Antiviral treatment of SARS: Can we draw any conclusions?

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Now that a novel coronavirus has been well established as the cause of severe acute respiratory syndrome (SARS),[1,2] it is important to evaluate what we have learned about the antiviral therapy of SARS. Is ribavirin effective? What other antiviral agents have been tried? What do we know about their efficacy and safety? What antiviral regimens should be applied if further outbreaks occur?

Because SARS was previously unknown and announced its arrival in a rather explosive fashion in multiple outbreaks around the world, it is understandable that there was no time to plan, let alone conduct, a prospective, multicentre, randomized clinical trial focusing on antiviral therapy or any other therapeutic approach to SARS. However, now that the disease has been contained, it is time to plan for such a trial should the disease recur this winter.

What can we learn from the more than 30 articles published internationally that mention antiviral treatment of SARS? I was able to locate 7 reports in which the clinical outcomes of ribavirin therapy in the treatment of SARS is described,[3–9] as well as 1 randomized clinical trial[10] (Table 1).

There are published reports in which combined therapy with ribavirin and steroids is considered to have had some benefit.[11] Tsang and associates[3] and Lee and colleagues[4] reported on the combined use of ribavirin and steroids and found that most patients showed clinical and radiologic improvement, although 2 of the 10 patients in the former report and 1 of the 138 patients in the latter died. On the other hand, Peiris and collaborators[5] pointed out that delayed initiation of ribavirin and steroid treatment was among the risk factors associated with severe complicated disease. Of 49 patients treated with combination therapy including ribavirin, only 1 patient died. Other reports demonstrate that, at least in some patients, severe hemolytic reactions occurred in conjunction with the administration of ribavirin and resolved with cessation of therapy.[8,9] The dosage of ribavirin was quite diverse (Table 1).

In the single randomized clinical study, Zhao and coworkers[10] randomly assigned 190 patients admitted to hospital Feb. 2–14, 2003, to 1 of 3 groups (groups A through C); 60 patients admitted after Feb. 14 were assigned to group D. All the patients were from Guangdong

Table 1: Experience with empirical treatment of SARS with ribavirin

Authors	No. of cases treated	Ribavirin dosages	Route of administration	Duration of treatment, d	Authors' evaluation
Avendano et al[9]	14	Loading dose of 2 g, then 1 g every 6 h for 4 d and then 500 mg every 8 h for 3 d	IV	5–10	Ribavirin may not have been effective and may have caused complications. Severe adverse effects attributed to the drug in 12 cases
Booth et al[6]	126	Loading dose of 2 g, then 1 g every 6 h for 4 d and 500 mg every 8 h for 3 d	IV	5–7	Significant toxicity attributed to ribavirin; effectiveness difficult to evaluate
Hsu et al[7]	14	20 mg/kg every 8 h	Oral	Not stated; in most cases ribavirin was started late in course of illness	No obvious effect observed; no comment on adverse effects
Lee et al[4]	138*	1.2 g every 8 h 400 mg every 8 h	Oral IV	Not stated	Most patients seemed to have some response to corticosteroid therapy in addition to ribavirin; no comment on adverse effects
Peiris et al[5]	49	8 mg/kg every 8 h	IV	7–10	Delayed use of ribavirin and steroid therapy associated with severe complicated disease
Tsang et al[3]	10	8 mg/kg every 8 h, or 1.2g every 8 h	IV Oral	2–8	Some improvement in most patients
Zhao et al[10]	40	400–600 mg/d	IV	10–14	No efficacy seen

Note: IV = intravenous.
*The total number of patients involved in this report was 138, but ribavirin was given (in combination with steroids) only to patients in whom fever persisted > 48 h and whose blood count showed leukopenia or thrombocytopenia, or both. Patients with persistent fever and worsening radiologic findings received the IV dosage. The exact number of patients treated with ribavirin was not mentioned.

province. There were 70 men and 120 women, ranging in age from 16 to 84 years (mean 28.6 ±10.3). The diagnosis of SARS was made according to clinical and radiologic criteria. The patients were treated in 2 hospitals, and the study was not blinded. Demographic characteristics and severity of disease were similar among the groups. Patients in group A (n = 40) were treated with ribavirin 400–600 mg /d plus antibiotics for 10–14 days; patients in group B (n = 30) were treated with intravenous antibiotics plus interferon alpha (3 million IU/d), without ribavirin. Group A and B patients received no steroids in the first 14 days of treatment; when used, the methylprednisolone dosage was 80–160 mg/d. Patients in group C (n = 60) were treated with intravenous antibiotics, plus methylprednisolone (80–160 mg/d) if symptoms worsened; some also received interferon-α. Patients in group D (n = 60) were treated with antibiotics and, in 45 cases, interferon-α. Patients who were still febrile after 3 days were given high-dose (160–1000 mg/d) methylprednisolone.

Interestingly, the best results were seen in group D. Time to defervescence, time needed for improvement of dyspnea, and time to marked absorption of chest X-ray opacities were significantly shorter in group D than in the other 3 groups ($p < 0.001$, while there were no significant differences among groups A, B and C with respect to these outcomes. The number of deaths among groups A through D was 2 (5.0%), 2 (6.7%), 7 (11.7%) and 0, respectively. No virologic monitoring methods were available at the time of the study. The authors concluded that ribavirin and interferon alpha were less effective than "the early and aggressive use of steroids combined with non-invasive ventilatory support."

Published results on the use of ribavirin in the treatment of SARS are controversial; the only randomized clinical study showed that the drug, given at a low dose (400–600 mg/d), was basically ineffective. The nonrandomized studies suggest that the combined treatments including ribavirin, given at quite different doses, might have been effective to some extent.

Most of the reports did not mention severe adverse events associated with the use of ribavirin. Booth and associates[6] observed that 76% of their patients had hemolysis, with hemoglobin levels declining by at least 2 g/dL in 49%, and that 18% of their patients had to discontinue treatment with ribavirin because of the adverse effects. Since no such serious adverse reaction was observed in the other reports listed in Table 1, the hemolysis reported by Booth and associates was probably associated with the relatively high dose (4 g/d). The limited data available suggest that doses of about 2 g/d might not cause severe adverse reactions and might be effective in the treatment of SARS. Therefore, such doses should be considered for further studies. Doses lower than 1 g/d might be ineffective.

What dosage regimens should be used if another outbreak of SARS occurs this winter? I believe that most physicians wish to see results of prospective, multicentre, randomized clinical studies, so that definite conclusions can be made on the efficacy and safety of ribavirin, interferon alpha and any other antiviral agents, as well as other therapeutic approaches, such as steroid therapy.

It is possible to conduct a well-designed, multicentre, randomized clinical study, even for a disease like SARS, as long as there is a ready-to-use study protocol, a consensus on the protocol, and a willingness on the part of regulators, caregivers and patients to facilitate such a trial. Such a study will have to be planned carefully and be capable of application almost anywhere in the world. The World Health Organization must take the lead in planning the study and assume leadership for its rapid implementation. An expert group should be formed now to consider the therapeutic strategies to be evaluated and to establish the necessary clinical and virologic monitoring. We should not emerge from the next SARS outbreak with as little information as gained from the first one.

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References

1. Ksiazek TG, Erdman D, Goldsmith CS, Zaki SR, Peret T, Emery S, et al. A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med* 2003; 348(20):1953-66.
2. Drosten C, Gunther S, Preiser W, van der Werf S, Brodt HR, Becker S, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med* 2003;348(20):1967-76.
3. Tsang KW, Ho PL, Ooi GC, Yee WK, Wang T, Chan-Yeung M, et al. A cluster of cases of severe acute respiratory syndrome in Hong Kong. *N Engl J Med* 2003;348(20):1977-85.
4. Lee N, Hui D, Wu A, Chan P, Cameron P, Joynt GM, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. *N Engl J Med* 2003;348(20):1986-94.
5. Peiris JSM, Lai ST, Poon LLM, Guan Y, Yam LYC, Lim W, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet* 2003;361:1319-25.
6. Booth CM, Matukas LM, Tomlinson GA, Rachlis AR, Rose DB, Dwosh HA, et al. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. *JAMA* 2003;289(21):2801-9.
7. Hsu LY, Lee CC, Green JA, Ang B, Paton NI, Lee L, et al. Severe acute respiratory syndrome (SARS) in Singapore: clinical features of index patient and initial contacts. *Emerg Infect Dis* 2003;9(6):713-7.
8. Dwosh HA, Long HHL, Austgarden D, Herman S, Schabas R. Identification and containment of an outbreak of SARS in a community hospital. *CMAJ* 2003;168(11):1415-20.
9. Avendano M, Derkach P, Swan S. Clinical course and management of SARS in health care workers in Toronto: a case series. *CMAJ* 2003;168(13):1649-60.
10. Zhao Z, Zhang F, Xu M, Huang K, Zhong W, Cai W, et al. Description and clinical treatment of an early outbreak of severe acute respiratory syndrome (SARS) in Guangzhou, PR China. *J Med Microbiol* 2003;52(8):715-20. Available: http://jmm.sgmjournals.org (accessed 2003 Oct 26).
11. Koren G, King S, Knowles S, Phillips E. Ribavirin in the treatment of SARS: a new trick for an old drug? *CMAJ* 2003;168:1289-92.

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