

# Short-term Outcomes of the Use of Intraventricular Ribavirin in Filipino Patients with Subacute Sclerosing Panencephalitis

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## ABSTRACT

**Background.** Subacute sclerosing panencephalitis (SSPE) is a fatal neurodegenerative disease caused by prolonged persistent infection of the central nervous system with a measles virus mutant. Though various treatment modalities have been tried, there is no effective treatment to completely cure SSPE and new therapeutic strategies are needed.

**Objective.** This is a prospective uncontrolled observational open label trial to describe the short-term outcomes and safety of intraventricular ribavirin in combination with oral isoprinosine in Filipino SSPE patients.

**Methods.** Sixteen (16) unrelated SSPE patients between ages 3-26 years and in various clinical stages were included in this study. Demographic data were described. Intraventricular instillation of ribavirin (1-3 mg/kg/dose) through an Ommaya reservoir was given for a duration of 3-6 months in 13 patients. The duration of follow-up was 48 weeks. The clinical outcome was assessed before, during, and after treatment using the Neurological Disability Index (NDI), Brief Assessment Examination (BAE), and clinical staging using the Jabbour Classification. Adverse side effects from intraventricular ribavirin were enumerated.

**Results.** Six of 13 (46.15%) patients mostly in Stage III illness had clinical improvement showing decreasing NDI and BAE scores during treatment and the clinical improvement was maintained or improved further during the 48-week follow-up period. Clinical improvement manifested as improved mental alertness, decrease in spasticity and reduction of seizures. The clinical staging of those who improved remained stable during and after treatment was discontinued. Five (38.46%) patients in Stage II disease worsened and progressed to Stage III despite ribavirin therapy including 1 (7.6%) patient who died after the treatment phase due to pneumonia and brainstem failure. The clinical course of two (15.38%) patients remained unchanged. Minor adverse side effects of ribavirin included transient fever, rash, oral sores, seizure episodes, drowsiness, bladder retention and mild increase in transaminases. Ommaya reservoir infection was a serious adverse event in 5 (31.25%) patients.

**Conclusion.** There is still no definitive cure for SSPE. Although ribavirin may help alleviate some of the symptoms of SSPE and prolong life, it may not reverse or halt the progression of the disease. Long term follow-up of these patients and continuous use of intraventricular ribavirin will better clarify its role in modifying the fatal course of SSPE. The role of ribavirin in Stage I patients and a controlled clinical trial in Stage II SSPE needs further studies.

**Keywords:** subacute sclerosing panencephalitis, SSPE, ribavirin, measles virus, neurodegenerative

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## INTRODUCTION

Subacute sclerosing panencephalitis (SSPE) is a slowly progressive but invariably fatal central nervous system (CNS) complication of measles infection which develops in a proportion of children and young adults who have been persistently infected with measles virus several years after the primary infection. Although reported to be rare globally with a worldwide incidence of 0.5 cases/million population, in Asian countries like the Philippines, SSPE still occurs frequently compared to other areas in the world since the incidence of measles infection in the country remains high. In the Philippine General Hospital (PGH) SSPE Registry of Cases, 161 new patients were diagnosed from 1999-2008 averaging 14-21 cases per year.<sup>1</sup>

Only the eradication of measles can prevent the development of SSPE as shown by studies in developed countries. Currently, there is no definite medical treatment to eradicate SSPE. Oral isoprinosine have been used since the 1960's with variable reported efficacy rate.<sup>2,3</sup> The intraventricular use of alpha interferon had only a 35% efficacy rate in the international multicenter randomized controlled trial by Gascon and co-workers.<sup>4</sup> Other treatment modalities such as intravenous immunoglobulin and amantadine have been described in case reports but do not show convincing evidence for complete cure. New therapeutic strategies are therefore urgently needed.

The use of the antiviral agent ribavirin which inhibits the replication of the SSPE virus strains may offer an alternative management for Filipino SSPE patients. Since SSPE is invariably fatal and survivors live a chronic vegetative function if untreated, this research on treatment may provide improved quality of life among patients with SSPE.

The objective of this study is to describe the outcomes and safety of intraventricular antiviral drug ribavirin the treatment of SSPE among Filipino patients.

### Review of Literature

Ribavirin is a broad-spectrum antiviral drug with inhibitory activity against many RNA viruses, including the measles virus and SSPE virus strains. In 1989, Hosoya and co-workers tested the inhibitory effects of several antiviral compounds and identified ribavirin to have the best activity against measles virus in vitro and in experimental animals.<sup>5,6</sup> In 1994 Honda and co-workers started testing ribavirin intrathecally to infected SSPE hamsters and found that ribavirin prevented mortality.<sup>7</sup> Ishii measured the ribavirin concentration in hamster brains and found that when administered intracranially at a dosage of 10 mg/kg body weight per day for 10 days, the dosage resulted in 100% survival of hamsters infected with SSPE virus and at this dose the replication of SSPE virus in the brains was inhibited. The effective ribavirin concentration in the brains which corresponds to the concentration at which ribavirin completely inhibits the replication of

SSPE virus in vitro, estimated by high performance liquid chromatography (HPLC) and bioassay, was 50 micrograms/g or higher. The maximal tolerable ribavirin concentration for hamsters was calculated to be 150 micrograms/g with a toxicity level of 250 to 400 micrograms/g.<sup>8</sup>

Testing in human patients started in 2001 with Hosoya giving ribavirin intravenously.<sup>6</sup> Intraventricular instillation of ribavirin was subsequently tried and was found to be safe and more effective.<sup>9-11</sup> Ten (10) patients with SSPE were surveyed by Tomoda et al during the last 4 years from the viewpoint of clinical safety with the use of ribavirin therapy. Although effectiveness varied among cases, they were all treated safely with intraventricular ribavirin suggesting that treatment is safe and well-tolerated.<sup>12</sup>

Five patients with SSPE were treated with ribavirin by intraventricular administration by Hosoya's group.<sup>13</sup> Although there were transient side effects attributed to ribavirin, such as drowsiness, headache, lip and gingival swelling, and conjunctival hyperemia, he found that intraventricular ribavirin therapy was generally safe and well tolerated. In addition, as in the initial studies with hamsters, he studied the pharmacokinetics of ribavirin intrathecally. He found that the cerebrospinal fluid (CSF) ribavirin concentration decreased, as described by a monoexponential function, after a single intraventricular dose and there was inter-individual variability in the peak level and half-life. Clinical effectiveness (significant neurologic improvement and/or a significant decrease in titers of hemagglutination inhibition antibodies against measles virus in CSF) was observed for four of five patients. For these four patients, CSF ribavirin concentrations were maintained at a level at which SSPE virus replication was almost completely inhibited in vitro and in vivo, which was 50 micrograms/g, whereas the concentration was lower in the patient without clinical improvement. These results suggested that intraventricular administration of ribavirin is effective against SSPE if the CSF ribavirin concentration is maintained at a high level and the clinically effective dose was 4 mg/kg/day in most patients.

## METHODS

### Study subjects

Sixteen (16) unrelated patients between ages 3-26 years who satisfied two major and at least one minor criterion using Dyken's diagnostic criteria for SSPE were included in this study.<sup>14</sup> The patients were recruited from the 2000-2005 registry of clinically diagnosed SSPE cases at the PGH and newly diagnosed cases from 2006-2007. Included in the study were patients in clinical SSPE Stage II or better or assessed to be in Stage III due to severe motor dysfunction but have preserved eye contact and show response to verbal communication. Parental consent for the insertion of an external ventricular device (Ommaya reservoir) and intraventricular instillation of ribavirin was given. One adult

patient in Stage I illness additionally gave his assent to the procedure. All patients had been receiving Isoprinosine at 50-100 mg/kg/day since the diagnosis of SSPE was confirmed. The study was approved by the Ethics Committee of the University.

Concomitant use of anticonvulsants such as carbamazepine, oxcarbazepine, clonazepam, levetiracetam, phenobarbital, valproic acid or a combination of these drugs for control of myoclonic jerks and seizures was allowed. Other patients were on baclofen and biperiden for spasticity and rigidity.

The following demographic and baseline data were collected and described:

1. sex and current age of patient
2. age when patient contracted measles infection (years)
3. age at measles vaccination (years)
4. age of SSPE expression (years) – age when first symptoms appeared
5. duration of symptoms prior to diagnosis (months)
6. latency period (months) – age of first SSPE symptoms minus age of measles infection
7. duration of illness (months) – age at appearance of SSPE symptoms until inclusion age in study

### Methods of Ribavirin administration

An external ventricular device (Ommaya reservoir) was surgically inserted under general anesthesia by one neurosurgeon. Using the administration schedule of Tomoda and co-workers,<sup>12</sup> ribavirin (1-B-d-ribofuranosyl-1, 2, 4 triazole-3-carboxamide) was administered intraventricularly through the reservoir five days after the Ommaya reservoir insertion. The treatment course consisted of ribavirin given consecutively for 5 days followed by a drug free interval of nine days. The first course consisted of a starting dose of 1 mg/kg/dose given at a 12-hour interval. When adverse events were not encountered, ribavirin was increased to 2mg/kg/dose at a 12-hour interval for the second course of treatment. Measurements of CSF ribavirin concentration was measured by high performance liquid chromatography (HPLC) in the 2<sup>nd</sup>, 6<sup>th</sup>, and 12<sup>th</sup> hour of day 1 and day 5 of the second treatment course, the results of which were used as a basis for the subsequent doses given on the 3<sup>rd</sup> to 12<sup>th</sup> course. Recommendations of Hosoya and co-workers to increase the dose to 3 mg/kg/day for the next courses if ribavirin concentration of 150-200 ug/ml by the 2nd hour after ribavirin instillation was not reached and to adjust the time dosing to 8-hr intervals if the concentrations were less than 20 ug/ml by the 12th hour after drug instillation were followed.<sup>6</sup> The study consisted of at least 6 courses (3 months duration) and was extended to 12 courses (6 months duration) if the patients showed no clinical deterioration secondary to ribavirin treatment and if no significant untoward adverse events were noted. Patients who discontinued treatment before the 6<sup>th</sup> course were dropped from the study.

### Data analysis of Outcome Measurements:

The patients were observed during the 12 - 24 weeks of ribavirin treatment and were followed up for the next 48 weeks post treatment. Their clinical course was objectively monitored using the Brief Assessment Examination (BAE) by Nester,<sup>15</sup> Neurological Disability Index (NDI) score by Dyken,<sup>14</sup> and the SSPE clinical staging by Jabbour.<sup>16</sup>

At the end of the treatment phase, the clinical outcome of the patients was described as either 1) improved, 2) unchanged, or 3) worsened. Improvement was defined as more than 2% decrease in NDI scores, or more than 2 points decrease in BAE scores. Improvement was considered significant if there was more than 10% decrease in NDI scores or a change to an improved clinical stage.

For patients who improved with treatment, their clinical course was described as either 1) improved and stabilized or 2) improved but deteriorated after treatment was stopped. Stabilization was defined as no change or further decrease of NDI and BAE scores 48 weeks after the end of the treatment phase compared to pretreatment phase. An increase of more than 2% in NDI or more than 2 points in BAE during the last month of follow-up was considered as deterioration. Patients who did not complete the treatment for at least three months or had to be discontinued from treatment due to severe adverse effects were censored from the analysis. All observed adverse clinical events and laboratory derangements during the treatment phase were noted.

## RESULTS

### Demographic Data

Sixteen (16) patients, 9 females and 7 males, aged 3-26 years were enrolled in the study. Table 1 shows the demographic and clinical characteristics of the patients included.

Ten (62.50%) patients received measles vaccination, nine of whom were immunized at age 9 months and one patient at age one year. Of these 10 children, five had measles infection before their measles vaccination. The remaining five patients had measles infection at a later age (10 months - 36 months) despite measles vaccination. Thirteen (81.25%) patients had measles infection at age 12 months or younger.

The age of expression of SSPE symptoms was observed to be present in two peak periods. The first was noted at the preschool age (range 3-6 years) in 8 (50%) patients and the second peak was observed during the school age (range 8-13 years) in 7 (43.75%) patients. The study enrolled 1 (6.25%) adult patient, a 25-year-old male with duration of illness of 10 months. Thirteen (81.25%) were diagnosed within 3 months from onset of SSPE symptoms. The latency period, the duration in years from measles infection to manifestation of SSPE symptoms, ranged from 2-21 years ( $\pm$  7.8).

Six (37.5%) of the enrolled 16 patients have been previously diagnosed with SSPE prior to inclusion with 36-84 months duration of illness. Ten (62.5%) patients were

**Table 1.** Demographic characteristics of 3-26 year old patients with SSPE

ID #	Age (years) / Sex	Age of measles infection (years)	Age at measles vaccination (years)	Age of SSPE expression (years)	Duration of symptoms prior to diagnosis (months)	Latency period (years)	Duration of illness prior to ribavirin therapy (months)
1	7/M	7/12	9/12	6	<1	6	7
2	11/F	2	9/12	10	4	9	11
3	18/F	1	None	13	8	12	72
4	15/F	6/12	None	8	<1	7	84
5	10/M	6/12	None	8	2	8	11
6	3/M	10/12	9/12	3	2	2	2
7	15/F	11/12	9/12	12	1	11	36
8	17/M	6/12	None	6	30	6	84
9	11/F	8/12	None	4	1	4	84
10	18/F	7/12	1	11	1	10	84
11	5/F	4/12	9/12	4	1	4	6
12	5/F	4/12	9/12	5	1	5	3
13	6/M	8/12	9/12	6	1	5	3
14	25/M	3	9/12	25	<1	21	10
15	6/M	9/12	None	5	3	5	3
16	13/F	2	9/12	12	3	10	7

newly diagnosed with less than 12 months duration of illness and a mean of 6 months.

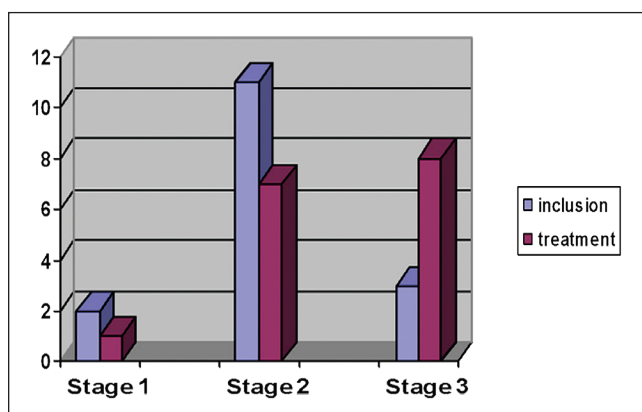
Using the Jabbour staging of illness, upon inclusion in the study, 2 (12.50%) patients were in Stage I, 11 (68.75%) in Stage II and the remaining 3 (18.75%) in Stage III. However, before initiation of ribavirin treatment, there was rapid progression of symptoms in 6 patients such that within one month, by the time of the first dose of ribavirin, only 1 (6.25%) patient remained at Stage I, 7 (43.75%) patients were in Stage II and 8 (50%) patients in Stage III (Figure 1).

At the end of the study period, the outcome of 13 (81.25%) patients who completed 3-6 months of ribavirin therapy was analyzed. Three (18.75%) patients were dropped from the study. Patient 6 had a deranged liver function test after the first course of treatment which persisted even with discontinuation of ribavirin and thus was postulated to be due to an underlying liver pathology. Due to the uncertainty of the hepatic function, further courses were deferred. Patient 10 had an Ommaya shunt infection after the 2<sup>nd</sup> course of treatment and did not consent to the insertion of a new reservoir to complete the treatment. Patient 16 did not return for treatment after the first course.

**Efficacy**

**Survival rate**

The survival rate is 93.75%. There was one mortality in this group (6.25%). Patient 4, a 15-year-old girl was diagnosed with SSPE at 8 years of age. The patient was in clinical Stage II when diagnosed but stabilized to Stage I for 5 years. A year before inclusion in the study, the patient started to deteriorate and was back to Stage II prior to the



**Figure 1.** Proportion of SSPE patients at different stages of illness at inclusion of study and at initiation of therapy.

start of ribavirin therapy. She completed 6 months of ribavirin therapy but died two months after completion of the trial due to pneumonia and brainstem failure.

**Clinical Outcomes**

Table 2 shows the NDI and BAE scores of the SSPE patients upon insertion of Ommaya reservoir prior to treatment, at initiation of treatment (T1), at the end of 3 months (T3) and 6 months (T6) of ribavirin therapy, and during the 48 weeks of the follow-up phase (M1-M12). Individual scores of these patients are plotted over time in Figures 2 and 3. Table 3 shows the clinical staging and final outcomes of the patient during and after treatment.

Out of 13 patients who completed at least 3 months of ribavirin treatment, based on clinical outcomes, a total

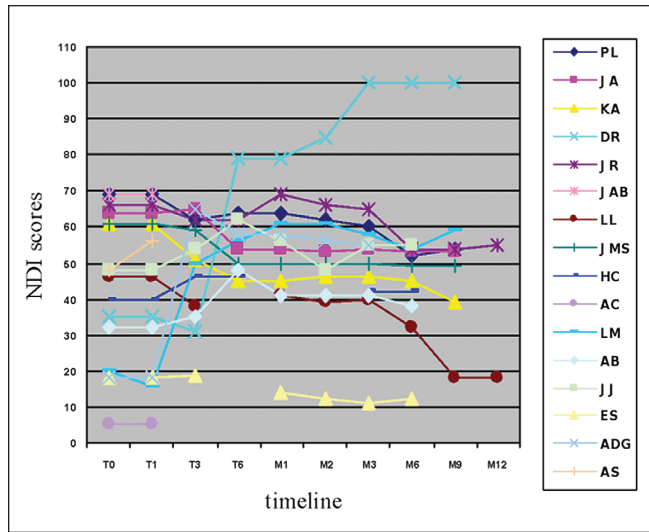


Figure 2. Change in NDI scores of SSPE patients over time.

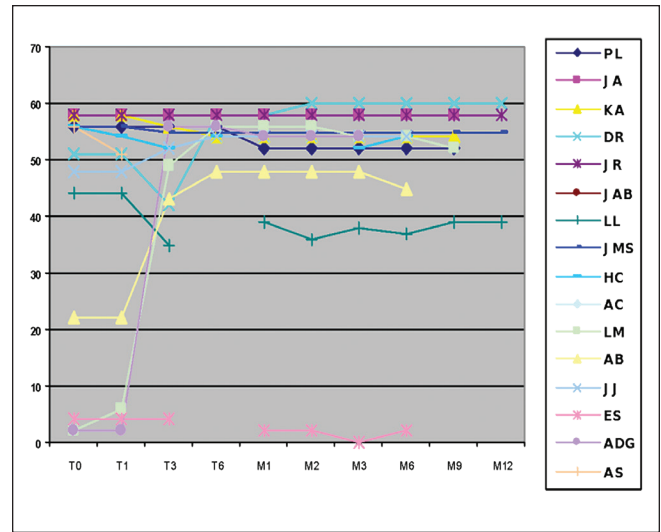


Figure 3. Change in BAE scores of SSPE patients over time.

Table 2. NDI and BAE scores before, during and after ribavirin treatment of 3-26 year old SSPE patients

Pt #	Pre Tx	Ribavirin Treatment Phase				Follow-up Phase					Comments (Change in NDI/BAE scores from T1)
	T0 NDI/BAE	T1 NDI/BAE	T3 NDI/BAE	T6 NDI/BAE	M1 NDI/BAE	M2 NDI/BAE	M3 NDI/BAE	M6 NDI/BAE	M9 NDI/BAE	M12 NDI/BAE	
1	69/56	69/56	62/56	64/56	64/52	62/52	59/52	52/52	54/52	52/52	Decr 17 NDI Decr 4 BAE
2	64/58	71/58	65/58	54/58	54/58	52/58	54/58	52/58	52/58	58/58	Decr 13 NDI No change in BAE
3	61/58	60/58	51/58	49/56	45/54	45/54	46/54	45/54	39/54	39/54	Decr 21 NDI Decr 4 BAE
4	35/51	34/51	31/42	56/58	79/58	85/60	Died	x	x	x	Incr in NDI/BAE before death
5	66/58	64/58	62/58	62/58	69/58	66/58	65/58	54/58	54/58	55/58	Decr 9 NDI No change in BAE
6	69/56	76/56	Dropped	Dropped	-	-	-	-	-	-	Dropped
7	46/44	39/44	38/35	Stopped	45/39	39/36	40/38	32/37	24/39	24/39	Decr 15 NDI Decr 5 BAE
8	58/56	51/56	51/55	50/55	50/55	50/55	50/55	49/55	49/55	49/55	Decr 2 NDI Decr 1 BAE
9	40/56	40/54	46/52	46/54	NA	NA	42/52	42/54	42/54	42/54	Incr 2 NDI No change in BAE
10	5/0	5/2	Dropped	Dropped	-	-	-	-	-	-	Dropped
11	16/6	54/47	50/47	58/56	64/56	61/56	58/54	54/54	59/52	54/50	No change in NDI Incr 3 BAE
12	31/22	28/22	35/43	41/48	42/48	42/48	42/48	40/45	42/45	40/45	Incr 12 NDI Incr 23 BAE
13	48/48	50/50	54/52	62/54	56/54	58/54	55/54	55/54	62/56	68/56	Incr 18 NDI Incr 6 BAE
14	16/4	21/4	19/4	Stopped	14/2	12/2	11/0	12/2	12/2	10/8	Decr 11 NDI Incr 4 BAE
15	18/2	24/4	65/56	58/56	58/56	56/56	56/56	56/56	58/56	-	Incr 24 NDI Incr 54 BAE
16	48/56	58/51	Dropped	-	-	-	-	-	-	-	Dropped

Decr-decreased; Incr-increased; NDI, Neurological Disability Index; BAE, Brief Assessment Exam; T0, at time of Ommaya insertion; T1, at start of treatment; T3 and T6, after 3<sup>rd</sup> and 6<sup>th</sup> month of treatment; M1-M12, monthly follow up after treatment

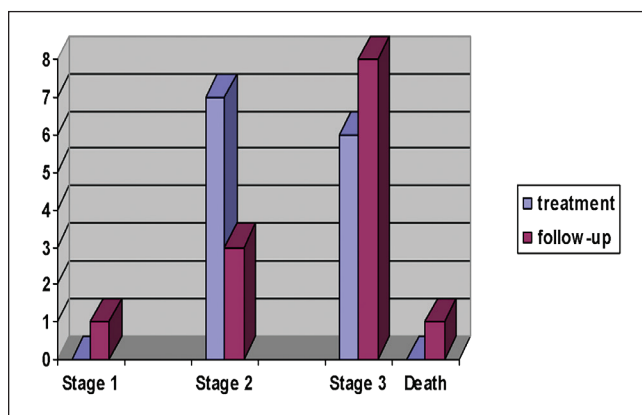
**Table 3.** Clinical Outcome of 3-26 year old SSPE patients based on change in NDI and SSPE Staging

Pt #	Pre- treatment phase		Ribavirin Treatment Phase			Follow-up Phase		Outcome
	Staging at inclusion to study	Staging before ribavirin treatment (0 week)	Staging after 3 months of treatment (12 <sup>th</sup> week)	Staging after 6 months of treatment (24 <sup>th</sup> week)	Staging on first 12 weeks of follow-up (36 <sup>th</sup> week)	Stage after 24 weeks of follow-up (48 <sup>th</sup> week)	Stage on final follow-up (72 <sup>nd</sup> week)	
1	IIA	IIIB	Improved / IIIB	Improved / IIIB	Stabilized / IIIA	Stabilized / IIIA	Stabilized / IIIA	Improved and stabilized
2	IIA	IIIB	Improved / IIIB	Improved / IIIA	Stabilized / IIIA	Stabilized / IIIA	Stabilized / IIIA	Improved and stabilized
3	IIIA	IIIA	Improved / IIIA	Improved / IIIA	Stabilized / IIIA	Stabilized / IIIA	Stabilized / IIIA	Improved and stabilized
4	IIB	IIB	Improved / IIB	Worsened / IIIA	Died	Died	Died	Worsened and died
5	IIB	IIIB	No change / IIIB	No change / IIIB	Stabilized / IIIB	Stabilized / IIIA	Stabilized / IIIA	No change and stabilized
6	IIIA	IIIB	IIIB	Dropped	Dropped	Dropped	Dropped	Dropped
7	IIB	IIB	Improved / IIB	Stopped at 14 weeks	Stabilized / IIB	Stabilized / IIA	Stabilized / IIA	Improved and stabilized
8	IIIA	IIIA	No change / IIIA	No change / IIIA	Stabilized / IIIA	Stabilized / IIIA	Stabilized / IIIA	No change and stabilized
9	IIB	IIB	Worsened / IIB	Worsened / IIB	Stabilized / IIB	Stabilized / IIB	Stabilized / IIB	Worsened
10	IB	IB	Dropped	Dropped	Dropped	Dropped	Dropped	Dropped
11	IIA	IIA	Worsened / IIB	Worsened / IIIA	IIIA	IIIA	IIIA	Worsened
12	IIA	IIA	Worsened / IIA	Worsened / IIB	IIB	IIB	IB	Worsened
13	IIB	IIB	IIIA	IIIA	IIIA	IIIA	IIIA	Worsened
14	IA	IIB	Improved / IIB	Stopped at 12 weeks	Stabilized / IB	Stabilized / IB	Stabilized / IB	Improved and stabilized
15	IIA	IIA	Worsened / IIIB	Worsened / IIIA	IIIA	IIIA	IIIA	Worsened
16	IIB	IIIA	Dropped	Dropped	Dropped	Dropped	Dropped	Dropped

of 6 patients (46.15%) experienced clinical improvement, 5 of whom showed significant improvement with more than 10% decrease in NDI scores. Three of these patients had simultaneous decreases in BAE scores (Table 2). The decrease in NDI scores was primarily due to resolution of myoclonic jerks and decreased spasticity. The decrease in BAE scores was due to improvement in the patient's level of alertness.

During the 48 weeks of follow-up after treatment, the clinical improvement based on NDI scores which was noted during treatment was maintained or improved further for most patients. However, the changes in these scores did not translate to improvement in clinical staging. These patients remained in their pre-treatment SSPE stage, 4 patients in Stage III and one patient each in Stage I and II. None of these patients deteriorated after discontinuation of ribavirin.

Two patients (15.38%) had no change in NDI and BAE scores and remained stable at Stage II. Five patients (38.46%) worsened showing increased NDI scores, 4 of whom had similar increases in BAE scores. These were the patients who were in Stage II prior to treatment but deteriorated to Stage III despite ribavirin therapy. Of these, one patient died two months after completion of therapy due to pneumonia and brainstem failure.



**Figure 4.** Proportion of 3-26 year old SSPE patients in the clinical stage before and after ribavirin therapy.

By the end of the study period the proportion of patients in the different SSPE stages are shown in Figure 4. Most of those in Stage II deteriorated to Stage III and those in Stage III remained in the same clinical stage but showed improved NDI and BAE scores.

## Adverse Events

Six (37.5%) patients experienced fever right after ribavirin instillation which was resolved with the use of paracetamol. Transient rash was experienced by 3 (18.75%) patients and 2 (12.5%) patients developed oral sores. Other complaints include headache and increased seizure episodes after ribavirin instillation (Patient 10), drowsiness and bladder retention (Patient 14). None of the patients developed anemia or azotemia, but increased hepatic transaminases were noted in 2 patients (12.5%).

Five (31.25%) patients developed Ommaya reservoir infection necessitating discontinuation of ribavirin treatment for 2 weeks and reinsertion of a new reservoir for the continuation of the trial.

## DISCUSSION

A study in Wales and England showed that 37 out of 47 (78.7%) patients died with a median of 2.7 years from onset of the disease to death.<sup>17</sup> In China, 6 out of their 10 (60%) patients died even with immunomodulators/antiviral drugs.<sup>18</sup> Canada and US studies also show same trend of fatality rates. In an Indian study of adult patients with SSPE, the patients generally have a more aggressive course with 6 out of 7 (86%) patients succumbed to the disease after 1 year, with a mean survival of 2 years.<sup>19</sup> Conversely, there was also a rapid progression in younger patients, as was seen in a Turkish study where the clinical profile of patients less than 4 years old was described.<sup>20</sup> They found that 3/5 patients followed up died after 1-5 months from admission, and the other 2 patients went to Stage IV from 6 months to 1 year after admission. In 2002 our epidemiological study reported a 9.5% mortality rate in our registry.<sup>1</sup> With a universally fatal disease like SSPE, ribavirin as an antiviral agent and immunomodulator may hold some promise in modifying the course of the disease and stabilizing the neurological status of SSPE patients.

Various published reports suggest that certain anti-viral drugs and immunomodulatory agents can prolong the life of SSPE patients if long term treatment is given.<sup>2-6,12</sup> Although spontaneous remission in SSPE has been reported in 5-10% of patients, stabilization in the disease progression and long-term survival is seen in those receiving treatment (whether inosiplex, interferon or ribavirin) compared to no treatment at all. The evaluation of the success of treatment is however complicated by the disease's extremely variable natural course. It is believed that SSPE patients with the slowly progressive course would respond to treatment better than those with the rapidly progressive course.

Our study included patients in all stages of the disease and with varying disease progression. It however appears that the chronic cases who were already in Stage III illness prior to ribavirin therapy still responded to ribavirin treatment showing improved NDI scores. The improved scores were however insufficient to improve clinical staging.

On the other hand, for the newly diagnosed cases who were initially enrolled in Stage II disease, they appear to be the rapidly progressive type of SSPE as they worsened to Stage III during treatment. It appears that for these types of patients, ribavirin did not halt the progression to a poorer stage.

Ommaya reservoir infection was a severe adverse event in our cohort. Although Ommaya reservoir is a highly effective implant for simplified administration of antimicrobials, antifungals, antineoplastic, and analgesic medications directly into the brain, a proportion of patients get Ommaya reservoir-related infections, varying from 5.5% to 8%.<sup>21,22</sup> In the retrospective study of Mead on the use on Ommaya reservoir for the intraventricular installation of antineoplastic drugs, Ommaya reservoir access and length of time the device was present for each patient (Ommaya days) were considered risk factors for infection. Despite ensuring aseptic techniques in our procedure, our high infection rate may be explained by the repeated access of the device for the delivery of the ribavirin and the long duration of Ommaya days as required by the protocol.

In previous studies, the most common non-serious and transient side effects of intraventricular administration of ribavirin include gingival/lip swelling (50%), sleepiness (40%), and headache (30%). There were no fatal toxic side effects. The non-serious side effects in our cohort included transient fever, rash, oral sores, and slight elevation of transaminases which were also transient.

## CONCLUSION

Intraventricular instillation of ribavirin (1-3 mg/kg/dose) for a duration of 3-6 months is an alternative therapeutic strategy for SSPE. Six of 13 (46.15%) patients had clinical improvement with ribavirin therapy showing alleviation of symptoms such as decreased spasticity, control of myoclonic spasms and improved level of alertness which was sustained up to 48 weeks post treatment. However, the clinical improvement was insufficient to change these patients' SSPE stage. In 5 of 13 patients (38.46%), ribavirin was not able to reverse or halt the progression of the disease. The clinical course of two patients (15.38%) remained unchanged. Long term follow-up of these patients and continued use of intraventricular ribavirin will better clarify the role of ribavirin in modifying the fatal course of SSPE. The role of ribavirin in Stage I patients and a controlled clinical trial in Stage II patients needs to be further elucidated in future studies.

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### Statement of Authorship

All authors contributed in the conceptualization of work, acquisition and analysis of data, drafting and revising and approved the final version submitted.

### Author Disclosure

All authors declared no conflicts of interest.

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