

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Chan-Tack KM, Murray JS, Birnkrant DB. Use of ribavirin to treat influenza. *N Engl J Med* 2009;361:1713-4.

Table 1. Summary of Clinical Data from Double-blind, Randomized, Placebo-controlled Trials with Ribavirin and Influenza

Reference‡ (Publication Year)	Dose; timing of drug initiation	Duration (days)	Number of subjects in ribavirin arms	Outcomes (Clinical, Laboratory, Microbiologic, and Adverse Events)
Oral capsule formulation				
Challenge study				
Togo (1976)	600 mg/day (200 mg TID); Initiated 48 hours before viral inoculation	10	15 healthy adult volunteers (ages 19- 43) given intrasal influenza virus B/Georgia/26/74	1) No differences in clinical signs and symptoms of influenza between ribavirin and placebo groups. 2) Ribavirin recipients reported elevated bilirubin (n=2) and elevated AST (n=3). No laboratory abnormalities were reported in placebo recipients.
Cohen (1976)	600 mg/day (200 mg TID); Initiated 48 hours before viral inoculation	10	10 healthy adult volunteers (ages 21- 39) given intrasal influenza virus A/U Md/2/74 (H3N2)	1) Clinical signs and symptoms of influenza were reported in 9/10 ribavirin recipients versus 8/9 placebo recipients. 2) No significant differences in quantitative viral shedding.
Magnussen (1977)	1000 mg/day in 4 divided doses	5	14 healthy adult volunteers (ages 19- 30) given intrasal influenza virus A/Victoria/3/75 H3N2 (viral inoculation occurred 6 hours before dosing began)	1) Temperature >100°F reported in 2/14 ribavirin recipients versus 5/15 placebo recipients. 2) No significant difference in resolution of clinical signs and symptoms of influenza. 3) Mean duration of virus shedding was similar (ribavirin - 3.3 days; placebo- 3.5 days). 4) Lower viral titer/day in ribavirin group (1.64 versus 2.38 log ₁₀ TCID ₅₀ /ml) 5) Elevated bilirubin (1.4, 2.0, 2.0, 3.7 mg/dl) in 4 subjects who received ribavirin; bilirubin returned to normal when rechecked 4 weeks post drug discontinuation
Treatment of natural infection				
Salido- Rengell (1977)	300 mg/day (100 mg TID); Initiated as soon as patients had clinical symptoms	3	21 girls (ages 8-16); study occurred during influenza outbreak at a Mexico city boarding school	1) Severe clinical signs and symptoms of influenza were reported in 2/21 ribavirin recipients versus 16/24 placebo recipients. 2) Virus was isolated on from 3/21 ribavirin recipients versus 22/24 placebo recipients on Day 1 or 2 after

				beginning treatment. 3) Drowsiness was reported in two ribavirin recipients.
Smith (1980)	1000 mg/day in 4 divided doses; Initiated within 24-48 hours of clinical symptoms	5	49 previously healthy young adult* males with confirmed influenza A	1) Ribavirin recipients had 16 patient-days with temperature >101°F compared to 9 patient-days for placebo recipients. 2) No significant difference in resolution of clinical signs and symptoms of influenza. 3) No significant differences in quantitative viral shedding. 4) Bilirubin abnormalities (>1.2 mg/dl) were reported in 25% of ribavirin recipients compared to 7% of placebo recipients. 5) Reticulocytosis was reported in 51% of ribavirin recipients compared to 14% of placebo recipients.
Stein (1987)	Loading dose 3600 mg; maintenance dose 1200 mg every 12 hours; Initiated within 30 hours of clinical symptoms	7	15 previously healthy young adult* males with confirmed influenza	1) Clinical signs and symptoms of influenza were less in ribavirin recipients compared to placebo recipients. 2) Viral shedding was reduced in ribavirin recipients compared to placebo. 3) No difference in rate of viral clearance between groups. 4) Elevated bilirubin, decreased hemoglobin, and increased reticulocyte counts occurred in the ribavirin recipients.
Aerosolized formulation (Treatment of natural infection)				
Knight (1981)	Mean total dose: 1.15 grams given over 3 days; 8 hours each day	3	14 previously healthy college students* with confirmed influenza A	Ribavirin group showed reduction in magnitude and duration of fever, reduction in systemic illness, and disappearance of influenza virus from respiratory secretions.
McClung (1983)	Total dose: 2 grams given over 3 days	3	11 previously healthy college students* with confirmed influenza B	1) Ribavirin recipients had more rapid defervescence of fever, disappearance of systemic illness, and reduction of virus shedding in nasal secretions than ten control patients treated with a saline aerosol. 2) No laboratory abnormalities were reported.
Wilson (1984)	Total dose: 1.9 grams given over 3 days; Initiated within 24	3	8 previously healthy college students* with confirmed	1) Trend toward faster resolution of clinical signs and symptoms of influenza observed among ribavirin recipients at Day 2.

	hours of clinical symptoms		influenza A	2) No significant differences in quantitative viral shedding. 3) No laboratory abnormalities were reported.
Gilbert (1985)	Mean total dose: 2 ± 0.8 grams (range 0.7-5 grams) given over 3 days; Initiated within 24 hours of clinical symptoms	3	63 previously healthy college students* with confirmed influenza A or B	“More rapid reduction in duration and magnitude of fever (<100°F [$<37.8^{\circ}\text{C}$]), by the concentration of virus present in nasal secretions, and by systemic illness. Reductions in clinical severity in treated patients paralleled the decreases observed in fever and virus titer.”
Bernstein (1988)	Total dose 6 grams (given over 4 days, 12 hours each day); Initiated within 30 hours of clinical symptoms	3	10 previously healthy young adult males* with confirmed influenza B	1) No significant difference in resolution of clinical signs and symptoms of influenza. 2) No significant differences in quantitative viral shedding.
Rodriguez (1994)	Total dose 6 grams (given over 3 days, 18 hours each day); Initiated within 48 hours of clinical symptoms	3†	27 children (mean age: 11.9 months) hospitalized with confirmed influenza A or B	1) Time to reduction of temperature $<38.3^{\circ}\text{C}$ was 8.9 hours for the ribavirin group compared with 22.6 hours for the placebo group ($p = 0.04$). 2) There were no significant differences between the groups in outcome of respiratory rate, pulse rate, cough, or level of consciousness.

*Age 18 years or older (no additional data on ages were provided in the publication).

†Or until hospital discharge.

‡Full references available in the Supplementary Appendix.

Supplementary Appendix – References for Double-blind, Randomized, Placebo-controlled Trials with Ribavirin and Influenza

Oral capsule formulation

1. Togo Y, McCracken EA. Double-blind clinical assessment of ribavirin (virazole) in the prevention of induced infection with type B influenza virus. *J Infect Dis.* 1976; 133 Suppl:A109-13.
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3. Salido-Rengell F, Nasser-Quinones H, Briseno-Garcia B. Clinical evaluation of 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (ribavirin) in a double-blind study during an outbreak of influenza. *Ann N Y Acad Sci.* 1977; 284:272-7.
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5. Smith CB, Charette RP, Fox JP, Cooney MK, Hall CE. Lack of effect of oral ribavirin in naturally occurring influenza A virus (H1N1) infection. *J Infect Dis.* 1980; 141:548-54.
6. Stein DS, Creticos CM, Jackson GG, et al. Oral ribavirin treatment of influenza A and B. *Antimicrob Agents Chemother.* 1987; 31:1285-7.

Aerosolized formulation

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2. McClung HW, Knight V, Gilbert BE, Wilson SZ, Quarles JM, Divine GW. Ribavirin aerosol treatment of influenza B virus infection. *JAMA*. 1983; 249:2671-4.
3. Wilson SZ, Gilbert BE, Quarles JM, et al. Treatment of influenza A (H1N1) virus infection with ribavirin aerosol. *Antimicrob Agents Chemother*. 1984; 26:200-3.
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6. Rodriguez WJ, Hall CB, Welliver R, et al. Efficacy and safety of aerosolized ribavirin in young children hospitalized with influenza: a double-blind, multicenter, placebo-controlled trial. *J Pediatr*. 1994; 125:129-35.