acquired immunodeficiency syndrome. Pediatr Infect Dis 1986;5: S207–S210.

15 Gupta A, Novivk BE, Rubinstein A: Restoration of suppressor T cell functions in children with AIDS following intravenous gammaglobulin treatment. Am J Dis Child 1986;140:143–146.

16 Estreich S, Goh BT, Forster GE, et al: Bacterial infections on patients with human immunodeficiency virus infection (abstract No. 7087); in IV Int Conf on AIDS, Stockholm, June, 1988.

17 Krasinski K, Borkowski W, Bonk S, et al: Bacterial infections in human immunodeficiency virus-infected children. Pediatr Infect Dis 1988;7:323–328.

18 Rolston K, Radentz S, Rodriguez S, et al: Bacterial infections in AIDS patients (abstract No. 7083); in IV Int Conf on AIDS, Stockholm. June, 1988.

19 Schrager LK: Bacterial infections in AIDS patients. Aids 1988 2(suppl 1):S183–S189.

20 Krueger GRF: Infectious cofactors in HIV (HTLV-III/LAV)-positive individuals and their implication for cause and prognosis of acquired immune deficiency. AIDS-Forschung 1986;1:652–660.

21 Krueger GRF, Koch B, Ramon H, et al: Antibody prevalence to HBLV (human herpes virus 6, HHV6) and suggestive pathogenicity in the general population and in patients with immunodeficiency syndrome. J Virol Methods 1988;21:125–131.

22 Quinn TC, Piot P, McCormick JB, et al: Serologic and immunologic studies in patients with AIDS in North America and Africa JAMA 1987;257:2617–2621.

23 Rinaldo CR, Kingsley LA, Lyter DW, et al: Association of HTLV III with Epstein-Barr virus infection and abnormalities of T lymphocytes in homosexual men. J Infect Dis 1986;154:556–56

24 Sumaya CV, Boswell RN; Ench Y, et al: Enhanced serological an