Coronaviruses with Special Emphasis on First Insights Concerning SARS
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Current status of therapy of SARS

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Introduction

The severe acute respiratory syndrome (SARS) caused by the SARS-associated coronavirus (SARS-CoV) has caused a worldwide outbreak in 2003. This chapter will start with a description of the pathogenesis of this disease, followed by a review of the various pharmacological treatments and supportive ventilatory strategies adopted during the outbreak. The principles used to design various combinations of therapeutic agents and treatment modalities will also be described based on the present knowledge.

Pathogenesis

SARS has been postulated to cause a three-phased illness [1]. The first is the viral replication phase, which is associated with increasing viral load and the resultant host reaction in the form of fever and other systemic symptoms. While symptoms may improve or subside in some patients, the second phase of immunopathological damage occurs in the majority, and is reflected by pulmonary manifestations with varying degrees of clinical severity about 10 days after symptom onset. This phase corresponds to peaking of the viral load followed by it fall subsequent to the onset of IgG seroconversion. It is characterized by the recrudescence of fever, oxygen desaturation and radiological progression of pneumonitis, as well as intense macrophage activation in the lungs [2]. About 20% of patients may develop acute respiratory distress syndrome (ARDS) at this stage. The final phase is pulmonary destruction in a proportion of cases, especially if the over-exuberant host response in the second immunopathological phase remains uncontrolled.

Pharmacological therapy

There is no consensus on the types of pharmacological therapy which may be effective for SARS. In general, since the definitive laboratory diagnosis of SARS may only be made 3–5 days after symptom onset, empirical antibiotics are still indicated in the presence of pulmonary infiltrates. Antiviral and immunomodulatory agents have also been used empirically in the 2003 outbreak and will also be reviewed in this chapter.

Antibiotics

Although not active against SARS-CoV, antibiotics are prescribed by most physicians to SARS patients on initial presentation, before microbiological confirmation is obtained [3–5]. Antibiotics are chosen to cover both typical and atypical organisms according to published treatment guidelines for community-acquired pneumonia (CAP) [6]. Co-infection with other organisms which may or may not benefit from antibiotics was not uncommon in the last outbreak, including metapneumovirus [7], *Chlamydia*-like agents [8], influenza virus and parvovirus B19 [9]. Amoxicillin-clavulanate and clarithromycin, or levofloxacin alone are often used as initial treatment [3]. Broader spectrum antibiotics may be used in the presence of severe CAP, whereas potent anti-pseudomonal antibiotics like piperacillin-tazobactam, imipenam-cilastatin or cefoperazone-sulbactam should be reserved for potential complication by superimposed sepsis, which may be expected when corticosteroids are used or mechanical ventilation is instituted. A centre has recommended the early use of potent and broad spectrum antibiotics coverage (ceftriaxone or cefipime or levofloxacin) to treat and/or prevent possible underlying bacterial infection which may be associated with early use of pulsed doses of corticosteroid for SARS [10].

Antiviral therapy

Ribavirin

Because of its broad-spectrum antiviral activity against many DNA and RNA viruses, this nucleoside analogue was chosen as empirical treatment early in the 2003 outbreak even before the SARS-CoV was identified. Subsequent clinical experience showed that ribavirin did not appear to have significant effects on the clinical course in terms of fever subsidence, improvement in oxygen saturation and clearing up of chest radiograph shadows. The use of ribavirin was however continued in most centres because no better anti-viral agents were available, and there were reports suggesting that, despite only weak viral inhibitory activity, it appeared to

possess some immunomodulatory effects. In the treatment of mouse coronavirus hepatitis these were mediated by inhibition of induction of macrophage pro-inflammatory cytokines and Th2 cytokines while preserving Th1 cytokines [11]. Monitoring of quantitative reverse transcriptase polymerase chain reaction (RT-PCR) in nasopharyngeal aspirates could not however demonstrate any antiviral effect *in vivo* [1]. Subsequently, it was also found that ribavirin has no or only slight *in vitro* activity against SARS-CoV [12], and inhibitory dosages may not be achievable clinically [13]. Because of its teratogenic effect, double contraception for up to seven months must be practised after the cessation of ribavirin therapy. Other side effects are dose related and are more common in the elderly. They include haemolytic anemia, elevated transaminase levels and bradycardia. Health Canada has stopped further use of ribavirin for SARS [14], while Hong Kong has planned to test this drug in a randomized controlled trial together with Kaletra should there be another outbreak.

Lopinavir-ritonavir (kaletra)

Among various anti-viral drugs screened, lopinavir-ritonavir co-formulation (Kaletra®, Abbott Laboratories, USA) was found to be active against the prototype SARS-CoV HKU39849 *in vitro* [15]. Only the lopinavir component has activity against SARS-CoV, while ritonavir inhibits the CYP3A-mediated metabolism of lopinavir and increases its serum concentration. Lopinavir can inhibit the coronaviral proteases and block the processing of the viral replicase polyprotein, thus preventing the replication of viral RNA. Synergism was also demonstrated with lopinavir and ribavirin when used in combination [15]. In a retrospective matched cohort study from Hong Kong, the only SARS outbreak area having experience with this drug [15], 75 patients given kaletra (lopinavir 400 mg/ritonavir 100 mg orally every 12 hours), ribavirin and corticosteroid were divided into two subgroups for analysis. Forty-four patients in whom kaletra was given as initial treatment at 5.5 days (median) after symptom onset were compared with a matched cohort who received only ribavirin and corticosteroid. The kaletra group showed reduction in the overall death rate and intubation rate, and a lower requirement for pulsed methylprednisolone rescue. In 31 patients who had received kaletra later in the course of the illness as rescue therapy following poor response to ribavirin and corticosteroid, such benefits were not seen. In another Hong Kong study [16], 41 SARS patients treated with a combination of kaletra, ribavirin and corticosteroid were compared with 111 matched historical controls given ribavirin and corticosteroid only. Lower incidences of adverse clinical outcomes in terms of ARDS or death at day 21 after symptom onset were seen in the kaletra group. The findings from these two studies suggest that kaletra when combined with ribavirin may be effective as anti-viral agent against SARS. If this is the case, then

early use of kaletra may decrease initial viral load during the viral replicative phase and hence ameliorate the subsequent immunopathological lung damage. Based on these retrospective data, kaletra will be studied in combination with ribavirin in a randomized controlled trial planned for future SARS treatment in Hong Kong.

Interferons

Interferons belong to a group of cytokines controlling the cellular immune response. Their antiviral activities are mediated by direct effects on infected cells and by modulating the host's immune response [17]. *In vitro* testing of three recombinant interferons against SARS-CoV showed that interferon (IFN)-β was more potent than IFN-α or IFN-γ in prophylaxis and as antiviral agent after infection [18]. Another study reported complete inhibition of the cytopathic effects of SARS-CoV in culture by IFN subtypes, β 1b, α n1, α n3, and human leukocyte IFN-α [13]. Similar activity was also reported for IFN-β 1a in a third *in vitro* study [19], with therapeutic dosages shown to be effective and acceptable in monkeys [20]. IFN-α has been used for treatment of SARS in China and Canada [21, 22]. In an open-label uncontrolled Canadian study [22], 13 patients treated with corticosteroids alone as initial treatment were compared with nine given corticosteroids plus IFN alfacon-1 (Infergen®, InterMune Inc., Brisbane, CA, USA). The latter group showed shorter time to 50% resolution of radiographic abnormalities in the lungs, better oxygen saturation and earlier cessation of supplemental oxygen with decreased elevations in creatine kinase levels. Based on these *in vitro* and *in vivo* data, selected interferons, either alone or in combination with other antiviral drugs, appear to show promising treatment efficacy in human.

Immunomodulatory therapy

Corticosteroids

When the patient enters the immunopathological phase, intense macrophage and cytokine activation occurs in the lungs, resulting in severe pneumonitis and respiratory failure [23]. An immunomodulatory agent is usually given to control the over-exuberant host response, and corticosteroids had been most commonly used for this purpose in the 2003 outbreak.

Different series have reported different methods of corticosteroid prescription. Treatment had been started after no demonstrable response to antibiotics, as soon as epidemiologic history of contact with SARS could be established [24], or based on a set of surrogate clinical markers which may reflect over-reactive host response [3]. Because of the diversities regarding

the route of administration, dosages and types (prednisolone, methylprednisolone, hydrocortisone, and dexamethasone) of corticosteroids used, as well as the duration of administration, conclusions about the efficacy of this drug are difficult to reach. Moreover, more severe disease may prompt the use of higher dosages of corticosteroid, making the relationship between efficacy and corticosteroid use obtained in retrospective analysis not straightforward.

Based on the present knowledge about the disease, it appears logical that immunomodulatory agents like corticosteroids should be avoided in the early phase of viral replication. On the other hand, they have to be considered when there are signs suggestive of an over-reactive host response, which may be reflected by clinical and radiographic deterioration. Beneficial results may depend on the administration of adequate initial corticosteroid dosages for long enough to dampen the over-active immune response while avoiding rebound or over-immunosuppression [3, 25]. Initial steroid dosages ranged from oral prednisolone 1 mg/kg/day [4] to as high as pulsed methylprednisolone 500 mg intravenous daily for 5 days [10]. Retrospective data suggest that higher doses given for two to three weeks in the more severe cases had been of benefit [3, 10, 26, 27], although some "good responders" develop recurrence of respiratory failure after initial response. For these as well as for some "poor responders" [28], pulsed corticosteroid in the form of methylprednisolone 500 mg–1 g for two days may be effective as rescue therapy [3, 9, 21, 29].

Corticosteroids must be used cautiously because side effects are common. In addition to hospital-acquired infections which are associated with comparatively more adverse outcome in patients requiring mechanical ventilation, post-SARS avascular necrosis of hips and knees are common, in the order of 10 to 30% [30]. Fibrin thrombi have been found in small pulmonary arteries in autopsy studies [2, 31, 32], together with initial swelling of pulmonary vessels [2]. Moreover, systemic vasculitis including oedema, localised fibrinoid necrosis and infiltration of lymphocytes, monocytes and plasma cells into the vessel walls of the heart, lung, liver, kidneys, adrenals and stroma of striated muscles, as well as thrombosis of small veins, were seen in three SARS cases from Guangzhou, China [33]. SARS-CoV may thus have deleterious effects on the endothelium which predispose to small vessel thrombosis. In addition, up to 74% of 31 patients diagnosed to be suffering from osteonecrosis, primarily of the hip, were found to be suffering from one or more primary coagulation disorder, including 15/18 (83%) who initially were diagnosed as "idiopathic" avascular necrosis [34]. The coagulation disorders included thrombophilia and hypofibrinolysis. Further analyses are required to clarify whether or not avascular necrosis is due to corticosteroids, to underlying coagulation abnormalities, or to the SARS-CoV infection *per se*.

Our group first developed a standard treatment protocol in mid-March 2003, very early in the SARS outbreak in Hong Kong and before

the SARS-CoV was identified. The protocol allowed commencement of high (but not pulsed) dose methylprednisolone only on worsening of clinical and radiographic parameters after a trial of antibiotics, with subsequent tapering over the next three weeks should there be satisfactory response [3]. This standard protocol was eventually applied to a total of 88 consecutively admitted SARS patients (mean age 42 years), of whom 97% had laboratory-confirmed SARS [9]. An overall mortality of 3.4% was observed, with all three deaths occurring in patients above the age of 65 years. A multi-centre study [21] comparing four treatment regimens in Guangzhou, China, also found that high dosages of corticosteroids adjusted according to clinical and radiological severity produced zero mortality in 60 clinically-defined SARS patients (mean age 30.5 years). These figures compared favourably with the estimated case fatality rates of 13.2% for patients < 60 years old and 43.3% for patients > 60 years old [35].

Immunoglobulin

Human gamma immunoglobulins have been used to treat SARS patients with poor response to corticosteroids. Pentaglobin (Pentaglobin®, Biotest Pharma GmbH, Dreieich, Germany), an IgM-enriched immunoglobulin product, has been tried in Hong Kong and hospitals in mainland China. When pentaglobin was given at 5 mg/kg/day for three consecutive days to 12 patients who deteriorated despite ribavirin and repeated rescue methylprednisolone, some improvement in radiographic scores and oxygen requirement was noted [36]. In a Singaporean series [37], methylprednisolone in combination with high-dose intravenous immunoglobulin (0.4 g/kg) was administered once daily for three consecutive days to 15 critically ill probable SARS patients with acute lung injury or ARDS. Compared to patients not given immunoglobulin, lower mortality and a trend towards earlier recovery were found. Randomized controlled trials in larger patient groups are required to confirm the efficacy of immunoglobulins.

Convalescent plasma

Convalescent plasma was used in several centres in Hong Kong in the more severe cases not apparently responding to other treatments. Plasma was taken from SARS patients in convalescence and re-infused into these sick patients in 200 ml aliquots daily for 2–3 days. It was believed that the neutralizing immunoglobulins in convalescent plasma may be able to decrease viral load, and early infusion was reported to provide some clinical benefits [38].

Other drugs

Many other drugs have been tried or considered in desperation during the 2003 outbreak. These included thymosin alpha 1 (Zadaxin®, SciClone Pharmaceuticals Inc., San Carlos, CA, USA), tumour necrosis factor blocking agents, namely etanercept (Enbrel®, Immunex Corp., Seattle, WA, USA) and infliximab (Remicade®, Centocor Inc., Malvem, PA, USA), and some other compounds including cyclophosphamide, azathioprine, cyclosporin and thalidomide.

Traditional Chinese medicine

Traditional Chinese herbal medicine had been used with Western medicine to treat SARS with good results reported from some centres in mainland China [39–41]. Compared to using Western medicine alone, shorter time to symptom improvement and fever subsidence, shorter duration of hospitalization, and corticosteroid use were seen. Because herbal medicines are traditionally used in combination, it is difficult to dissect out the efficacy of individual agents. Glycyrrhizin, an active component derived from liquorice roots, has been found to be effective against SARS-CoV *in vitro* when administered either during or after the viral adsorption period [12]. Since it is only effective at very high concentrations, however, its clinical utility remains uncertain. Another herb called baicalin has also demonstrated some anti-SARS-CoV activity (unpublished data).

Assisted ventilation

Despite all treatment efforts, many SARS patients still developed acute hypoxemic respiratory failure. Overall, 20–30% required intensive care unit (ICU) or high dependency care, and 13–26% developed ARDS [42]. The initial management of SARS-related respiratory failure is oxygen supplementation. Assisted ventilation through non-invasive or invasive means should be considered when hypoxaemia or dyspnoea persists.

Non-invasive ventilation (NIV) delivers continuous positive airway pressure (CPAP) or bi-level pressure support through a tight-fitting facial or nasal mask. It was commonly employed in many Chinese hospitals [43] and in our own centre in Hong Kong [44]. Advantages of NIV include: (1) rapid improvement in vital signs, oxygenation and tachypnoea, especially when applied early; (2) reduction of the need for increasing dosages of corticosteroids to treat progressive respiratory failure; (3) avoidance of intubation and invasive ventilation in up to two-thirds of critically ill SARS patients; (4) reduction of infective risk for such patients through reduction in mechanical ventilation requirement and hence ventilator-associated

pneumonia which may be further aggravated by the use of corticosteroids; and (5) reduction of risks to healthcare workers through obviating the need for the potentially highly infectious procedure of intubation. Since patients who respond to NIV usually do so within 24 hours, non-responders who will eventually need endotracheal intubation can be identified early [44]. CPAP of 4–10 cm H_2O, or bi-level pressure support with inspiratory positive airway pressure (IPAP) < 10 cm H_2O and expiratory positive airway pressure (EPAP) of 4–6 cm H_2O are reasonable starting pressures [42]. Lower pressures are safer to start with because of the high frequency of spontaneous pneumomediastinum and subcutaneous emphysema [1] which would naturally be aggravated by positive pressure ventilation in any form.

Our centre had applied NIV to 20 out of 88 patients with persistent SARS-related acute respiratory failure [44]. Mean age was 51.4 and coronavirus serology was positive in 95%. NIV was started 9.6 days (mean) from symptom onset and the mean duration of usage was 84.3 hours. Endotracheal intubation was avoided in 14 patients (70%), in whom ICU stay could be shortened significantly (3.1 ± 2.1 days vs. 21.3 ± 21.2 days in intubated cases) and chest radiography scores within the first 24 hours of NIV were also lower. Successful avoidance of intubation was predicted by a marked reduction in respiratory rate and supplemental oxygen requirement within 24 hours of NIV. Complications were few and reversible. No infection was documented among the 105 health care workers caring for SARS patients on NIV in a high air change (initially eight and later > 12 per hour) and uni-directional negative pressure ventilation environment.

Invasive mechanical ventilation

When patients do not improve within 1–2 days of NIV or continue to deteriorate, or if NIV is contraindicated, endotracheal intubation and mechanical ventilation should be considered. It should be emphasised that endotracheal intubation is a procedure with high infective risk, and all staff involved must adhere to stringent infection control measures must be strictly adhered to [45]. Most centres adopted a ventilatory strategy similar to that recommended for ARDS from other causes [46]. The tidal volume should be kept low at 5–6 ml/kg predicted body weight and plateau pressures maintained below 30 cm H_2O because of a higher risk of barotrauma in SARS [1].

Treatment principles in relation to clinical course

While many patients had suffered from a severe illness in the 2003 outbreak, SARS can also present with a wide spectrum of severity. A minority of patients with mild respiratory illnesses recover, either without any spe-

cific form of treatment or on antibiotic therapy alone [3]. All four sporadic cases from Guangzhou in December 2003 – January 2004 belonged to this category [47]. For the majority of patients with definite epidemiological links or microbiological confirmation, it may be prudent to administer an anti-viral agent (kaletra ± ribavirin, ± interferon) as soon as SARS is diagnosed. An effective anti-viral agent may decrease the severity of the subsequent immunopathological damage and thus the need for salvage therapy with immunosuppressants. When a patient has entered the immunopathological phase, an immunomodulatory agent will likely be indicated. The optimal choice, dosages and duration of such therapy are not known, but retrospective experience suggest that dosages may be titrated according to disease severity, and that sufficiently large dosages given for longer durations may be required for the more severe cases. Pulsed methylprednisolone may be effective as rescue therapy in case of unsatisfactory response or recurrence of respiratory failure after initial response. If response remains poor despite the above treatment, immunoglobulin or other forms of treatment may be tried. Assisted ventilation in the form of NIV should be instituted early if the clinical course is complicated with significant respiratory failure. If response remains poor after 24 hours, elective intubation should be considered early so that ample time is available for institution of infection control measures before managing the airway in this highly infectious disease. When fever recurs later in the course of SARS treatment, the clinical picture may not be easily distinguishable from superimposed bacterial or even fungal sepsis [48]. Empirical anti-pseudomonal antibiotics would usually be indicated considering that the patient would have been put on immunomodulatory agents for some time. If clinical response is still not apparent and opportunistic infection is reasonably excluded, higher dosage of methylprednisolone can be considered in pulses for SARS rescue (e.g. MP 1 g for 2 days), especially if this had not been given previously. Most patients will respond with fever subsidence, improvement in chest radiograph and oxygen saturation. Chest radiograph may slightly lag behind clinical improvement but this feature *per se* may not warrant the use of additional steroid [49]. Radiological infiltrates will usually improve gradually despite reducing dosages of corticosteroids over the next 2–3 weeks. However, in a small proportion of critical SARS patients, the course is relentless and the 28-day intensive care unit mortality could be up to 26–37% [50, 51].

Conclusion

In this chapter, we have reviewed the pathogenesis, various treatment modalities and the treatment principles of SARS. Subsequent to unprecedented collaborative efforts among medical and research communities worldwide, we have already gained a large amount of knowledge about this

novel virus within the short space of just over a year. However, randomized controlled treatment trials remain to be performed to improve our understanding of the most optimal treatment for this new disease.

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