Randomized Treatment Study of Inosiplex Versus Combined Inosiplex and Intraventricular Interferon- α in Subacute Sclerosing Panencephalitis (SSPE): International Multicenter Study

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J Child Neurol 2003 18: 819
DOI: 10.1177/088307380301801201

Original Article

Randomized Treatment Study of Inosiplex Versus Combined Inosiplex and Intraventricular Interferon-α in Subacute Sclerosing Panencephalitis (SSPE): International Multicenter Study

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ABSTRACT

The efficacy of oral inosiplex alone (group A) versus combined treatment of inosiplex (Isoprinosine) and intraventricular interferon-α2b (Intron A) (group B) in patients with subacute sclerosing panencephalitis (SSPE) was compared. One hundred and twenty-one patients who met the diagnostic criteria for subacute sclerosing panencephalitis and presented at stage 2 or less were randomized into group A or B. Data were analyzable on 67 patients who met the inclusion criteria and adhered to the protocol. The inosiplex dosage was 100 mg/kg/day to a maximum of 3 g/day, taken orally in three divided doses for 6 months. Interferon-α2b started with 100,000 U/m^2 and escalated to 1,000,000 U/m^2 over 5 inpatient days and then 1,000,000 U/m^2 twice a week for 6 months. Neurologic status was rated by the Neurological Disability Index, Brief Assessment Examination, and stages. Kaplan-Meier survival rates were not statistically significant between group A and group B (log-rank test $\chi^2 = .1374$, $P = .7109$). In longitudinal morbidity analyses, regression results were fitted to three outcome measures: the Neurological Disability Index, the Brief Assessment Examination, and stage. Group medians of the estimated regression slopes were then compared using the Wilcoxon rank-sum test. There was no statistically significant difference between the two groups on any of these three measures. Morbidity comparisons of clinical classification of outcomes (improvement, stabilization, worsening after treatment stopped, deterioration) also showed no statistically signficant difference between groups. There were no statistically significant differences between the two treatment groups on any efficacy measure. However, the observed rates of satisfactory outcome (stabilization, improvement) of 34% in group A and 35% in group B were higher than the spontaneous remission rates of 5 to 10% reported in the literature, suggesting that treatment was superior to no treatment. (*J Child Neurol* 2003;18:819–827).

Before 1985, many articles reviewed by Dyken[1] reported anecdotally the use of various antiviral or immunomodulatory agents to treat subacute sclerosing panencephalitis (SSPE). Haslam et al[2] and Robertson et al[3] reported con-

Received July 2, 2003. Accepted for publication July 25, 2003.

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Coinvestigators worked in South and Southeast Asia, the Middle East, and Eastern Europe, primarily with direction from Providence, RI; data tabulation and analysis were conducted in Riyadh, and additional analysis was done in Dublin.

Schering-Plough Corporation, New Jersey, supported the study by providing interferon-α2b and a travel grant for the principal investigator, and Newport Pharmaceuticals Ltd provided the inosiplex at cost.

Presented, in part, at the International Child Neurology Association meeting in Beijing, China, September 23, 2002.

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flicting results with amantadine. In the 1980s two large multicenter studies, one from the United States[4] and one from Japan,[5] showed, using actuarial analyses, that inosiplex (Isoprinosine) prolongs life compared with results in historical controls.

In the 1990s, two open-label studies using combined oral inosiplex and intraventricular interferon-α, one with 20 patients and human lymphoblastoid interferon-α[6] and the other with 18 patients and recombinant interferon-α,[7] resulted in arrest or improvement of 45 to 50% of patients during the follow-up periods reported. These results were significantly different from the reported spontaneous remission rates in historical controls (5%) and from a control group (10%).[6]

Panitch had suggested in 1988 that future therapeutic trials in subacute sclerosing panencephalitis follow these guidelines: statistically meaningful numbers of patients could be obtained only in treatment trials outside the United States because the disease was so rare there; virologic and immunologic studies should be incorporated, and treatment should be started early, in stage 1 or 2; recombinant interferons should be used because of their availability, cost, and safety; the intraventricular route using indwelling intraventricular catheters and subcutaneous reservoirs should be pursued because bacterial complications are acceptably low with a meticulous aseptic technique, and relatively low doses of interferon produce high cerebrospinal fluid concentrations with modest side effects.[8] A trial of combination therapy with inosiplex could determine whether partial responses with each agent would be additive and result in greater improvement and more sustained remissions. Protocols must be designed carefully and not be too simple or too complex. Success would depend on meticulous organization and international cooperation.

The International Consortium on Subacute Sclerosing Panencephalitis was formed in San Francisco in October 1994, the outcome of a satellite symposium during the joint meetings of the Child Neurology Society (CNS) and the International Child Neurology Association (ICNA). In addition to maintaining an international registry, the consortium's other express purpose was to conduct the kind of international multicenter treatment study advocated by Panitch[8] and others present at the symposium. We report the results of this study.

METHODS

Goal and Inclusion/Exclusion Criteria

The goal of the study was to determine the efficacy and toxicity of treatment with inosiplex alone versus combined oral inosiplex and intraventricular interferon-α in subacute sclerosing panencephalitis. The hypothesis, because of the literature on interferon-α in the late 1980s[8] and the open-label studies in the early 1990s,[6,7] was that the combined treatment group would do better against the standard drug, inosiplex. The inclusion criteria were that subjects must first meet the diagnostic criteria for subacute sclerosing panencephalitis (two major and one minor; Table 1) and must be in stage 2 or better. The stages used in this study have been previously published.[7] Exclusion criteria were stage 3 or 4, previous treatment with interferon-α in the preceding year, known contraindication to inosiplex or interferon-α, or inability to comply with the treatment regimen. A comparison group would be formed from patients who did not meet the inclusion criteria.

Table 1. Subacute Sclerosing Panencephalitis: Diagnostic Criteria

Major
Elevated CSF measles antibody titers
Typical or atypical clinical history
Typical: acute (rapidly) progressive, subacute progressive, chronic progressive, chronic remitting/relapsing
Atypical: seizures, prolonged stage I, unusual age (infancy, adulthood)
Minor
Typical EEG (periodic slow wave complexes)
CSF IgG increased
Brain biopsy: typical inflammatory pathology, extra-/intranuclear inclusions, neurofibrillary tangles
Special
Molecular diagnostic techniques to identify mutations of wild-type measles virus genome
The more atypical the case, the more criteria 5 and/or 6 are required.

CSF = cerebrospinal fluid; EEG = electroencephalography.

Randomization

Each collaborating site obtained Institutional Review Board (or its equivalent) approval, and subjects were enrolled after signing an informed consent form. Using a table of random numbers generated by the Moses-Oakford assignment algorithm, an allocation ratio of 1, and blocks of 8, subjects were randomized into either group A (inosiplex alone) or group B (combined therapy). Two strata were used: 1 = Middle East, Europe, and Africa and 2 = South Asia, Far East, and South America. The consortium felt that it was unethical to have a nontreated, or placebo, group because it has been standard practice, despite reservations, since the studies by the Dyken[1] (United States) and Fukuyama et al[5] (Japan) groups, to treat all patients with subacute sclerosing panencephalitis with inosiplex.

Clinical and Laboratory Monitoring

Neither subjects nor treating physicians were blinded for treatment conditions. However, clinical raters, who were not the treating physicians, were blinded. At the time of rating, all subjects wore some kind of head cover to hide whether or not they had an Ommaya device. The clinical variables monitored were the stage (rated by the physician), the Neurological Disability Index,[9] the Brief Assessment Examination,[10] or the Haceteppe version of the Brief Assessment Examination.[11] The main laboratory variable was the cerebrospinal fluid IgG synthesis index.[12]

Dosage Regimens

The dosage of inosiplex was 100 mg/kg/day orally in three divided doses, for 6 months, but no higher than 3 g daily, to avoid hyperuricemia and renal calculi. Interferon-α was given through an Ommaya or other similar device, with an initial escalating 5-day regimen. After 2 days' rest, the treatment was 1,000,000 U/m^2 twice a week for 6 months (Table 2).

Table 2. Intraventricular Interferon-α Dosing Regimen

Inosiplex = 100 mg/kg/day orally in 2–3 divided doses for 6 months.
Treatment regimen for intraventricular interferon-α given through an Ommaya or similar device
Day 1: 100,000 units/M^2
Day 2: 200,000 units/M^2
Day 3: 400,000 units/M^2
Day 4: 800,000 units/M^2
Day 5: 1,000,000 units/M^2
Next 2 days: no treatment, then 1,000,000 units/m^2 two times a week for 6 months

Table 3. Crossover and Escape Provisions

Treatment Group	*Relapse/ Treatment Failure*	*Provision*
A (Isoprinosine)	+	Add interferon-α (Crossover)
B (Combined)	+	Escape*

*If escape criteria are met, any medication could be tried at the discretion and experience of the coinvestigator.

Escape Provisions

Relapse was defined as the reappearance, during treatment or after treatment has stopped, of any previous neurologic symptoms or signs that had previously disappeared. Treatment failure was operationally defined as a downward change by one stage over a month or between monitoring visits, whichever is shorter, or worsening of the Neurological Disability Index by 30% over a month, or a change for the worse by 30 points between monitoring visits, while still being treated. Relapse or treatment failure effected withdrawal from primary efficacy data analysis and a crossover or an escape provision, in which coinvestigators were free to try other treatments (Table 3). The escape provisions applied when all groups failed combined treatment.

Follow-up

When subjects met the inclusion/exclusion criteria, names were electronically mailed or faxed to Providence, RI, where the principal investigator randomized them and informed coinvestigators likewise by electronic mail or fax. This information was also transmitted to the data manager at the Biostatistics, Epidemiology, and Scientific Computing Department of the King Faisal Specialist Hospital and Research Centre, Riyadh, where they were entered into a master database (*Excel*). Data flow sheets at baseline (demographic data) and periodic follow-up intervals (monitoring data), up to 2 years, were faxed to the study coordinator, who, after clarification, transmitted them to the data manager for tabulation. Site visits were conducted once during the 3-year period of data collection to ensure uniformity and compliance.

RESULTS

Randomization

From July 2, 1996, to October 30, 2000, 121 subjects were randomized to either group A (inosiplex) or group B (combined inosiplex and interferon-α2b). The number randomized to group A was 62 and to group B 59.

Demographic Data

Baseline data sheets were not received on all randomized patients. The age at presentation was 3 to 22 years. The median age was 8.5 years. There were 60 male patients (70%) and 26 female patients (30%). The age at which the patients were exposed to measles, in 70 subjects, was 3 months to 5 years (median 18 months). The age at which symptoms started ranged from 2 to 21 years (median 8 years). Clinical ratings on initial presentation were as follows:

- Stage (n = 80): 1A = 3, 1B = 17, 2A = 33, 2B = 27
- Neurological Disability Index (n = 80): range 5 to 75, median 21
- Brief Assessment Examination (n = 81): range 0 to 82, median 33

Efficacy Analysis

Efficacy was analyzed in three ways: (1) mortality rates between treatment groups were compared, (2) morbidity trends on the three clinical efficacy variables (staging, Neurological Disability Index, Brief Assessment Examination) were analyzed and compared by treatment group, and (3) overall clinical classifications of outcome were compared by treatment group.

Mortality Rates Between Treatment Groups

Standard survival analyses were performed based on time from initial therapy to death (or last follow-up), with censoring included, using the Kaplan-Meier method. There was significant censoring from each initial treatment group because of the protocol provision for crossover or escape drugs in case of treatment failure. Of the original 121 cases randomized, a total of 35 were excluded because of failure to turn in data flow sheets. Another 19 were disqualified for protocol noncompliance. That left an n of 67 for survival analysis: 39 in group A and 28 in group B. Survival analyses focused only on those patients still assigned to the original treatment group at the time of death.

Eight patients from group 1 died and 4 from group 2 died. Table 4 compares survival rates using the log-rank test of difference and showed no statistically significant difference. Figure 1 shows the Kaplan-Meier survival function by treatment group. Although survival rates were slightly lower for the inosiplex group, this difference was not statistically significant. The circles on each line depict censoring (when subjects were removed from a group for reasons other than death).

Survival analysis could be carried out statistically only for the first 6 months because that was the period in which there were sufficient numbers in group A and group B still in the original treatment groups. When followed after 6 months until the last follow-up, a total of 18 from both groups had died. Another additional 20 patients were lost to follow-up by October 30, 2000, 4 3/12 years after accepting subjects for randomization. In other words, in long-term follow-up, 38 of 67 patients, or 57%, had either died or were lost to follow-up.

Table 4. Survival Rate Comparison by Treatment Group

Category	N	Observed Deaths	Censored	Percent Censored
Inosiplex	39	8	31	79.49
Inosiplex + interferon-α	28	4	24	85.71
Total	67	12	55	82.09
Log-rank test of difference				
χ^2	.1374			
P value	.7109			

Morbidity Analysis: Comparison of Morbidity Profiles

The Brief Assessment Examination, the Neurological Disability Index, and stage were measured for each subject at weeks 0, 3, 6, 12, 18, 24, 32, 40, 52, and 104. The original protocol stated that the morbidity profiles on these measures were to be assessed over time and compared between groups. However, this longitudinal analysis posed a measurement problem because all patients were missing data for some of the follow-up weeks. Therefore, a regression framework was used to analyze morbidity trends for each subject, and the average effects were then compared between groups.

For each of the outcome measures (Brief Assessment Examination, Neurological Disability Index, and stage), a regression line was fit through each patient's recorded data where the response variable was the outcome measure and the independent variable was the week of follow-up. The slope coefficient resulting for each subject was then used as an indicator of that subject's morbidity trend and used in the Wilcoxon rank-sum test looking for statistically significant differences in trends between treatment groups. All *P* values were the two-sided normal approximation of the Wilcoxon test statistic, in which normality includes a continuity correction of 0.50. The results are depicted in Table 5. For each measure, slopes were estimated for 39 patients in group 1 and 26 patients in group 2. In each case, theWilcoxon rank-sum statistic was nonsignificant.

Morbidity Analysis: Morbidity Outcomes by Classification

For each subject, stage, Neurological Disability Index, and Brief Assessment Examination scores were plotted against time. Curves were visually inspected by the primary investigator and the statistician, and four kinds of curves emerged: curves that depicted improvement, arrest or stabilization of the disease course, steady worsening, or worsening after treatment stopped. The curves of each of the 67 subjects were then classified according to these four curves.

The results are displayed in Table 6. The Jonckheere-Terpstra *P* value of .3310 indicates no statistically significant difference between groups A and B. The Pearson χ^2 test of independence for the entire table, including the insufficient data category, with a χ^2 *P* value of .54, indicates no significant difference in outcomes between treatment groups.

Satisfactory Outcomes by Treatment Group

If those who had improvement or stabilization curves are classified as a "satisfactory outcome," the result is a 35% satisfactory outcome in group A and a 34% satisfactory outcome in group B, showing no significant difference (Table 7).

Crossovers

Of the 67 patients analyzed, 6 started off in group A but then were judged to be worsening; therefore, intraventricular interferon-α2b was added to the inosiplex they were already taking. In effect, they became group B subjects, to whom

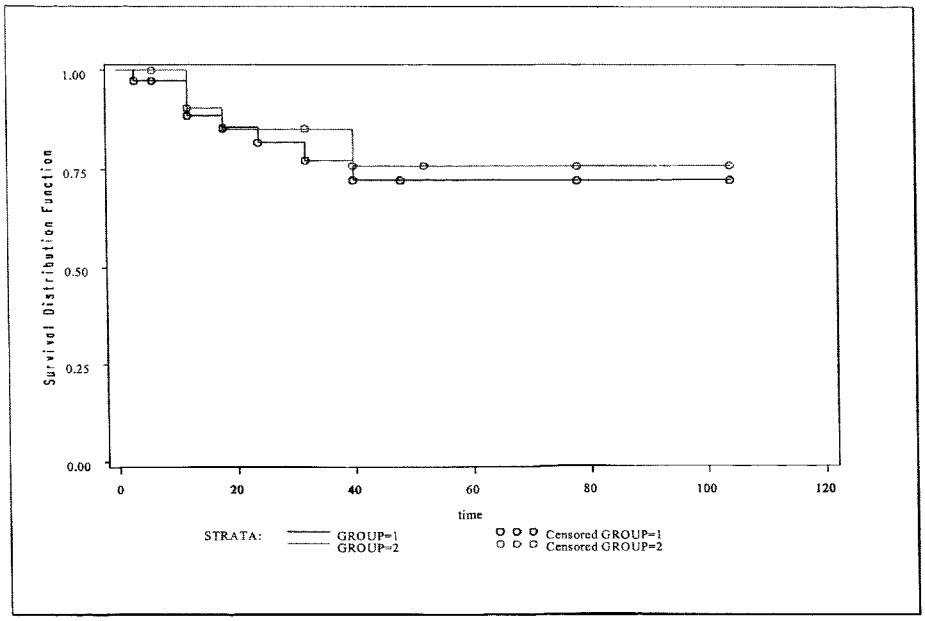

Figure 1. Kaplan-Meier survival function by treatment group. Group 1 = inosiplex; Group 2 = inosiplex plus interferon-α2b.

Table 5. Morbidity Trend Comparisons by Group

Measure Group	*Minimum*	*Maximum*	*Median*	*Quartile*	
				25th	*75th*
Neurological Disability Index*					
Group 1	−0.1057	5.1619	0.3333	0.0000	1.7783
Group 2	−1.833	6.0000	0.3420	0.0000	1.0000
Brief Assessment Examination†					
Group 1	−0.6667	3.0128	0.0708	0.0000	0.6667
Group 2	−2.6667	10.3333	0.0140	0.0000	0.8333
Stage‡					
Group 1	−0.1667	0.3333	0.0095	0.0000	**0.1000**
Group 2	−0.1667	0.6667	0.0000	0.0000	0.0833

*Wilcoxon rank-sum statistic = 810.50, $P = .5230$; †Wilcoxon rank-sum statistic = 878.00, $P = .7894$; ‡Wilcoxon rank-sum statistic = 824.50, $P = .6398$.

we refer as crossovers. The results are not statistically analyzable and therefore are presented as a table (Table 8).

Escape Drugs

Fifteen patients, who on combination therapy were judged to be worsening, went on to the escape provision. The drugs used were natural interferon, interferon-β, prednisolone, intravenous IgG, methylprednisolone, and amantadine. The results are listed in Table 9.

Cerebrospinal Fluid IgG Synthesis Index

Fifteen subjects had baseline indices determined, but only four had follow-ups (one each). See Table 10 for the results.

Adverse Effects

Twelve patients had hyperpyrexia, an expected adverse effect of intraventricular interferon-α, but four others had hyperpyrexia concomitant with other medications. One had encephalopathy on methylprednisolone, and in another, myoclonic spasms worsened on amantadine and prednisolone (Table 11).

Complications

Seven subjects experienced complications. These consisted of central nervous system infections in three, non–central nervous system infections in two, and intraventricular catheter obstruction in two. Table 12 lists the outcomes of subjects with these complications.

Table 6. Morbidity Outcomes by Clinical Classification

Category	*Group A (Inosiplex)*	*Group B (Combined Treatment)*
Improvement	2	**2**
Stabilization	**10**	**6**
Worsening, after treatment stopped	6	1
Downhill (deterioration)	17	14
Insufficient data	**4**	5
Total	**39**	28

Jonckheere-Terpstra Test J = 430, asymptotic standard error (ASE) = 0.44, $P = .3310$; Pearson χ^2 P value = .54.

DISCUSSION

Mortality

Survival analysis was carried out only for the first 6 months, mainly because the characteristics of the study population had changed and the dropout of subjects suitable for primary analysis (group A versus group B) after that was so great and that no statistically valid analysis was possible. Dropout meant essentially being lost to follow-up. The characteristics of the population changed because of the crossover and escape provisions. That is, if a patient had been deemed worsening and was originally randomized to group A, intraventricular interferon-α2b was added, with no limitation on how long treatment would then continue. If a patient had been in group B and worsened, an escape drug was added, again with no limitation on the duration of treatment. So, once a crossover or an escape occurred, those subjects were ineligible for the primary survival analysis, which was to determine whether there was a better survival rate if the patient was treated with combined therapy versus single-drug therapy.

One probable reason for the lack of a statistically significant difference between the groups is that so few deaths occurred in each group in the first 6 months. The arbitrary limitation of treatment to only 6 months may have imposed an artificial barrier. A significant difference might have emerged if follow-up on those two treatment regimens was longer. The n of 39 in group A and 28 in group B may not have been large enough to detect a difference in a 6-month time frame, but these are the largest n's so far reported in clinical research on subacute sclerosing panencephalitis.

Unfortunately, 20 subjects (of 67) were lost to follow-up, for a dropout rate of roughly 30%. This is in addition to

Table 7. Satisfactory Outcomes by Treatment Group

Classification	*Group A, n (%)*	*Group B, n (%)*
Improvement	**2**	2
Stabilization	**10**	6
Satisfactory: Subtotal	12 (34)	8 (35)
Patients classified	35 (100)	23 (100)
Patients with insufficient data	4	5
Total	39	28

Table 8. Crossovers

Serial No.	Survival (wk plus)	NDI (+ or −)	BAE (+ or −)	Stage (+ or −)	Last Known Stage	Last Follow-Up (wk)
21	29	0	0	—	4	32
30	6	?	?	?	3B	30
33	16	0	0	0	3A	40
43	40	—	—	+	3A	52
50	72	+	0	+	2B	104
76	0*	?	?	?	2B	3

*Subject 76 died just as the crossover occurred.
BAE = Brief Assessment Examination; NDI = Neurological Disability Index.

the 54 subjects (of 121 originally randomized) who did not turn in data flow sheets or who were disqualified for protocol noncompliance—a huge number in what is considered to be a rare disease and which affected statistical analysis both for mortality and morbidity.

Future studies need to carefully design provisions for keeping the subjects originally randomized from dropping out. This would require much more funding support than we obtained. Although coinvestigators worked in referral centers with up-to-date equipment in large cities, in these developing countries, many families either were not covered by government or private health care insurance or were unable to afford to pay privately for medical care. Our study was not funded to cover the costs for laboratory investigations and follow-up that would have occurred in the course of caring for the disease anyway. Another consistent reason given by coinvestigators for dropout included long distance from the center, which incurred additional transportation and housing costs for families. Although the follow-up protocols were simplified early, when the above reasons for dropping out were becoming evident, to require less studies and fewer follow-up visits, the large number of dropouts kept occurring.

As noted previously, there was no significant difference in survival rate between groups A and B up to 6 months. So with the assumption that that rate would have held up through total follow-up and that the crossover and escape treatments did not make any significant difference in ultimate outcome, the total deaths known up to the last follow-up of patients were pooled. The total number of deaths in the 67 subjects was 18. If we subtract the 6 subjects who had died by 6 months, that left 12 further deaths after the original treatment conditions, for a total death rate of 18 of 67, or roughly 27%, in the whole subject population until the time of the last known follow-up, the longest follow-up being 2 years. Prior to 6 months, although the original treatment conditions obtained, the total death rate (pooled group A and group B) was 9% (8% deaths in group A, 10% in group B). This could merely mean that, as expected in actuarial analysis, the death rate would increase over time anyway. It is tempting to speculate, however, whether that 9% death rate would have held up if patients were open-endedly treated, with no arbitrary cutoff of 6 months, as in this study.

Morbidity and Efficacy

The different curves analyzed emerged from inductive inspection of the plots generated for each subject from baseline through last follow-up. They fell into four patterns, which we labeled improvement, stabilizaton, steady worsening, and worsening after treatment had stopped. Again, there was no significant difference between groups A and B in morbidity patterns or course of the disease.

Table 9. Escape Drugs

Drug	Serial No.	Course, Initial	Wk Begun	NDI (+ or −)	BAE (+ or −)F	Stage (+ or −)	Stage, Last	Last Follow-Up (wk)
Natural IFN	3	SA	7	0	0	+	3A	104
	6	SA	34	—	—	0	4	78
	11	SA	48	—	0	0	3A	104
IFN-β	4	SA	6	—	0	—	3B	104
	38	SA	18	—	?	—	4	24
	42	RP	12	0	0	—	3A	12*
Prednisolone	59	SA	12	?	?	?	4	18
IV IgG	7	RP	12	—	0	—	3B	104
	8	SP	18	+	0	0	3A	104
	36	SA	12	+	—	—	3B	104
Methylprednisolone	24	RP	3	0	0	0	3B	12
	25	SA	6	0	0	—	4	18
Amantadine	26	SP	6	+	+	+	1B	78
	27	SP	3†	0	0	—	3B	24
	62	SA	3	0	0	0	1B	24

*Subject 42 died shortly after his 12th week follow-up.
†Subject 27 was on amantadine after a blocked intraventricular catheter developed and had to stop intraventricular interferon-α.
BAE = Brief Assessment Examination; IFN = interferon; IV = intravenous; NDI = Neurological Disability Index; RP = rapidly progressive; SA = subacute; SP = slowly progressive.

Table 10. Cerebrospinal Fluid IgG Synthesis Index

Serial No./City	*Baseline/Group*	*Follow-up (wk)*	*Outcome*
29/Mumbai	37/A		Downhill
30/Mumbai	38/A		Downhill
31/Mumbai	94/A	55 (6th)	Worse after treatment stopped
54/Mumbai	57/A		Improvement
63/Mumbai	62/A		Downhill
23/Mumbai	34/B	21 (24th)	Downhill
25/Mumbai	48/B		Downhill
27/Mumbai	29/B		Downhill
35/Manila	1/B		Stabilized
36/Manila	5.3/B	14.6 (6th)	Downhill
37/Mumbai	75/B	82 (6th)	Downhill
47/Mumbai	2.8/B		Downhill
56/Mumbai	81/B		Stabilized
58/Mumbai	3.50/B		Stabilized
61/Mumbai	26/B		Stabilized

The curve, worsening after treatment, is worrisome in that it indicates that some of those who had stabilized or improved while on treatment relapsed after treatment, with no intervention making any difference. This is in keeping with anecdotal observations by clinicians experienced in treating subacute sclerosing panencephalitis that once relapse occurs after previously satisfactory results, it is difficult to effect remission, and that the paradigm for treatment, rather than that of remitting/relapsing diseases such as multiple sclerosis or chronic relapsing inflammatory polyneuropathy, for which intermittent therapy protocols are used, the acquired immune deficiency syndrome (AIDS) model, in which continuous combination therapy is administered indefinitely, may be more appropriate for subacute sclerosing panencephalitis. The implication for future studies is that once a satisfactory outcome is achieved, with whatever treatment, the design of the study permits indefinite time of treatment and/or incorporates a design that might provide guidelines as to how treatment can be safely tapered.

How effective is treatment? Certainly, 34% or 35% with satisfactory outcomes does not reach the kind of standard used in clinical epilepsy research for the efficacy of antiepilepsy drugs: a 50% decrease in seizures. But subacute sclerosing panencephalitis is a disease, like most cancers, that is generally regarded as relentlessly progressive and ultimately fatal, although large cancer clinical trials are demonstrating more and more exceptions. The best estimated spontaneous remission rate for subacute sclerosing panencephalitis in the literature in untreated cases is 10%. Is 3.5 times the best estimated spontaneous remission rate acceptable? Perhaps a contemporary way to look at this is to compare the spontaneous remission rates in AIDS (almost none) with the rates with present combination therapy using antiretroviral agents and protease inhibitors and to consider subacute sclerosing panencephalitis treatment to be so far suppressive but not necessarily curative, as in AIDS. Our data indicate that treatment is better than no treatment but did not demonstrate a clear superiority of one kind of treatment (inosiplex combined with intraventricular interferon-α2b) over another kind (inosiplex alone).

Other possible reasons for the discrepancy between earlier studies[6,7] and this study, other than the general observation that in randomized clinical trials, therapeutic efficacy generally turns out lower than in open-label studies, are as follows:

1. We used recombinant interferon-α, rather than natural human-derived interferon, as in Yalaz et al's study.[6]
2. The duration of treatment was shorter (6 months) than in both earlier studies.[6,7]
3. The general care and follow-up in the earlier studies[6,7] were possibly better overall because the subjects were followed in each institution by one dedicated team.
4. There were fewer complications in earlier studies; for example, tuberculosis contaminated the results in some centers in this study.
5. The pattern of presentation of subacute sclerosing panencephalitis is changing[13]; patients are presenting younger, at least in Turkey, where younger age was an unfavorable risk factor for response to treatment. The 1992 group of patients was older.[6]

Table 11. Adverse Effects

High fever, 12 (5 group A, 7 group B)
1 gammaglobulin
1 developed tuberculosis
1 unexplained
1 interferon-β
Encephalopathy, 1 (methylprednisolone)
Jerks worsened, 1 (amantadine, prednisolone)

Table 12. Complications

Total, 7 subjects
Infection, central nervous system
Meningitis, 2 (1 death, 1 3B at 40 wk)
Shunt infection, 1 (death at 32 wk)
Blocked reservoir, 2 (amantadine, 1B 78 wk, 3B at 24 wk)
Infection, other
Pneumonia, 1 (crossover 18 wk, death at 24 wk)
Tuberculosis, 1 (stage 4 at 78 wk)

Crossovers, Complications, and Escape Drugs

The number of patients involved here is so small that it is not statistically analyzable. However, in the crossovers, if one eliminates Serial No. 76, who died too soon after crossover, to determine if there was any effect of the crossover drug, only 1 of 5 (20%) of those who crossed over had a satisfactory result: the longest follow-up at 104 weeks (2 years) and a good stage (2B). However, none had died at last follow-up. Two subjects (40%) were at stage 3A at last follow-up, which is like that of a nonambulatory child with cerebral palsy who sits, may stand, and has some communication skills. These results mildly support and would not contraindicate a clinical therapeutic regimen in which if a patient worsens on a more benign therapeutic regimen, given inosiplex alone, he/she could benefit from a more aggressive addition (ie, surgical insertion of an Ommaya device and intraventricular interferon-α). This would have to be weighed against the risk of complications (see Table 10). The complication rate in our series was 7 of 67, or 10.4%, but was almost entirely related (5 of the 7) to the intraventricular route of administration.

In the escape drugs, if one looks at the longest follow-up, and therefore known survival (104 weeks—the limit of the study), two subjects (of three tried) were on natural (nonrecombinant) interferon-α, one (of three tried) was on interferon-β, and three (of three tried) were on intravenous IgG. These six were split evenly between stage 3A and stage 3B. If one looks at the criteria we have been using for satisfactory outcome (stage 2 or better), two of three patients tried on amantadine wound up at last follow-up at stage 1B, although follow-up was nowhere as long as the six mentioned in the previous paragraph. One should not conclude too much from such meager numbers; however, these results suggest that it might be worthwhile for future larger clinical trials to consider at least amantadine because two earlier noncontrolled studies[2,3] had shown conflicting results and perhaps natural interferon and intravenous IgG. Recent studies indicate that a number of new antiviral drugs could be included into clinical trials for subacute sclerosing panencephalitis treatment, particularly ribavarin and lamivudine,[14–17] although their mechanism of action against the altered measles virus is unclear.

Adverse Effects

The most common adverse effect was hyperpyrexia, but contrary to expectations, this occurred almost equally between groups A and B. It is well known that intraventricular interferon-α will have high fever as a side effect, which was the reason for incorporating a regimen of routine pre-/post-treatment with ibuprofen when intraventricular interferon-α was used. It turns out that, despite this regimen, 7 of 28 patients in group B (25%) developed febrile reactions. The other adverse effects may have been related to other escape drugs (see Table 9), although these would be hard to distinguish from worsening of the underlying disease itself. Interestingly, no neurotoxic effects of intraventricular interferon-α were reported, which usually present as what seems to be acute worsening of the disease (encephalopathy and spasms) within hours of a dose. This would seem to indicate that the dosages of interferon-α2b used in this study have a high safety margin. Whether higher dosages would be more effective, without risking more adverse effects, is a question that could be posed for future clinical trials.

Cerebrospinal Fluid IgG Synthesis Index

Unfortunately, only four patients had follow-up determinations. This was due primarily to cost and the difficulties in technical availability in the developing countries from which all our subjects came. Our hypotheses had been that the amount of IgG being produced in the central nervous system daily, as measured by this index, would increase if the patient worsened, reflecting increased disease activity, but would decrease if the patient improved and would reflect decreased disease activity. In the two patients who had a steadily downhill course (Serial No. 36 and 37), the index, in fact, increased. In the patient who improved (Serial No. 23), the index decreased. Serial No. 31 had a decrease when his index was determined at the sixth week of follow-up. He had stabilized because, ultimately, he was one of the seven patients who worsened when all treatment was stopped at 24 weeks (6 months). Even in this small number, the trends went the way of our hypothesis. Future treatment studies should routinely incorporate the Cerebrospinal Fluid IgG Synthesis Index as the most important laboratory variable to follow the efficacy of treatment and perhaps help confirm relapses.

Other Data

Cerebrospinal fluid measles antibody levels and absolute cerebrospinal fluid IgG levels had been shown in previous published studies and, from clinicians' experience, to have no direct relationship to improvement or worsening, so these were not incorporated for analysis in this study. Although neurovirologic study protocols (through the University of Leipzig) were originally included in the study protocol, no brain biopsies or postmortem specimens were ever obtained. A neuroimmunologic study protocol was also incorporated, but, primarily because of transportation and cost to the study laboratory on Staten Island, New York, no samples were sent. No abnormalities in routine complete blood counts or chemistries were related to study drugs. Brain magnetic resonance imaging and electroencephalography were done but are not being reported or analyzed in this report because these kinds of findings in SSPE are already well known in the literature.[18,19]

CONCLUSIONS

1. There were no statistically significant differences in mortality between the group treated with inosiplex alone (group A) versus the group treated with combined inosiplex and intraventricular interferon-α2b (group B).
2. Satisfactory outcomes, defined as those whose courses stabilized or improved with treatment, were higher than the spontaneous remission rates reported in the literature (5–10%), but there was no statistically significant dif-

ference between groups A (35%) and B (34%). Taken together, these two conclusions strongly suggest that treatment is better than no treatment, although no clear mandate emerges to choose combined therapy over single-drug therapy with inosiplex.

3. The occurrence of 7 subjects, 6 on inosiplex alone, of 67 who worsened after treatment was stopped at 6 months suggests that patients who have stabilized or improved should continue to be treated, probably indefinitely (as in patients with AIDS on combination therapy). There are no guidelines from this study as to how long treatment should continue or when it can safely be tapered.
4. No "escape drugs" emerged as strong alternatives because the numbers treated with each drug were so small. However, it may be worthwhile to include amantadine more systematically in future randomized clinical trials.
5. Adverse effects occurred in 14 of 67 subjects, with no difference between groups A and B, whereas in 2 of the 14, these occurred with escape drugs. Complications occurred in 7 of 67, primarily in group B, and were related to intraventricular administration and the subcutaneous reservoir.
6. The International Consortium on Subacute Sclerosing Panencephalitis has demonstrated that it is possible to organize a multicenter international clinical comparative trial in developing countries in which subacute sclerosing panencephalitis is still endemic and accumulate larger *n*'s than had previously been reported in the clinical subacute sclerosing panencephalitis research literature, thereby providing a model and an infrastructure to conduct future clinical trials. However, much funding is needed to support the cost of follow-up clinical and laboratory monitoring, and local clinical research coordinators are imperative for tabulating data according to protocols.
7. We would recommend that future clinical trials continue to investigate different combination treatments of immunomodulators and antiviral drugs, although at this writing, we know of no new antiviral drugs that specifically prevent or inhibit the pathogenic mechanisms of intracellular replication of the measles virus genome in subacute sclerosing panencephalitis, despite anecdotal reports using ribavarin and lamivudine.[14–17]

Acknowledgments

We thank Dr Rudolf Kwan, former director of Neurological Research at Schering-Plough Corporation, New Jersey, for critical comments on the design, provision of a travel grant for site visits, and supplying recombinant interferon-α2b (Intron A) free of cost for the study. We thank James O'Malley, Jean Dreyer, and Eva Turgonyi of Newport Pharmaceuticals, Dublin, Ireland, for provision of background information on inosiplex, critical comments during execution, supplying inosiplex at cost to participating investigators and hospitals, and help with data analysis. Finally, we appreciate greatly the support of Sultan Al Sedairy, PhD, executive director of the Research Centre, at King Faisal Specialist Hospital and Research Centre—Riyadh, for provision of the Biostatistics, Epidemiology, and Scientific Computing Department as the central data tabulation and analysis center.

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