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Treatment of severe acute respiratory syndrome

Abstract The best treatment strategy for severe acute respiratory syndrome (SARS) is still unknown. Ribavirin and corticosteroids were used extensively during the SARS outbreak. Ribavirin has been criticized for its lack of efficacy. Corticosteroids are effective in lowering the fever and reversing changes in the chest radiograph but have the caveat of encouraging viral replication. The effectiveness of corticosteroids has only been suggested by uncontrolled observations, and the role of these agents in therapy remains to be established by randomized controlled studies. Both ribavirin and corticosteroids have very significant side effects. The lopinavir/ritonavir combination has been shown to reduce the intubation rate and the incidence of adverse clinical outcomes when used with ribavirin. When patients deteriorate clinically despite treatment with ribavirin and corticosteroids, rescue treatment with convalescent plasma and immunoglobulin may be beneficial. Noninvasive positive pressure ventilation is a sound treatment for SARS patients with respiratory failure if administered with due precaution in the correct environment. Interferons and other novel agents may hold promise as useful anti-SARS therapies in the future. The experience with traditional Chinese medicine is encouraging, and its use as an adjuvant should be further investigated.

Introduction

A global outbreak of severe acute respiratory syndrome (SARS) started in March 2003 and was caused by the SARS-associated coronavirus (SARS-CoV) [1–3]. The cumulative number of cases in 29 countries and regions up to 31 July 2003 was 8,096. The total number of deaths was 774, with a case–fatality ratio of 9.6% [4]. Owing to the lack of knowledge about this new and serious disease, different treatment modalities have been used empirically with much uncertainty. The overwhelming situation of large numbers of ill patients deteriorating rapidly prevented anxious physicians from performing randomized controlled treatment trials [5], which were regarded as dangerous and unethical in the face of a life-threatening condition.

Many treatment options, including antiviral agents, immunosuppressive agents, convalescent plasma, immunoglobulin, noninvasive positive pressure ventilation (NIPPV), and traditional Chinese medicine (TCM), have been introduced on the basis of different rationales. First, SARS has an initial viral replicative phase, which peaks at around day 10. Response to this viral load takes the form of inflammatory cell infiltration of tissues and overproduction of cytokines, resulting in immunopathological damage. Thus, there is a therapeutic window that can be exploited to prevent disease progression if a potent antiviral agent is available. Ribavirin has been chosen for use due to its wide spectrum of activity, despite being rather weak against SARS-CoV. Protease inhibitors are now under study because of the experimental evidence that they can inhibit the 3C-like (3CL) protease, which is essential for the life cycle of the SARS-CoV [6, 7]. Second, corticosteroids have been utilized to mitigate the tissue-damaging effects of inflammatory cells and cytokines and to treat the acute respiratory distress syndrome (ARDS) [8], bronchiolitis obliterans organizing pneumonia (BOOP) [9], and septic shock [10] that may occur. Third, convalescent plasma has been administered in the belief that the large amount of neutralizing antibodies present can block the action of the SARS-CoV. Fourth, immunoglobulin has been employed as a salvage therapy in patients with inexorable deterioration despite usual treatment. This approach is based on the immunomodulatory effect of immunoglobulin, which includes competitive occupation of macrophage receptors, neutralization of activated complements, cytokines and superantigens, and inhibition of activated T lymphocytes. Fifth, the application of NIPPV in SARS originates from its usefulness in the management of patients with chronic obstructive airways...
disease complicated by severe community-acquired pneumonia. Sixth, TCM has been used in China because of its known efficacy in the treatment of “fevers” throughout the ages. With the absence of a consensus on the optimal therapeutic strategy, various approaches have been devised elsewhere in the world.

**Antiviral agents**

Antiviral therapy was adopted at the start of the Hong Kong outbreak because SARS was considered to be a viral infection even before the identification of the SARS-CoV. Detection of the SARS-CoV in the early phase of the disease has been found to be a poor prognostic sign. In one retrospective case analysis, patients with a positive RT-PCR test in nasopharyngeal aspirate samples for SARS-CoV on admission, a mean of 4.3 days after the onset of illness, were more likely to have adverse outcomes in terms of survival, ICU care, and assisted ventilation when compared to patients with negative RT-PCR results [11]. A prospective study revealed that there is an initial viral replicative phase followed by an immunopathological phase and an end organ-damage phase [12]. It is hypothesized that the viral antigen triggers the immune response and that the best approach will be to halt the early viral replication so as to diminish the peak viral load and immunopathological damage. This will result in a lessened requirement for immunosuppressants, which may predispose patients to nosocomial infections, particularly those on mechanical ventilation.

Ribavirin was chosen for use empirically due to its broad antiviral spectrum [13] and the assumption that it could provide coverage for the corticosteroid treatment, which was widely utilized at that time. In the end, over 90% of the patients in Hong Kong received ribavirin. The mechanism of action of this nucleoside analogue has not been well established [14]. Ribavirin has attracted considerable criticism because of its relative lack of in vitro activity against the SARS-CoV [15–17]. Very high concentrations of ribavirin are needed to inhibit the virus transiently, and the levels are difficult to achieve clinically [18]. In a retrospective, uncontrolled cohort analysis, the use of ribavirin did not appear to confer any benefit to SARS patients [19]. Ribavirin is associated with a number of significant adverse effects. The most important one is anemia [12, 20, 21], with one study reporting a drop in hemoglobin of 2 g/dl or more in 49% of patients [20]. Anemia is related to hemolysis in most circumstances [16, 20, 22, 23]. Oxygen desaturation and tissue hypoxia are exacerbated by the reduced oxygen carriage capacity of low hemoglobin. Other important side effects include bradycardia (14% of patients) [20], raised serum transaminases (40% of patients) [20], and teratogenic potential [24]. Ribavirin, given together with corticosteroids, was shown to be incapable of preventing the peaking of viral load on day 10 after the onset of illness [25]. Thus, ribavirin is a controversial drug [26, 27] with low efficacy and significant toxicities. There is an urgent need to find more potent and safer antiviral agents.

In the quest for effective agents against the SARS-CoV, the protease inhibitor lopinavir, when combined with ribavirin, has been found to reach the synergistic inhibitory concentration against the SARS-CoV in laboratory testing [12]. Lopinavir, in combination with ritonavir (LPV/r), is licensed for the treatment of HIV infection. Ritonavir is a weak antiviral agent, but it increases the serum level of lopinavir through inhibition of the CYP3A-mediated metabolism of its partner. Though a satisfactory serum inhibitory concentration of lopinavir may not be achieved with the oral LPV/r combination [28], a sufficient level may be reached at the intestinal mucosa, since 20% of the drug is found excreted unchanged in the stool [29]. This is significant because severe watery diarrhea is a marked feature in 20.4–76.0% of SARS patients [12, 25, 30, 31] and the gastrointestinal mucosa could be an important reservoir for viral replication and fecal-oral transmission [32]. In an open trial of the use of the LPV/r combination together with ribavirin in 41 patients compared with 111 historical controls, it was shown that patients in the LPV/r group had fewer 21-day adverse clinical outcomes (death/acute respiratory distress syndrome) and their disease course was milder with regard to diarrhea, fever recurrence, and worsening of chest radiographs. In addition, the LPV/r group had a progressive decrease in the viral load, an early rise in the lymphocyte count, a reduction in the cumulative dose of pulse methylprednisolone, and fewer episodes of nosocomial infections [21]. In another larger multicenter study in Hong Kong, 75 patients were given the LPV/r combination as an initial therapy besides ribavirin and corticosteroids. This treatment was associated with a reduction in the overall death rate and intubation rate when compared with a matched cohort who received standard treatment (2.3% vs. 15.6% and 0% vs. 11.0%, respectively, p<0.05) and a lower rate of use of methylprednisolone at a lower mean dose [33]. The findings from the above two studies suggest that LPV/r, when combined with ribavirin, may be an effective agent against SARS.

**Corticosteroids**

It has been thought that the tissue damage in respiratory viral infection is caused by the vigorous systemic inflammation or cytokine storm [34] induced by early-response cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and interferon-gamma (IFN-γ) [35, 36]. This exaggerated host cytokine response has been assumed to be responsible for the second immunopathological phase of SARS. Evidence from a recent report showed marked elevation of Th1 cytokine IFN-γ and of inflammatory cytokines IL-1, IL-6, and interleukin-12 (IL-12) for at least 2 weeks after disease onset. There is also significant elevation of neutrophil chemokine interleukin-8 (IL-8), monocyte chemoattractant protein-1 (MCP-1), and Th1 chemokine IFN-γ-inducible protein-10 (IP-10). Corticosteroids significantly reduce IL-8, MCP-1, and IP-10 concentrations 5–8 days after treatment. The findings confirm the activation of Th1 cell-
mediated immunity and hyperinnate inflammatory response in SARS through the accumulation of monocytes/macrophages and neutrophils [37].

Another rationale favoring steroid usage is the necropsy evidence of infiltration by macrophages as the prominent leukocytes in the pulmonary alveoli, hemophagocytosis in the lungs, accompanied by pathological features of ARDS [38, 39], and BOOP [40]. Hemophagocytosis has been associated with cytokine dysregulation [41]. This cytokine response may be tempered by corticosteroids to prevent a fatal outcome, as suggested for ARDS of other etiologies [8, 42]. The final reason for the use of corticosteroids in SARS is that CT scans of the thorax have shown radiographic features of BOOP [43], which is a steroid-responsive condition suggestive of an immunological phenomenon [9]. Chest radiograph resolution may slightly lag behind clinical recovery, but it should not be the reason for additional doses of corticosteroids [44]. Despite a tapering down of the corticosteroids in the ensuing 2–3 weeks, the radiological opacities will usually continue to improve.

The use of corticosteroids may, nevertheless, be associated with enhanced viral replication due to suppression of the innate immune response. One study documented a case of increased viral load following pulse methylprednisolone [25]. Another study also found that early corticosteroid treatment (<7 days of illness) was associated with a higher subsequent plasma viral load [45].

Low-dose corticosteroids, like prednisolone at 0.5–1.0 mg/kg/day, are usually used in infections and ARDS. On the other hand, pulse doses of methylprednisolone at 0.5–1.0 g/day have been widely used in SARS, especially when patients deteriorated clinically in the second week. Whether pulse corticosteroids are efficacious is unknown. Although a number of reports on corticosteroid usage in SARS have emanated from Hong Kong [46–53] and China [54–59], meaningful interpretation of these retrospective analyses is hampered by methodological limitations generated by the different types of corticosteroid dosing regimens and the time of treatment initiation during the course of disease. Despite the number of studies published, no systematic review or meta-analysis on the efficacy of corticosteroids in SARS has been available. Anecdotal cases of SARS have been successfully treated by administering methylprednisolone pulses, which correspond to the immunosuppression doses used to prevent organ rejection [52]. The same group of researchers studied the response of patients with SARS to various steroid regimens and showed that high-dose pulse methylprednisolone therapy (in the organ rejection treatment range) was more efficacious and equally safe as regimens of lower dosage [53]. Another group, however, did not find the use of pulse methylprednisolone to be associated with a better outcome [50]. Furthermore, one retrospective case series found that pulse methylprednisolone was a predictor of 30-day mortality in multivariate analysis [11]. Some groups advocated the early introduction of high-dose corticosteroids, mostly pulse methylprednisolone, in the treatment of SARS [25, 53]. Others proposed that corticosteroids should be used only judiciously in the immunopathological phase of SARS, which is towards the end of the first week and the beginning of the second week of disease. The recommended doses are lower, and pulse methylprednisolone is used whenever a patient deteriorates clinically or develops respiratory distress [51, 59]. The latter approach seems to be gaining more acceptance.

The use of corticosteroids in SARS, especially at high doses and for prolonged periods, has been accompanied by significant side effects. These include hyperglycemia, hypokalemia, hypertension, gastrointestinal hemorrhage [21, 50, 51], and, in particular, nosocomial infections [48, 50, 51, 60]. The occurrence of nosocomial infections was more prevalent in patients managed in the ICU and could manifest as pneumonia, urinary tract infection, bacteremia, and deep-seated mycosis. It is not easy to distinguish whether the recurrence of fever later in the course of SARS therapy, particularly after a period of corticosteroid treatment, is due to nosocomial infection. Anti-pseudomonal antibiotics or antifungal agents are usually indicated under such circumstances. For patients with no apparent clinical response to empirical antimicrobial therapy and in whom opportunistic infection is reasonably excluded, higher pulse methylprednisolone doses can be tried.

Avascular necrosis of bone, or osteonecrosis, is probably one of the most distressing complications associated with the use of corticosteroids in SARS [61, 62]. In one recent study of 254 patients, magnetic resonance images showed evidence of subchondral osteonecrosis, mainly involving the proximal femur, in 12% of patients and additional nonspecific subchondral and intramedullary bone marrow abnormalities in 77% (30%). Results of multiple logistic regression analysis confirmed the cumulative prednisolone-equivalent dose to be the most important risk factor for osteonecrosis, while joint pain was common after SARS infection and was not a useful clinical indicator of this complication [63].

**Convalescent plasma**

In patients who deteriorated irrevocably despite receiving pulse methylprednisolone, convalescent plasma, obtained from patients who recovered from SARS, had been used as a last resort. A cell separator operating on the plasma exchange mode is used to harvest convalescent plasma by apheresis. The experience with this kind of treatment is very limited [64]. In a small retrospective nonrandomized study of patients with progressive disease after ribavirin and pulse methylprednisolone treatment, the plasma-treated group had a shorter hospital stay and lower mortality than the group that continued treatment with pulse methylprednisolone [65]. A later study from the same group showed a higher day-22 discharge rate among patients given the plasma infusion before day 14 of illness [66].

**Immunoglobulin**

Another form of salvage therapy for patients who run a relentless downhill course is intravenous immunoglobulin (IVIG) [67–69] or pentaglobin infusion. IVIG is a non-
Invasive mechanical ventilation

When patients deteriorate or fail to improve after 1–2 days of NIPPV, or if NIPPV is contraindicated, endotracheal intubation and mechanical ventilation have to be considered. The ventilatory approach is similar to that for other causes of ARDS. The plateau pressures are kept lower than 30 cm H₂O because of the tendency for barotrauma in SARS [25].

Novel treatment approaches

The present therapy of SARS is less than satisfactory, and much effort has been expended in looking for novel treatment modalities. It is well known that viral infections can stimulate the production of interferons (IFNs) in the early phase of the human hereditary immune response. The cytopathic effects of SARS-CoV have shown to be completely inhibited in vitro by IFN-β [75], by IFN-β-1b, IFN-α-1a, IFN-α-3, human leukocyte IFN-α [76], and by IFN-β-1a [77]. Synergistic inhibition of the replication of SARS-CoV has been achieved by the combination of IFN-β plus IFN-γ in animal cells [78], and by IFN-β plus ribavirin in both animal and human cells [79]. In vitro data from Hong Kong has shown that type I interferons (IFN-α and -β) can induce potent inhibition of the SARS-CoV, while type II interferons (IFN-γ) cannot [80]. An uncontrolled trial found that IFN alfacon-1 plus corticosteroids improved oxygen saturation, hastened radiographic resolution of lung opacities, and lowered the levels of creatine kinase [81]. In an animal study, pegylated IFN-α was associated with significantly reduced viral replication, excretion, and expression in lung tissue when administered prophylactically to cynomolgus macaques before experimental exposure to SARS-CoV. Postexposure treatment resulted in intermediate outcomes [82]. The above findings provide the basis for further pursuit of the role of interferons in the treatment and prophylaxis of SARS.

There has been some evidence indicating that the SARS-CoV can enter human cells through binding of the viral S1 protein to the angiotensin-converting enzyme-2 receptor [83], though the clinical significance of this finding was not confirmed by a recent study [84]. A high-affinity human monoclonal antibody, called 80R, has been demonstrated to have strong neutralizing activity in vitro and in vivo against the S1 protein and has been hypothesized to be a useful agent for SARS treatment and prophylaxis [85]. However, it should be noted that enhanced disease with other coronaviruses, including SARS-CoV, may occur with S1-specific antibodies.

There are several other potential treatment options that may eventually prove to be valuable anti-SARS agents after further investigation. The active component of liquorice root, glycyrrhizin, shows significant viral inhibition in vitro [17]. The SARS-CoV also exhibits in vitro susceptibility to baicalin, a chemical compound derived from the herb scute (huangqin) [86]. Nelfinavir was found to inhibit the cytopathic effect induced by SARS-CoV infection and decrease the production of virions from Vero cells [87]. More agents on the horizon are now under intensive research, including small interfering RNAs [88], small-molecule inhibitors identified by chemical genetics [89], target-designed proteinase inhibitors [90], existing drugs used for treatment of HIV, psychotic disorders, and parasitic infections [91, 92], tumor necrosis factor-alpha inhibitor [93], nitric oxide [94, 95], and aminopeptidase N inhibitors [96].

Specific hyperimmune globulin, and pentaglobin is an IgM-enriched immunoglobulin preparation. A retrospective analysis of 12 patients with severe SARS demonstrated that pentaglobin is a safe and probably effective treatment in case of corticosteroid resistance [70]. Nevertheless, the use of immunoglobulin is associated with the risk of venous thrombosis.
Traditional Chinese medicine

During the SARS outbreak, traditional Chinese medicine (TCM) was used extensively in China. A large experience has been accumulated in the TCM literature [97–99]. As compared with Western methods of treatment, integrated TCM and Western medicine treatment has been shown to be more effective in improving clinical symptoms, shortening the course of illness, clearing up lung inflammation, preventing rebound of fever, and reducing the duration of corticosteroid usage. Selected cases in Hong Kong also were treated with TCM as an adjuvant therapy, especially in the convalescent period. The benefits are difficult to establish, due to the heterogeneous type and amount of the concoction constituents, the different phases of disease when therapy was started, the diverse clinical condition of the patients, and the variable length of treatment. In an investigation on the relationships between the hazard for death and that for cure, a cure-death hazard plot was developed for the case-fatality rates in Hong Kong, Singapore, and Beijing. The results showed a significant difference in the case-fatality rates between Beijing and other areas. It is postulated that the phenomenon may be due to the difference in treatment methods, and it is possible that combining TCM with Western medicine gives better results than the latter alone in the treatment of SARS [100]. This aspect of anti-SARS therapy certainly warrants more investigations in the future.

Treatment protocols

A number of treatment protocols were reported in Hong Kong during the SARS outbreak. They were invariably composed of antibiotics, a combination of doses and route of administration for ribavirin, a step-down course of corticosteroids over a few weeks, and possibly pulse methylprednisolone rescue in cases of clinical worsening of patients [49–53]. It was found, in one report, that adherence to a standard treatment protocol resulted in overall satisfactory outcomes [101].

Treatment guidelines, intended for use should SARS return, were worked out through consensus among experts in Hong Kong at the end of 2003 [102]. The protocol has the format of a placebo-controlled double-blinded randomized trial. Patients who fulfill the WHO clinical case definition of SARS [103] are prescribed broad-spectrum antibiotics (3rd/4th-generation cephalosporin plus macrolide if not penicillin allergic; antipseudomocccal quinolone for penicillin-allergic patients) and supportive care. Upon laboratory confirmation of SARS according to the WHO definitions and if the patient’s condition is stable, informed consent is obtained and the patient is randomized to one of two arms: the antiviral arm or the placebo arm. Patients assigned to the antiviral arm receive the ribavirin and lopinavir/ritonavir combination. Ribavirin is started at a 2.4 g oral loading dose followed by 1.2 g orally for a total of 10 days. The lopinavir/ritonavir combination is administered as three tablets b.i.d. orally (each tablet contains lopinavir 400 mg and ritonavir 100 mg) for a total of 10 days. As a rescue measure, when patients in either arm have features of acute lung injury defined by a PaO2/FIO2 ratio of between 26.7 and 40 kPa (200–300 mm Hg), they are given either (i) prednisolone 1.0–1.5 mg/kg/day for 5 days or more, followed by tapering down of the dosage with clinical improvement every 5 days by 0.5 mg/kg decrements until off, or (ii) methylprednisolone 3 mg/kg/day intravenously for 5 days and tapered by 1 mg/kg every 5 days (further stepping down can be by oral prednisolone) for a total of 2 weeks. In patients with underlying cardiac or respiratory condition, initiation of NIPPV can be considered. If patients develop critical SARS as defined by a PaO2/FIO2 ratio of <26.7 kPa (200 mm Hg) and progressive deterioration of chest radiograph [104], NIPPV or invasive ventilation must be considered. Pulse steroids can be used at the discretion of the clinician. The suggested regimen is methylprednisolone at 0.5 mg per day intravenously for 3 days, followed by a tapering course at 3 mg/kg/day. The cumulative dose should preferably not exceed 2 g.

Similar consensus treatment guidelines, using ribavirin and corticosteroids, were promulgated in China in November 2003 [105]. Other centers in the world, like Canada and Singapore, have not been as liberal in the use of ribavirin and corticosteroids as in Hong Kong, but interestingly, their patients have had quite similar outcomes [106, 107]. In the USA, where supportive therapy alone has been used to treat SARS patients, the case-fatality rate is 0%. However, direct comparison is not possible since only 8 of 47 probable cases and none of the 162 suspected cases had virological evidence of SARS-CoV infection [108].

Conclusion

Ribavirin and corticosteroids were the cornerstones of treatment during the SARS outbreak. Ribavirin has shown a lack of efficacy in a number of studies. The usefulness of corticosteroids has been reported in some uncontrolled trials, but further investigations are required. The antiretroviral formulation of lopinavir/ritonavir, when used with ribavirin, was found to be associated with clinical benefits. The survival of patients who deteriorate despite pulse methylprednisolone therapy may be improved by the use of convalescent plasma or immunoglobulins like pentaglobin. NIPPV, when performed in an appropriate setting under adequate precautions, has proved to be effective in patients who develop respiratory failure. Interferons and other novel agents are now under active investigation and may considerably strengthen the anti-SARS armamentarium in the future. TCM is yet an untapped wealth of knowledge and can become an important partner to the conventional treatment strategy. Finally, the optimal treatment regimen for SARS remains elusive. Randomized controlled treatment trials should be done, especially through international collaboration, to discover the best form of therapy.
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