RIBAVIRIN TREATMENT IN MURINE AUTOIMMUNE DISEASE

I. Therapeutic Efficacy and Effect on the Immune Response

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NZB/W F_1 female mice were treated from 20 weeks of age with ribavirin (a broad spectrum antiviral drug), cyclophosphamide, or saline. Treatment with ribavirin (250 mg/kg twice weekly) prolonged survival from 9.8 to 18.5 months, reduced anti-DNA antibodies, and prevented proteinuria. Ability of ribavirin to prolong survival was dose related when given on a twice weekly schedule. However, daily ribavirin (25 mg/kg/day) was as effective as higher intermittent doses. Optimal ribavirin therapy was equal to cyclophosphamide treatment with regard to prolongation of survival. Ribavirin treatment did not significantly alter the body weight, hematocrit, WBC count, serum immunoglobulins, or Coombs reactivity. No alterations in either cellular or humoral immune responses were noted in NZB/W F_1 or BALB/c mice treated for prolonged periods with ribavirin. The impressive therapeutic response to a broad spectrum antiviral agent seen in mice already manifesting immune complex nephritis provides a new therapeutic approach to the treatment of autoimmunity.

New Zealand Black (NZB) and the New Zealand Black by White F_1 hybrid mice (NZB/W F_1) spontaneously develop an autoimmune syndrome similar to that of patients with systemic lupus erythematosus (SLE) (1,2). Female NZB/W mice predictably develop antinucleic acid antibodies, immune complex glomerulonephritis, proteinuria, uremia, and shortened life expectancy. Genetic factors, disordered immunologic regulation, and hormonal effects have all been implicated in the pathogenesis of clinical disease in these mice (3–5). Additionally, current evidence suggests a possible role for type C oncornaviruses in either the pathogenesis or the modulation of lupus in both mice and humans (6–13).

Recently, the effects of several antiviral drugs on the natural history of established NZB/W lupus nephritis have been reported (14). Ribavirin, a triazole ribonucleoside with known in vitro and in vivo antiviral activity against a wide range of RNA and DNA viruses (15–21), was effective in reducing anti-DNA antibodies and proteinuria and in prolonging survival. This study suggested that ribavirin might provide a new approach to the therapy of autoimmune mediated immune complex disease.

The present study expands our preliminary find-

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ings and confirms the clinical efficacy of ribavirin in murine lupus. The effects on survival, renal disease, and antinucleic acid antibodies at various drug doses are detailed. Daily administration of ribavirin or cyclophosphamide was compared with regard to both efficacy and toxicity. Finally, a study of immune responses after ribavirin treatment is presented.

MATERIALS AND METHODS

Animals. NZB/W female mice were obtained from NZB female × NZW male matings. Stock animal colonies of NZB, NZW, BALB/c, and Swiss mice were maintained at the National Institutes of Health. All mice studied were virgin females housed in the same area and allowed food and water ad libitum. Individual mice were identified by ear tagging.

Drug administration. Ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, Virazole®) was kindly supplied by ICN Pharmaceuticals, Irvine, California. The drug was dissolved in phosphate buffered saline (PBS) and injected intraperitoneally as indicated. Cyclophosphamide (Cytoxan®, Mead-Johnson, Evansville, Indiana) was dissolved in PBS and injected intraperitoneally within 1 hour of constitution. Control animals received PBS intraperitoneally. Four different ribavirin treatment schedules and one cyclophosphamide treatment were assigned randomly: ribavirin at doses of 250 mg/kg twice weekly, 150 mg/kg twice weekly, 50 mg/kg twice weekly, or 25 mg/kg 6 times weekly (daily); or cyclophosphamide at 12.5 mg/kg twice weekly. Treatment commenced when mice were 20 weeks of age (4.5 calendar months) and continued until death. All experimental groups for survival studies initially contained 29 to 36 animals. Additional mice were similarly treated for varying periods of time for evaluation of immune function.

Studies of natural history. Mice were examined during injections for gross clinical abnormalities. Survival was noted weekly and summarized monthly. All animals were weighed and their proteinuria was determined monthly by measuring the protein concentration of freshly expressed urine with tetrabromophenol paper (Albustix®, Ames Company, Elkart, Indiana). Animals were considered to have significant proteinuria if the urinary protein was greater than 100 mg/dl. Blood was periodically obtained from individual mice by retroorbital sinus puncture for microhematocrit determinations, WBC counts by Coulter counter, and sera for subsequent assays. At the time of median survival of one ribavirin treated group (250 mg/kg), 16 mice were randomly selected for gross pathologic examination. Histologic details will be reported elsewhere.

Measurement of antibodies to nucleic acids. Antibodies to native DNA (nDNA), primarily but not exclusively double-stranded, were measured in sera from individual mice by the modified Farr technique using ^{14}C-nDNA prepared from human cells as the ligand (22). Antibodies to single-stranded heat denatured DNA were similarly measured using the same ligand heated to 100°C for 10 minutes and then rapidly cooled. Antibodies to double-stranded RNA (dsRNA) were likewise determined using synthetic ^{14}C–poly I·poly C (Miles Laboratory, Elkhart, Indiana) as the ligand (22). Known positive and negative controls were included in each assay.

Serum immunoglobulin concentrations (mg/ml) were measured by radial immunodiffusion using commercially available immunoplates containing monospecific antisera to mouse immunoglobulins (Meloy Labs, Annandale, Virginia). Antierythrocyte antibodies were determined by the direct Coombs method (23) in one group of ribavirin treated mice at median survival.

Evaluation of immunologic status

Skin graft rejection. Skin allograft rejection was determined in 3-month-old NZB/W and BALB/c recipients receiving either 250 mg/kg ribavirin or saline twice weekly. After one month of treatment, full thickness primary skin grafts from C57Bl/6 mice were sutured onto the dorsum of 6 mice in each group as previously described (24). Grafts were inspected daily in a coded fashion and rejection was recorded when less than 10% of the graft was viable. Treatment with either ribavirin or saline was continued after grafting. Control syngeneic skin grafts underwent no rejection.

Mixed lymphocyte reaction. NZB/W mice were treated with 1) 250 mg/kg ribavirin twice weekly for 6 months, 2) 250 mg/kg ribavirin twice weekly for 3 months, 3) 25 mg/kg ribavirin daily for 3 months, or 4) saline. When the mice were 8 months of age, their spleen cells were stimulated by allogeneic irradiated C57Bl/6 spleen cells in a standard mixed lymphocyte reaction (MLR) as previously described (25). Cultures from each animal (4 to 6 mice per experimental group) were run in sextuplicate. Net stimulation (cpm) was defined as the difference between the average cpm in the mixed cultures minus the average cpm in cultures containing only responding or stimulating cells.

Graft versus host disease. Spleen cells from 8-month-old NZB/W mice that had been treated with either 250 mg/kg ribavirin or saline for 6 months were assayed for the ability to produce graft-versus-host (GVH) response by use of a modified Simonsen spleen weight assay (26). Five × 10^6 spleen cells were injected intraperitoneally into newborn Swiss mice and the spleen index of each experimental group was determined 9 days later by dividing the mean spleen-weight/body-weight ratio of the experimental group by that of Swiss littermates receiving media only. Spleens from donor animals were individually assayed, and each Swiss litter was divided into groups receiving ribavirin-treated spleen cells, saline-treated spleen cells, or media, and were identified by ear-tagging. A total of 128 newborn Swiss mice was studied.

Antibodies to synthetic double-stranded RNA. Three-month-old NZB/W and BALB/c mice treated with ribavirin 250 mg/kg twice weekly or saline were injected with 100 μg aqueous poly I·poly C intravenously. Six mice per treatment group were studied. Therapy was started 2 months prior to the immunizing dose of poly I·poly C and was continued until the final bleeding.

Antibody to SRBC. NZB/W and BALB/c mice (7 per group) received either ribavirin 250 mg/kg twice weekly or saline for 1 month prior to immunization with SRBC at 3 months of age. Additional NZB/W and BALB/c mice were treated for 5 months prior to immunization at 7 months of

age. Treatment was continued in all groups after the primary immunization with sheep erythrocytes (SRBC). Production of circulating hemagglutinins to SRBC was measured 6 days after the administration of 2×10^8 SRBC by the standard microtiter method using serial dilutions of sera, a 0.5% suspension of SRBC, and sheep anti-mouse Ig. In this assay the last well giving greater than 2+ agglutination was accepted as the titer of the serum.

The effect of ribavirin (250 mg/kg twice weekly or 25 mg/kg daily), cyclophosphamide (12.5 mg/kg twice weekly), or saline on the splenic plaque-forming cell (PFC) response of NZB/W mice to SRBC was determined by a standard Jerne plaque assay as detailed elsewhere (27). Treatment was started at 5 weeks of age and continued until sacrifice for the PFC assay. After 2.5 weeks of treatment the mice were immunized intravenously with 2×10^8 SRBC. Four to 5 mice per experimental group were killed at intervals after immunization, and the spleen cells assayed for both direct (IgM) and indirect (IgG) antibody production. Responses were expressed as $\log_{10}$ (PFC/spleen).

The effect of ribavirin on the primary in vitro PFC response to SRBC was determined by the method of Mosier et al (28). Primary in vitro PFC were generated in the presence of varying dilutions of ribavirin (moles/liter) and the number of PFC/culture well was determined on day 5. Cell cytotoxicity at each ribavirin concentration was determined by trypan blue exclusion.

Statistical analysis

Prolongation of survival was evaluated by Wilcoxon analysis at monthly intervals throughout the study period. Significant differences in proteinuria among treatment groups was determined by chi square analysis. Mean spontaneously produced antinucleic acid antibodies, body weights, hematocrits and WBC counts, GVH, allograft survival, and induced circulating antibodies to SRBC and poly I·poly C were compared by Student's *t*-test. Geometric means were calculated for MLR, serum immunoglobulins, and PFC/spleen; the log transformed (normalized) data were used to compare the different groups by Student's *t*-test.

RESULTS

Effect of ribavirin on survival and proteinuria. Mice treated with ribavirin, 250 mg/kg twice weekly, had a median survival of 18.5 months; in contrast, the median survival of control animals was only 9.8 months (Figure 1). Urinary protein excretion was also significantly ($P < 0.01$) lower in this ribavirin treated group from 7 months of age until the study ended (Figure 1). Interestingly, 34% of the 250 mg/kg treated mice developed proteinuria at age 7 months, but most individuals displayed a regression of their established proteinuria over the next 3 months. No increase in proteinuria was seen in this ribavirin treated group as it approached median survival.

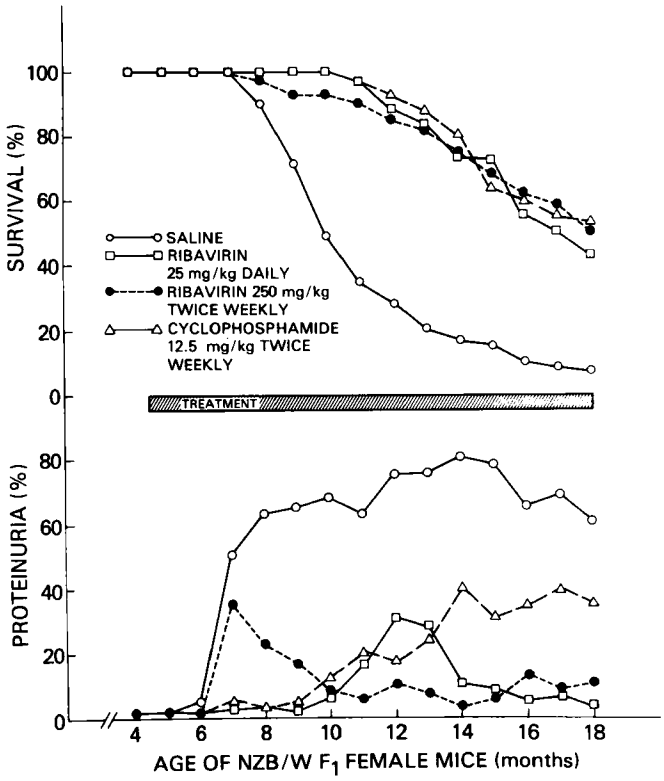

Figure 1. NZB/NZW female mice were treated with ribavirin or cyclophosphate or saline as indicated. Each group contained 30 to 70 mice. The percent of mice with proteinuria (100 mg/dl) at each point is indicated in the lower panel. Survival is shown in the upper panel. No significant differences in survival were noted among the nonsaline treatment groups.

When given at a dose of 25 mg/kg daily, ribavirin was an effective agent in prolonging survival and reducing proteinuria (Figure 1). At 14 months of age, 82% of the ribavirin-treated mice were alive compared with 19% of the saline control animals ($P < 0.01$). Likewise, the percentage of animals with proteinuria in the 25 mg/kg/day ribavirin treated group was significantly reduced ($P < 0.01$). When compared with cyclophosphamide, 12.5 mg/kg twice weekly, ribavirin given daily at the 25 mg/kg/day dose was as effective in prolonging survival and in preventing proteinuria (Figure 1).

Lower doses of twice weekly ribavirin were not as effective as 250 mg/kg in prolonging survival or preventing proteinuria. When 150 mg/kg twice weekly were used, the median survival was 15.5 months; when 50 mg/kg twice weekly of ribavirin were given, the median survival was only 13 months (Figure 2). However, survival in both of these ribavirin treated groups was

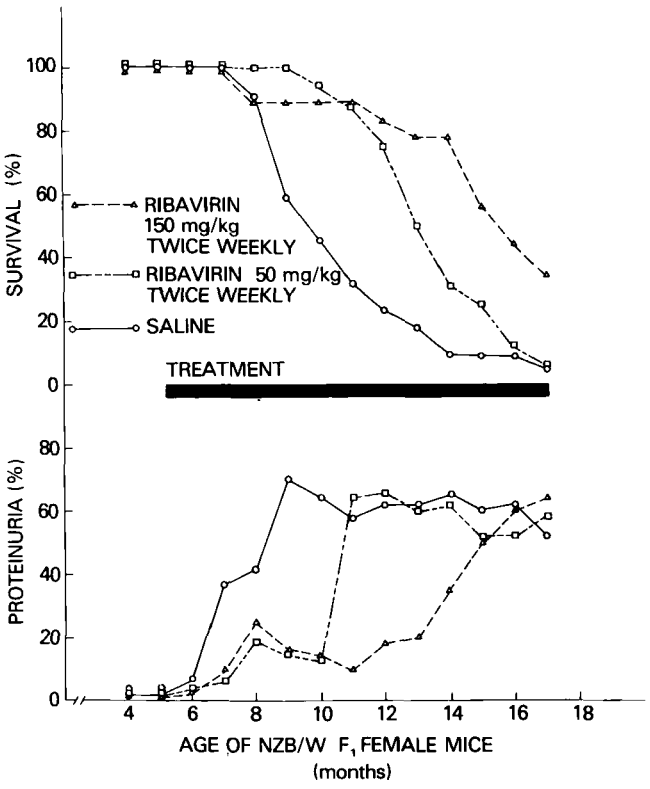

Figure 2. Effect of ribavirin (150 mg/kg or 50 mg/kg twice weekly) on survival and proteinuria (100 mg/dl) in female NZB/W mice treated from 20 weeks of age. Thirty-four animals per group.

significantly prolonged over that of control mice ($P < 0.01$). In addition, each ribavirin treated group had a significantly ($P < 0.05$) prolonged survival when compared with the next lower dosage group. The percent of mice with proteinuria in both the 150 mg/kg and 50 mg/kg twice weekly ribavirin groups sharply increased to control levels shortly before median survival was reached. It thus appears that ribavirin at 150 mg/kg and 50 mg/kg twice weekly delays but does not prevent the development of glomerulonephritis.

Effect of ribavirin on antinucleic acid antibodies. Antibodies to nDNA were already present in each experimental group prior to the institution of treatment (Table 1). Nonautoimmune strains of mice bind less than 20% of nDNA in our assay system. Therefore, the binding of about 40% of the nDNA indicates presence of active disease prior to drug treatment. At 7.5 and 11 months of age there was a significant decrease in anti-nDNA titer in mice treated with 250 mg/kg ribavirin twice weekly when compared with saline controls (Table 1). The reduction seen in the mean nDNA binding activity in the control group as they age is characteristic of the natural history of the mice (29). Ribavirin at 25 mg/kg daily was not as effective in reducing the titer of anti-DNA. The positive control, cyclophosphamide treatment, also resulted in reduced anti-DNA antibody titers, confirming previous observations (30). The reduction in antibodies to single-stranded DNA was similar to those found for native DNA (data not shown).

Spontaneously occurring antibodies to dsRNA, as measured by serum binding activity for poly I·poly C, were increased in both the high dose ribavirin treated and control groups from 4 to 7 months of age. Thereafter they remained elevated in the ribavirin treatment group while the control mice had a decrease in mean dsRNA binding ($P < 0.01$) (Figure 3).

Effect of ribavirin on body weight, hematocrit, WBC counts, and gross pathology. Figure 4 outlines the results of ribavirin therapy at both 250 mg/kg twice

Table 1. Effect of ribavirin or cyclophosphamide therapy on serum antibodies to nDNA in female NZB/W F_1 mice treated from 21 weeks of age

Treatment group	Serum DNA binding activity*				
	4.5 Months	7.5 Months	11 Months	14 Months	16 Months
Ribavirin 250 mg/kg twice weekly	39.8±3.2 (42)§	44.2±2.0† (42)	42.0±3.5‡ (26)	43.5±3.2 (10)	24.3±9 (20)
Ribavirin 25 mg/kg daily	44.6±4.9 (15)	55.2±3.5 (15)	ND	57.8±6.7 (15)	ND
Cyclophosphamide 12.5 mg/kg twice weekly	42.6±4.1 (15)	49.9±3.8‡ (15)	ND	51.1±6.4 (15)	ND
Saline	41.0±2.3 (47)	62.0±2.8 (47)	53.4±2.0 (13)	54.8±5.5 (6)	21.5±9 (4)

* Mean percent binding of ^{14}C-DNA by 25 μl serum (±SEM). Normal mouse sera bound less than 20% in all assays; 25% binding represents 2 SD above mean binding of normal mouse sera.
† $P < 0.01$ compared with saline control.
‡ $P < 0.05$ compared with saline control.
§ Number of animals per group in parentheses.
ND = not done.

weekly and 25 mg/kg daily on weight, hematocrit, and WBC counts. No significant weight loss is seen with ribavirin therapy from 4.5 to 10 months of age. At 12 months, the control group is heavier, probably because of increased fluid retention seen in mice dying of glomerulonephritis. Hematocrit determinations did not differ from control mice throughout the study period. WBC counts were initially determined 3 weeks after therapy had begun and revealed a decrease in the 25 mg/kg/day ribavirin-treated mice at that time only. After 9 months of age, 250 mg/kg ribavirin treatment was associated with a significant ($P < 0.01$) and consistent increase in WBC counts. No tumors were seen on gross pathologic examination after 14 months of ribavirin treatment. One of the 16 mice examined had a severe Coombs negative anemia, but the average hematocrit for the entire group was normal.

Effect of ribavirin on serum immunoglobulin levels and antierythrocyte antibodies. Serum levels of IgM, IgG1, IgG2a, IgG2b were determined before and 3, 7, 10, and 13 months after treatment with either saline or ribavirin 250 mg/kg twice weekly. No significant differences in serum immunoglobulin concentrations were found. (Data not shown.) At 18 months of age, the remaining animals in the 250 mg/kg twice weekly ribavirin group were tested for anti-RBC antibodies by the direct Coombs test. Four of 15 (27%) had detectable antierythrocyte antibodies, which is similar to results seen in untreated animals prior to median survival (2).

Effect of ribavirin and cyclophosphamide on immune responses. Ribavirin therapy given for prolonged periods to either NZB/W or BALB/c mice did not alter the animals' skin allograft rejection, mixed lymphocyte response, graft-versus-host response, or antibody response to SRBC or poly I·poly C (Table 2). When studied in an in vivo PFC system, ribavirin given at either 250 mg/kg twice weekly or 25 mg/kg daily did not alter the number of direct PFC (IgM producing cells), whereas cyclophosphamide did on days 5, 7, and 11 (Figure 5). However, when the numbers of indirect PFC (IgG producing cells) were quantified, ribavirin at 250 mg/kg twice weekly, ribavirin 25 mg/kg daily, and cyclophosphamide all caused a small but significant reduction in the number of IgG producing cells (Figure 6).

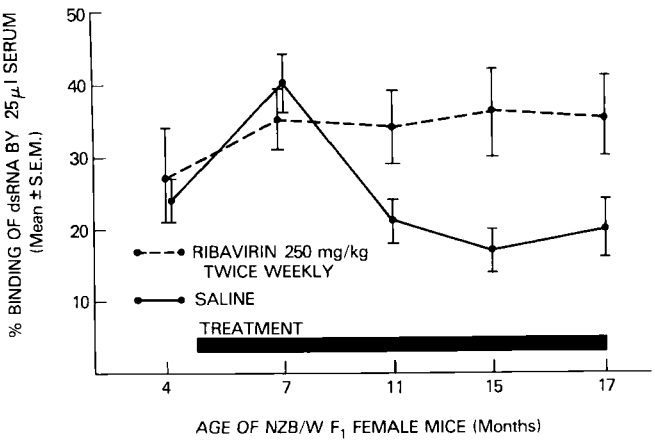

Figure 3. Effect of ribavirin (250 mg/kg twice weekly) on the titer of spontaneous anti-dsRNA antibodies in female NZB/W mice.

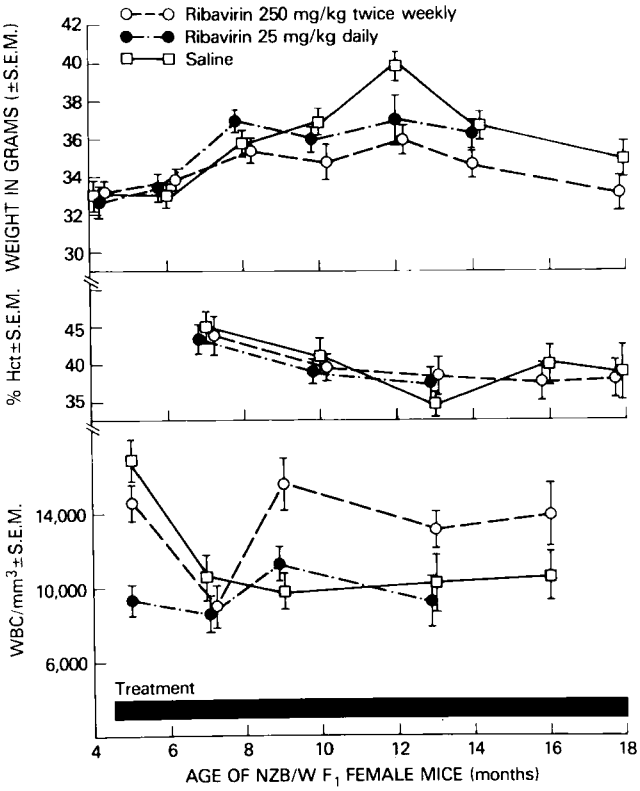

Figure 4. Effect of ribavirin (250 mg/kg twice weekly or 25 mg/kg daily) on WBC counts, body weight, and hematocrit in NZB/W female mice treated from 20 weeks of age.

When studied in vitro, ribavirin had no effect on either viability or direct PFC at concentrations of 10^{-7} or 10^{-6} moles/liter. At greater concentrations, there was a progressive decline in viability and a more abrupt fall in antibody forming cells (Figure 7).

DISCUSSION

The therapeutic efficacy of ribavirin in treatment of the spontaneous autoimmune disease of female

Table 2. Immune responses after ribavirin therapy

Immune function*	Mouse strain†	Age when assayed (months)	Length of prior treatment (months)	Ribavirin dose‡	Response indicator	Group mean ± SEM: Ribavirin treated	Group mean ± SEM: Saline control§
Skin	NZB/W	3	1	A	Mean graft	11.6 ± 0.7	10.2 ± 0.5§
allograft	BALB/c	3	1	A	survival (days)	10.6 ± 0.6	10.2 ± 0.8
rejection							
Mixed	NZB/W	8	6	A	CPM	16,850 ± 1700	15,960 ± 2230
lymphocyte	NZB/W	8	3	A		16,020 ± 1650	15,380 ± 1100
response	NZB/W	8	3	B		15,260 ± 1540	15,380 ± 1200
Antibody	NZB/W	3	1	A	Log_2 hemagglu-	7.2 ± 0.4	7.6 ± 0.7
response	BALB/c	3	1	A	tinin titer	7.0 ± 0.3	7.3 ± 0.2
to SRBC	NZB/W	7	5	A		6.3 ± 0.5	6.5 ± 0.8
	BALB/c	7	5	A		5.4 ± 0.4	5.6 ± 0.3
Graft versus	NZB/W	8	6	A	Spleen index	1.72	1.84
host				A			
Antibody	NZB/W	3	2	A	% Binding of	29.0 ± 2.3	34.1 ± 5.8
response to	BALB/c	3	2	A	poly I·poly C	29.8 ± 2.9	32.0 ± 3.3
aqueous poly I·poly C							

* Conditions of assay systems are detailed in methods section.
† Five to 7 treated mice per group.
‡ A = 250 mg/kg twice a week; B = 25 mg/kg daily.
§ Significant differences from control groups were not observed.

NZB/W mice has been tested. As the preliminary results indicated (14), ribavirin prolonged survival, decreased serum anti-DNA activity, and prevented proteinuria. The observed reduction in anti-nDNA antibodies with high-dose ribavirin therapy is consistent with other studies showing a correlation between drug-induced reduction in circulating anti-nDNA and increased survival (30–33). The ability of ribavirin to prolong survival was found to be dose related when the drug was given on a twice per week schedule. Daily ribavirin was as effective in prolonging survival as twice weekly administration at much lower cumulative dosages. For example, ribavirin was more effective when given at 25 mg/kg, 6 days per week (150 mg/kg/week) than when given at 150 mg/kg twice weekly (300 mg/kg/week). However, daily ribavirin did not lead to the major reduction in antibodies to DNA seen with 250 mg/kg twice weekly administration. This suggests that anti-DNA reduction is not the sole mechanism by which ribavirin suppresses NZB/W disease.

In these studies ribavirin might have prolonged survival in murine lupus nephritis by any of several possible mechanisms. Clear antiviral activity has been demonstrated by this drug against many DNA and RNA viruses, including documented in vitro activity against the murine leukemia virus (MuLV) of AKR mice, without apparent cytotoxicity to the mammalian cells (19). Other reports suggest that pharmacologic doses of ribavirin may have some direct anti-tumor (17) or immunosuppressive effects (34–36). The immunosuppressive ability of ribavirin in therapeutic doses is unclear. Huffman et al (37) failed to demonstrate significant immunosuppressive activity in amounts that were clearly antiviral in mice. The present studies failed to document any significant change in the cellular or humoral immune status of either NZB/W of BALB/c mice when treated for prolonged periods of time with therapeutically effective doses of ribavirin. The only abnormality noted in the most effective therapy group (250 mg/kg twice weekly) was a slight delay in reaching the peak IgG antibody response in the splenic PFC assay. One might speculate that this delay in IgG antibody synthesis is a factor in the reduction in glomerulonephritis by reducing the quantity of IgG anti-DNA antibodies without reducing IgM anti-DNA antibodies since IgG anti-DNA antibodies appear to be particularly associated with glomerulonephritis.

The immunologic studies reported in this article were performed on mice treated for varying periods of time and analyzed at different ages. This was necessitated by the known immune abnormalities of aging NZB/W mice (3). Longer treatment prior to analysis or study at an older age might demonstrate greater immune effects of ribavirin therapy in NZB/W mice. Nevertheless, studies on the nonautoimmune BALB/c mice suggest that there are no dramatic immunosuppressive

effects in the dosages used in NZB/W mice. Finally, it was noted that, in vitro, increasing concentrations of ribavirin were associated with both reduced cellular viability and reduced number of antibody forming cells. The results leave open the possibility that at a critical concentration of approximately 10^{-5} moles/liter ribavirin might have a preferential effect in reducing the number of antibody forming cells.

Elevated levels of anti-dsRNA antibodies were seen in the ribavirin treated group. It is possible that spontaneous production of anti-dsRNA in mammals may be caused by "immunization" with viral nucleic acid. Therefore, the elevated levels of anti-dsRNA found in association with ribavirin treatment cautions against assuming a reduction in virus activity in the treated NZB/W mouse. Detailed studies of the effect of ribavirin on viral expression in New Zealand mice and in tissue culture are in progress in collaboration with Dr. T. Pincus and may provide some insight into the mechanisms by which ribavirin favorably influences the expression of autoimmunity in NZB/W mice.

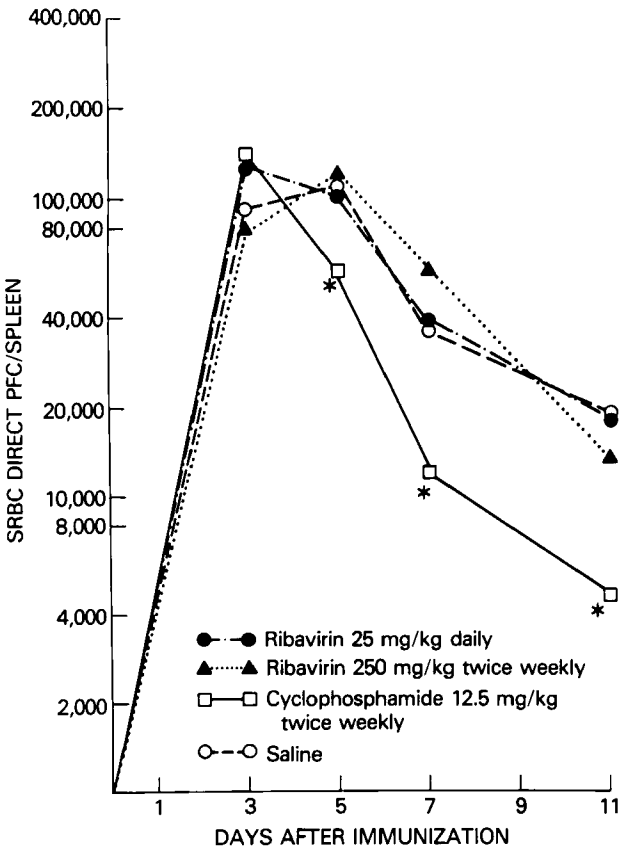

Figure 5. Effect of ribavirin (250 mg/kg twice weekly or 25 mg/kg daily) and cyclophosphamide (12.5 mg/kg twice weekly) on the splenic plaque-forming cell (PFC) response of NZB/W mice to SRBC after 2.5 weeks of drug treatment. Direct (IgM) plaques per spleen were determined at varying intervals after immunization. $*P < 0.05$ when compared to saline controls.

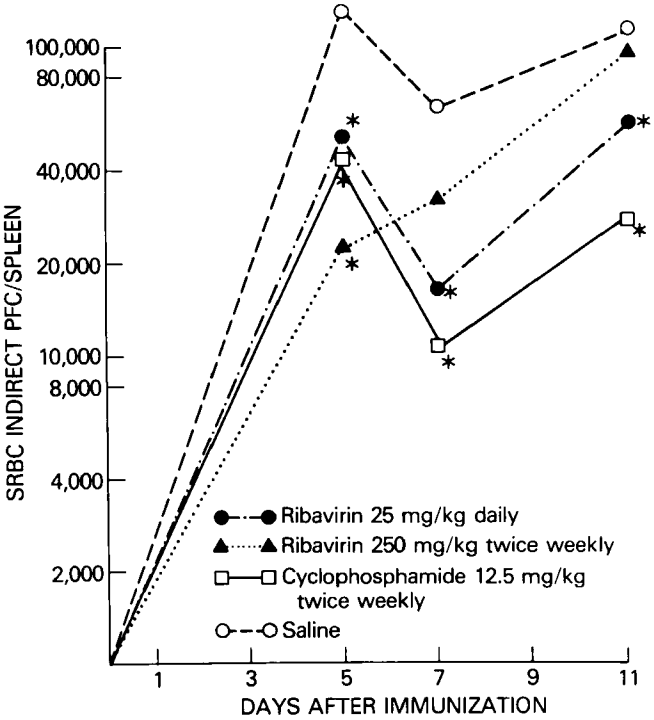

Figure 6. Effect of ribavirin (250 mg/kg twice weekly or 25 mg/kg daily) and cyclophosphamide (12.5 mg/kg twice weekly) on the splenic plaque-forming cell (PFC) response of NZB/W mice to SRBC after 2.5 weeks of drug treatment. Indirect (IgG) plaques per spleen were determined at varying intervals after immunization. $*P < 0.05$ when compared to saline controls.

No clinical evidence of drug toxicity was seen in these animals during the more than 12 months of ribavirin treatment. In particular, no significant decrease in weight or hematocrit was noted. The initial modest reduction in WBC counts seen in the 25 mg/kg group was not evident after the second month of therapy; in fact the highest drug dosage was associated with the highest WBC counts. The causes of death in the longest survival group (250 mg/kg twice weekly) have not been determined. Gross pathologic examination after 14 months of ribavirin treatment showed unremarkable results.

Many modes of therapy have been tried in murine lupus with varying success (3): immunosuppressive agents (30–33), L-asparaginase (38), dactinomycin (39), induction of immunologic tolerance to nucleic acids

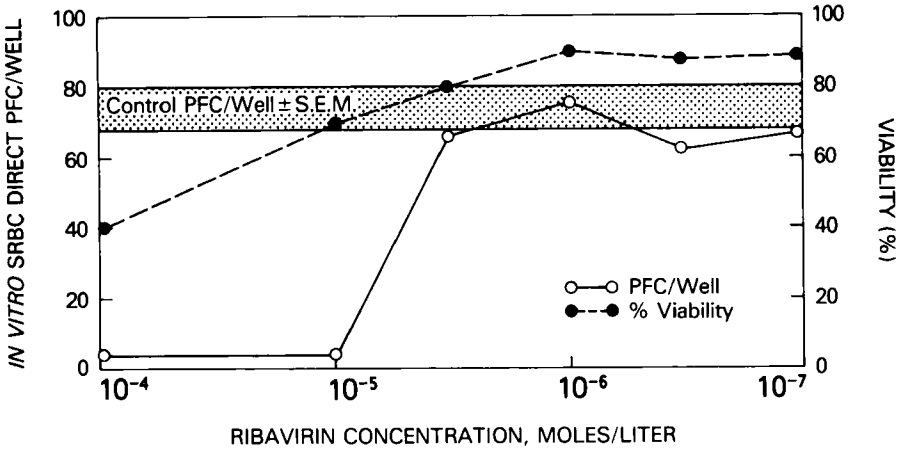

Figure 7. In vitro effect of ribavirin on the primary splenic plaque-forming cell (PFC) response to SRBC. Cell cytotoxicity for each ribavirin concentration is reported as percent variability of spleen cells after 5 days of culture.

(40–42), immunostimulation (43,44), diet (45), natural suppressor factors (46), and prostaglandins (47). Many studies have been prophylactic in nature; treatment was begun before any immunologic or clinical abnormalities became evident. The present trial of ribavirin was started in mice with elevated circulating anti-DNA levels, abnormalities in the immune system (4,5), and deposition of immune complexes in the kidneys (2). Thus, it is a trial of early treatment in diseased animals. No treatment regimen has produced a substantially longer survival time in female NZB/W mice than that seen with ribavirin.

Of the current methods now used to treat human Systemic lupus erythematosus, most have serious side effects that limit their usefulness (48,49). Despite the fact that the mechanism of action of ribavirin in the treatment of murine lupus is unknown, the minimal toxicity of the drug suggests that it may be a candidate for human studies. Although extrapolation from animal models to human disease should be done with extreme caution, the finding that ribavirin can significantly alter the natural history of murine lupus nephritis offers a new possibility for further investigations in human SLE.

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