How Prepared are we to Control Severe Acute Respiratory Syndrome in Future

Kanchan Bhardwaj
Department of Pediatrics,
All India Institute of Medical Sciences, Ansari Nagar, New Delhi, 110029, India

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ABSTRACT
No non-human reservoirs for smallpox- and polio-viruses has contributed to the success of worldwide eradication of smallpox and a significant control of poliomyelitis. Most emerging and re-emerging viruses including SARS Coronavirus (SARS-CoV), have animal reservoirs and therefore, they impose a constant threat of host jump leading to outbreaks in humans. It is desirable to be ready for control of infections that are caused by zoonotic pathogens, even after an outbreak has ended. This literature review is a compilation of advances made so far for diagnosis and treatment of SARS.

Keywords: SARS Coronavirus (SARS-CoV), Antivirals, Vaccines, Human Monoclonal Antibody

1. INTRODUCTION
According to the World Health Organization, there were 8,098 reported cases and 774 deaths worldwide during the Severe Acute Respiratory Syndrome (SARS) outbreak in 2002-2003. First case of SARS appeared in November 2002 in Guangdong Province, China. By April 2003, it had spread to around 30 countries including Vietnam, Hong Kong, Singapore, Taiwan, India, Canada and United States of America.

On 24th March 2003, Center for Disease Control and Prevention, Atlanta, USA announced that the possible etiologic agent of SARS is either a human metapneumovirus or a previously unrecognized coronavirus. Shortly, it was confirmed to be a novel coronavirus based on electron microscopy, immunostaining, seroconversion as well as RT-PCR and sequencing of polymerase gene fragment (Drosten et al., 2003; Ksiazek et al., 2003). Availability and affordability of DNA sequencing facilitated genotyping of several isolates of SARS-CoV. By 29th April 2003, complete genome sequences of SARS-CoV isolates, Tor2, Urbani, HKU-39849, CUHK-W1 and KYK were posted on the web. Facilities at the BCCA Genome Sciences Centre in Vancouver, Centers for Disease Control and Prevention in Atlanta, University of Hong Kong, Chinese University of Hong Kong, Genome Institute of Singapore and Beijing Genomics Institute were involved in this seminal work. Many others are isolates were sequenced and compared subsequently. The information obtained from such analyses was of epidemiologic significance. One, it revealed mutability of SARS-CoV, which, would have implications in vaccine development (Ruan et al., 2003; Tsui et al., 2003). Second, it led to the understanding that the organization of SARS-CoV genome is similar to the other coronaviruses although, at the primary sequence level, they were only distantly related (Rota et al., 2003). This ruled out the possibility of simple recombination event(s) among existing coronaviruses being responsible for the emergence of SARS-CoV. It was also indicative of the fact that this virus might have originated from animals. In fact, virus isolated from SARS patients was able to cause a similar disease in cynomolgus macaques (Fouchier et al., 2003). Scientists began a search for the source of the SARS-CoV by scanning wild and domestic animals and indeed found SARS virus-like coronaviruses from Himalayan palm civets and a raccoon dog found in a market in Guangdong, China. From sequence analysis, it was apparent that the viruses of human and civet origin shared more than 99% homology. However, phylogenetic analysis of S proteins, placed viruses of
human and civet origin in separate clusters. Also, the animal isolates contained a 29-nucleotide sequence in ORF 8 region that was absent in most human isolates (Guan et al., 2003). These analyses and the fact that palm civets did not show a widespread infection indicated that palm civets might not have been the natural reservoir host for SARS-CoV. Instead, they may have only served a medium to facilitate animal-to-human transition. This led to further searches on other animals including bats, rodents and monkeys for SARS-CoV host. SARS-CoV like viruses were found in bats. Sequence analysis showed that there was a significant homology between bat and human viruses. Interestingly, the 29-nucleotides in the ORF-8 was present in the virus of bat origin and the most variability between the two was found to be in the S1 region of spike protein, which is responsible for receptor binding (Li et al., 2005a). Findings from all such studies were put together to establish origin of SARS-CoV. The most accepted theory is that bats are the natural reservoirs of SARS-CoV. Civets and other wild animals came in contact with SARS-CoV infected bats in a market, where they acquired the virus. It evolved in these animals before hoping to animals. Major species-specific determinants are traced to the viral S protein.

Even after the outbreak came under control, scientists around the world continued to treat the situation as urgent and have made significant advances in understanding the SARS-CoV biology, developing diagnostics, identifying a number of drug targets, potential antivirals, tools for vaccines and immunotherapy for SARS.

1.1. Diagnostics

Early and sensitive detection of SARS-CoV is important not only for treatment but also for control of disease spread. Initially, clinical symptoms and epidemiologic linkage were diagnostics for SARS followed by serologic testing, viral culture and PCR-based methods (Wu et al., 2003; Yam et al., 2003). Now, reagents are also available for Nucleocapsid (N) protein and Spike (S) protein detection (Che et al., 2004; Sunwoo et al., 2012).

1.2. Antivirals

During the outbreak, spread of SARS-CoV was predominantly controlled by surveillance and quarantine. Agents that were usually adapted for treatment were ribavirin, corticosteroids, human interferons (IFN-β and IFN-γ) and convalescent plasma (Barnard et al., 2004; He et al., 2004; Keyaerts et al., 2004; Wu et al., 2004a; Cinatl et al., 2005; Groneberg et al., 2005; Lai, 2005; Morgenstern et al., 2005; Saijo et al., 2005; Lau et al., 2006; Stockman et al., 2006). However, a systematic review of clinical trials and in vitro studies revealed that although agents such as ribavirin, corticosteroids, lopinavir and type I interferon showed inhibition of SARS-CoV in tissue culture, their usefulness was inconclusive in most patient studies (Stockman et al., 2006). Some studies have in fact shown possible harm from some of them (Lau et al., 2006; Stockman et al., 2006). Since then, several other small molecules have been investigated for effect on SARS-CoV in vitro and are listed with their observed effects in Table 1. In addition, progress made in understanding cellular and biochemical processes of the virus has allowed the identification of several novel antiviral targets and molecules to inhibit them.

1.3. Entry Inhibitors

Three important steps for SARS viral entry into the host cell include its binding to the host cells through an interaction between viral spike protein (S protein) and its receptor, the angiotensin-converting enzyme 2 (ACE 2) followed by conformational changes in the S protein and its activation by proteolysis. Agents that target these steps have been identified and analyzed for their inhibitory effects on SARS-CoV entry. Classes of entry inhibitor include siRNA to spike protein gene (Qin et al., 2004), peptides or recombinant proteins derived from S protein (Ni et al., 2005; Sainz et al., 2006; Ujike et al., 2008; Struck et al., 2012) or ACE2 (Imai et al., 2005; Han et al., 2006), small molecules that bind S protein (Yi et al., 2004) and inhibitors of cellular protease (Simmons et al., 2005; Wang et al., 2007; Zhou et al., 2011). In addition, TNF-α Converting Enzyme (TACE) and lactoferrin bound to heparin sulfate proteoglycans have also been identified as targets for inhibition of viral entry (Haga et al., 2010; Lang et al., 2011).

1.4. Viral Protease Inhibitors

SARS viral replicase polyprotein is proteolytically processed by the viral proteases to generate functional enzymes. Owing to their essential role, 3CL protease, the main protease and the Papain-Like Protease (PLP2) of SARS-CoV are considered important drug targets. Based on homology modeling using crystal structures for human coronavirus and an inhibitor complex of porcine coronavirus, Anand et al. (2003) proposed that rhinovirus 3C protease inhibitors might be modified for inhibiting SARS protease (Anand et al., 2003; Regnier et al., 2009).
Table 1. Effect of antiviral agents on SARS-CoV in vitro

| Agent                              | Major effects reported                                                                 |
|------------------------------------|----------------------------------------------------------------------------------------|
| Calpain                            | A class of cellular cysteine proteinases that inhibited SARS virus yield with an effective concentration in micro molar range (Barnard et al., 2004) |
| Niclosamide                        | An existing antihelminthic drug that abolished viral antigen synthesis at concentration of 1.56 uM (Wu et al., 2004b) |
| Aaurintricarboxylic Acid (ATA)     | ATA is known to inhibit protein and nucleic acid interaction. It was reported to be 10 or 100 times more potent inhibitor of SARS-CoV than IFN-α and IFN-β, respectively (He et al., 2004) |
| Chloroquine                        | A clinically approved drug for malaria was effective with an IC50 in lower μM range (Keyaerts et al., 2004). In addition to its effect through elevation of endosomal pH, chloroquine seems to interfere with terminal glycosylation of ACE2, the receptor for SARS-CoV (Vincent et al., 2005) |
| Nitric oxide                       | Nitric oxide donor S-nitroso-N-acetylpenicillamine inhibited SARS-CoV by 2 logs at 100 μM (Akerstrom et al., 2005) |
| Hydrocortisone                     | Only at very high concentrations, hydrocortisone showed a moderate effect on chemokine production by SARS-CoV (Cinatl et al., 2005) |
| Procyanidins and butanol           | A moderate inhibitory activity in wild-type SARS-CoV and HIV/SARS-CoV extracts of cinnamomi cortex | pseudovirus assay is reported (Zhuang and Jiang, 2009) |
| Synthetic peptides outside of spike protein heptad | S protein fragments spanning sequence variation hotspots reduced |
| Dippeptide glutaminyl fluoromethyl ketone | An inhibition with EC50 value in low μmolar range is observed (Zhang et al., 2008) |
| Cyclopentenyl carbocyclic nucleosides | 1,2,3-trizole analogs which, exhibited an antiviral activity with an |
| Indomethacin                       | Inhibits viral RNA synthesis with > 1,000 fold reduction in CC0-V infected dogs (Amici et al., 2006) |
| Phenanthroindolizines              | Tylophorine compounds inhibited SARS-CoV with EC50 in nM range (Yang et al., 2010) |
| Emodin                             | Emodin is shown to inhibit SARS-CoV via its ion channel protein, 3a (Schwarz and Wang, 2011) |
| Glycyrrhizin                       | Glycyrrhizin inhibits SARS but some of its derivatives showed reduced specificity (Hoever and Baltina, 2005) |
| Antisense Peptide Nucleic Acids (PNAs) | PNAs that were targeted to interfere with programmed -1 ribosomal shifting and fused to cell penetrating peptides resulted in inhibition of SARS-CoV replication with IC50 of 4.4 μM (Ahn et al., 2011) |
| Antisense morpholino oligomers     | Oligomers targeted to Transcription-Regulatory Sequence (TRS) are reported to show a low inhibitory activity against SARS-CoV (Neuman et al., 2005) |
| SiRNA                              | siRNAs for various targets including, interferons, leader sequence or N protein have been tested (Li et al., 2005a; 2005b; Wu and Huang, 2005; Zhao and Qin, 2005; Tang and Li, 2008) |

Homology modeling also formed a basis for designing mechanism-based irreversible inhibitors of 3CLpro with an activity of wide spectrum across coronaviruses (Yang et al., 2005a). Besides, several groups have identified a number of inhibitors of 3CLpro using a variety of approaches. Virtual screening (Plewczynski et al., 2007; Mukherjee et al., 2008; 2011; Nguyen et al., 2011) or a high-throughput screening of small molecule libraries have identified inhibitors including an anti-HIV agent and serotonin antagonist, cinanserin (Blanchard et al., 2004; Kao et al., 2004; Wu et al., 2004a; Chen et al., 2005). Other 3CL protease inhibitors identified so far belong to categories such as plant derived phenolic or flavonoid compounds (Lin et al., 2005; Nguyen et al., 2012), active site, non-active site or competitive inhibitors (Kaeppler et al., 2005; Lee et al., 2005; Du et al., 2007; Ryu et al., 2010), ketones or ester based inhibitors (Goetz et al., 2007; Zhang et al., 2007; Ghosh et al., 2008; Shao et al., 2008; Verschueren et al., 2008; Zhang et al., 2008), modified peptidomimetic inhibitors (Ghosh et al., 2007), metal conjugated inhibitors (Lee et al., 2007; 2009), common inhibitors of Corona and Picornaviruses
potential antiviral drug targets have been identified (Kuo et al., 2009) and pyrimidines (Ramajayam et al., 2010). Protease inhibitors have also been reviewed elsewhere (Liang, 2006; Ramajayam et al., 2011).

In addition to its role in proteolytic processing of the viral polymerase, PLP2 is also involved in host evasion. Some of the first identified small molecule lead compounds for inhibition of PLP2 were thiopurine analogs (Chou et al., 2008; Chen et al., 2009). Besides, Ratia et al. (2008) have synthetically evolved a noncovalent inhibitor demonstrating an IC_{50} of around 15 µM in a cell based SARS-CoV replication assay (Ratia et al., 2008). Dooley et al. (2006) and Ghosh et al. (2009) have identified small molecules with EC_{50} values in lower micromolar range (Dooley et al., 2006; Ghosh et al., 2009). Recently, a yeast-based assay for measurement of papain-like protease activity that is suitable for screening of inhibitors was established (Frieman et al., 2011).

1.5. Helicase Inhibitors

Bismuth complexes and RNA aptamers have been shown to inhibit activity of SARS-CoV helicase (Yang et al., 2007; Jang et al., 2008; Adedeji et al., 2012; Keum and Jeong, 2012).

1.6. Host Pathway Inhibitors

Although, inhibitors of viral proteins have been used for treating some other viral infections, asignificant issue with targeting the viral proteins has been the development of drug resistant virus. This is likely due to the selection of mutant virus under drug pressure. Inhibitors of host systems, including immune and housekeeping, that may be critical for virus survival are alternatives that are worth an investigation. Cyclosporine and FK506 have emerged as examples of such inhibitors (De Wilde et al., 2011; Pfefferle et al., 2011; Carbajo-Lozoya et al., 2012). Other host pathway protein targets have been identified (Ma et al., 2010; Bhardwaj et al., 2012; Millet et al., 2012; Smith et al., 2012; Zhao et al., 2012).

1.7. Vaccines and Immunotherapy for SARS-CoV

Coronaviruses cause significant infections in humans and animals. Although, no vaccines against coronaviruses are available at this time for use in human, they are produced for use in animals (Olsen et al., 1993; Anton et al., 1996). A need for prophylactic treatment for a vaccine is underscored by what happened during the 2002-2003 SARS outbreak. In the Vietnamese outbreak of SARS, all patients who died apart from the index patient were healthcare professionals including a WHO scientist, Dr. Carlo Urbani. It was Dr. Urbani’s initiatives that led to the successful containment of the disease in Hanoi. He died of SARS on March 29th 2003.

Roberts et al. (2008) and Roper and Rehm (2009) have reviewed the SARS animal models and the initial vaccine studies in great detail (Roberts et al., 2008; Roper and Rehm, 2009). Several animal models that have been developed for SARS vaccine studies include mice, African green monkey, ferrets, macaques, hamsters and Chinese masked palm civet. Multiple labshave demonstrated the feasibility of various types of vaccines (Table 2). However, vaccine efficacy and safety issues are still being investigated (Table 2). Studies related to SARS vaccine have taught us several lessons about pathogenesis and host responses to SARS-CoV, in addition to unraveling the need for caution. With certain experimental vaccines, such as the viral vectorsbased ones, immunopathology and redirection of the viral vector to brain was reported (Czub et al., 2005; Deming et al., 2006; Kam et al., 2007; Jaume et al., 2011; Tseng et al., 2012). Subsequent studies demonstrated that a sub lingual immunization can prevent the viral vector entry into the brain (Shim et al., 2012). Also, an intranasal route of vaccination was shown to protect mice from SARS-CoV challenge better than an intramuscular delivery of the same vaccine (See et al., 2006; Hu et al., 2007). Expression of full length S protein is shown to result in enhanced hepatitis or infection whereas, expression of just the ectodomain of S protein eliminated infection enhancement (Weingartl et al., 2004; Yang et al., 2005b). All these reports point to that it will be important to establish appropriatecombination of vaccination route, vaccine vector and choice of epitopes for each vaccine type. SARS vaccines that generates predominantly cellular or a predominantly humoral response, as well as therapeutic monoclonal antibodies, have been shown protectiveor effects in animal models. Therefore, what kind of responses are important for protection has not been clear (Subbarao et al., 2004; Zakhartchoak et al., 2005; Lin et al., 2007; See et al., 2008; Zhao and Perlman, 2010). Cameron et al. (2012) have recently reported an analysis of transcripts expressed during SARS-CoV infection in vaccination and reinfection trials in ferrets (Cameron et al., 2012). Such studies can potentially reveal new therapeuticoptions in addition to providing the basic understanding of host responses during infection, vaccination and re-infection.
2. CONCLUSION

Although, a myriad of compounds have been identified to show inhibitory effects on SARS-CoV \textit{in vitro}, only a few of those are reported for their safety and efficacy in animal models. Of the tested compounds, a hybrid interferon alpha (IFN-α) and an IFN- inducer, a mismatch double stranded RNA, have shown potent inhibition of SARS-CoV replication in the lungs of infected mice (Barnard et al., 2006). It would be useful and desirable to evaluate the other compounds in animal models for their safety and efficacy. With identification of epitopes that will not generate antibodies cross-reactive to self-antigens and care taken to eliminate antibody dependent enhancement of disease, therapeutic use of human monoclonal antibodies seems a promising option for SARS. Coughlin and Prabhakar (2012) have reviewed the human monoclonal antibodies generated for anti-SARS therapy (Coughlin and Prabhakar 2012). For active immunization, efficacy of the developed vaccines needs to be established in a most relevant disease model. Efforts have gone into improving animal models for SARS; however, they still have limitation.

A novel SARS-like human coronavirus, HCoV-EMC/2012 was identified earlier this year (Lu and Liu, 2012; Boheemen \textit{et al.}, 2012). Although, HCoV-EMC/2012 is only distantly related to SARS-CoV, the knowledge and reagents acquired from SARS-CoV research may prove useful in understanding and controlling this novel and other coronavirus (Elshabrawy \textit{et al.}, 2012; Graham \textit{et al.}, 2012).

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