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Severe Acute Respiratory Syndrome, a Pathological Immune Response to the New Coronavirus—Implications for Understanding of Pathogenesis, Therapy, Design of Vaccines, and Epidemiology

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ABSTRACT

Findings coming from autopsies and serum of SARS patients suggest an important immune-inflammatory implication in the evolution to respiratory distress. Conditions such as HIV infection or treatment with immunosuppressors (in cancer or autoimmune diseases) are not among the bad prognosis factors for development of distress. To date, there have been no reported case fatalities in children, probably due to their more immature immune system. Our conclusions follow: (1) The milder form of SARS in children and the apparent protective factor that immunosupression represent rules out a significant viral cytopathic effect (they would be the most affected). (2) The evidence for immune implication in distress strongly supports immunomodulators for therapy: phosphodiesterase inhibitors (due to their down-modulating activity on proinflammatory cytokines); inhaled corticoids (aimed at producing a local immunomodulation); teophylline or nedocromil sodium (which prevents inflammatory cell recruitment into the airway wall). (3) An early immunomodulatory therapy, based on the levels of proinflammatory cytokines and clinical parameters to evaluate the respiratory function such as arterial oxygen saturation, could prevent the occurrence of distress. (4) Vaccine design should consider the immune origin of distress. (5) Physicians should be aware of mildly symptomatic patients (children, immuno-compromised hosts) to avoid transmission to immunocompetent adults.

INTRODUCTION

Severe acute respiratory syndrome (SARS) produced 774 deaths worldwide during the first (and so far the main) outburst in 2003. SARS has returned in 2004 in the form of limited focuses that have been controlled satisfactorily. The causal agent was identified as a new Coronavirus that fulfilled Koch's postulates (13). Once the causal agent was identified, the following steps were taken to understand the viral cycle, transmission, and disease spread better: study of viral tropism, identification of tissues and fluids where the virus was present, characterization of possible reservoirs, and achievement of an animal model (30,36). However, we feel there are still unsolved questions regarding SARS pathogenesis: What is the underlying cause of respiratory distress? Is it a direct viral cytopathic damage or an immune-mediated damage in response to the viral infection? What is the relevance and weight of both components in the pathogenesis of SARS?

In adult SARS patients, respiratory distress is the principal cause of mortality (14). When the scientific com-

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munity deals with a viral infectious disease, the first rational approach is to attribute the damage to a direct viral action. SARS has not been an exception. This explains why the most important international initiatives have involved achieving an effective vaccine, to test drugs that could show an antiviral effect, and to design new ones for this purpose. However, there is strong evidence that the immune system is implicated in SARS pathogenesis.

Anatomopathological findings. The first evidence came from autopsies (42), which showed flooding of alveolar lumina with edema fluid mixed with inflammatory cells, a pronounced increase in macrophages in the alveoli and the interstitium of the lung and hemophagocytosis. Hemophagocytosis has been previously attributed to dysregulation of T lymphocytes and proinflammatory cytokines (24). As suggested by Nicholls et al., proinflammatory cytokines released by stimulated macrophages in the alveoli could have a prominent role in SARS pathogenesis (42).

Cytokine profile. In concordance with these findings, various authors have observed elevation of several proinflammatory cytokines and chemokines in the serum samples of SARS patients (Table 1). This fact may be associated with lung infiltration and proliferation (2,12,53,56). In contrast, Zhang et al. have recently reported finding no elevation of proinflammatory cytokines in SARS patients, except interleukin-6 (IL-6) (57). The possible reason for these differences will be discussed later. Wong et al. found increases in interferon (IFN)–gamma in addition to a number of other cytokines and chemokines during the 2 weeks after onset (53). IFN-gamma plays an important role in regulating the balance between Th1 and Th2 cells. Firstly, it increases the synthesis of IL-12 in antigen-presenting cells. IL-12 is the primary effector that drives developing $CD4^+$ T cells to become Th1 cells. Secondly, IFN-gamma prevents the development of Th2 cells by inhibiting the production of IL-4, which is required for Th2 cell formation. IFN-gamma also plays an important role in macrophage activation (18). A group of Canadian researchers of the University Health Network (Toronto) and the Canadian Network for Vaccines and Immunotherapeutics (CANVAC) have studied the role of chemokines in SARS. CXCL10 (IFN-gamma–inducible protein 10/IP-10) is a chemokine associated with inflammation and proliferation. In a study on SARS patients, they observed that plasma levels of IFN-gamma were significantly elevated at onset of symptoms. Levels of CXCL10 were also significantly increased in SARS patients at onset, but remained specifically elevated in critical patients and were highest in dying SARS patients. Furthermore, CXCL10 and its receptor, CXCR3, were elevated locally in lung specimens from deceased patients (25). They hypothesize that the maintenance of high CXCL10 expression in the lung in SARS patients may generate a positive feedback loop, resulting in the continual recruitment of activated T cells. This would lead to severe lung inflammation. Thus, IFN-gamma could be promoting the secretion of proinflammatory chemokines in SARS; in consequence, IFN-gamma down-modulation could translate into clinical benefit. On the other hand, interferon-alpha and -beta are known to induce cells into the antiviral state. Preliminary studies with interferon-alpha and -beta reveal a promising antiviral activity of these drugs

Table 1. Cytokine Profile in SARS

	Duan et al.	*Beijing Group of National Research Project for SARS*	*Wong et al.*	*Xie et al.*
IL-1b	**X**		**X**	
IL-2	**X**			
IL-4	X			
IL-6	**X**	**X**	**X**	
IL-8	**X**	**X**	**X**	**X**
IL-10	X			
IL-12			**X**	
IL-13		X		
IL-16		**X**		
TNF-alpha	**X**	**X**		**X**
TGF-beta1		X		
IFN-gamma			**X**	
MCP-1			**X**	
IP-10			**X**	

Proinflammatory cytokines and chemokines are bold faced. IL, interleukine; TNF, tumour necrosis factor; TGF, transforming growth factor; IFN, interferon; MCP, monocyte chemoattractant protein; IP-10, IFN-gamma-inducible protein-10.

(10,20,48). The authors of these studies suggest their clinical testing for SARS treatment. To conclude, the virus is believed to come from an animal host, with further transmission to humans. Based on this, it does not seem to be hazardous to suppose that an incorrect or exacerbated immune response against this uncommon virus could lead to an intense inflammatory response. In the opinion of Duan et al., this inflammatory response is systemic (12), focusing mainly on the lungs (Table 1).

Viral load evolution. An important event that supports the immune implication in the development of respiratory distress is the evolution of viral load. The timing of the IgG seroconversion in SARS patients, which starts on day 10, seems to correlate with falls in viral load, which occur from day 10 to 15. Severe clinical worsening also occurs at this time, which cannot be explained by an uncontrolled viral replication. The findings suggest that the lung damage at this phase is related to an immunopathological damage resulting from an overly exuberant host response, rather than an uncontrolled viral replication (45).

Clinical course in children. The first reports about SARS in pediatric patients yielded a surprising conclusion: SARS in children seems to appear in a more benign form than in adults. There is currently abundant evidence that the disease in children under 12 is less severe than in adults, while adolescents' clinical features are similar to those found in adults. To date, there have been no reported fatalities in children with this disease (5,8,11,22,31,50,54). Three possible explanations have been suggested: (a) children were kept relatively isolated from the outside world during the epidemic, therefore avoiding the infection; (b) their immature immune system does not cause acute lung injury; and (c) children have anti-SARS antibodies. GuanFu and ZhongYuan studied the possibility of the existence of protective anti-SARS antibodies in children as a result of multiple vaccinations in the childhood (19). Their studies with vaccinated mice showed that there was essentially no cross-immunoreactivity between the SARS-coronavirus and the 13 common vaccinal immunogens tested. This study, along with the communications reporting that anti-SARS activity can be detected in very few if any non-SARS children's serum samples (33,34), leads to the conclusion that the presence of anti-SARS antibodies in children can be apparently ruled out as the cause of the low morbidity. In regard to the "children's isolation" theory, in our opinion it is difficult to maintain that, in the affected Asiatic countries, with an elevated population density and strong familial communities, children could be kept away from infected adults. Thus, the immaturity of children's immune system appears to be the most plausible explanation for the low incidence of respiratory distress in children under 12 years old and, in general, for the milder course of the disease in children. These conclusions again support a pathogenic role of immune response against the virus that could explain the pathogenic events in immunocompetent adults (4).

Immunosuppression as a probable protective factor. In the context of a viral disease, immunosuppressed hosts are thought to be the most affected. Fowler et al. (14) reported a cohort of critically ill patients with SARS. Patients who died were more often older people with comorbidities such as diabetes. However, immunosuppressive conditions, such as HIV infection or treatment with immunosuppressors (employed in cancer patients or autoimmune disorders for example), were not listed among the negative prognosis factors. The Chinese Ministry of Health has estimated that more than 1 million people were infected by HIV in China by the end of 2002. In contrast, to date no reports indicating that HIV infection is a risk factor for development of SARS have been published in China (neither from other affected countries, such as Taiwan, Canada or Singapore). There has been only one documented case of an HIV patient infected with the SARS-associated coronavirus (52). He was on highly active antiretroviral therapy (HAART), including lopinavir/ritonavir (Kaletra), efavirenz, abacavir and tenofovir. The patient's disease ran a relatively mild course, and in 39 days, he was declared SARS free. The authors offer two possible explanations: the protective effect of HAART or the immunosuppression due to HIV infection. HIV patients in contact with SARS patients have been shown not to develop respiratory distress (7). Most of these HIV patients were in treatment with HAART, so a protective effect of HAART in SARS has been hypothesized. Some of the drugs used for HIV treatment could display antiviral activity against the SARS associated Coronavirus. Chu et al. observed an apparently favourable clinical response in their patients treated with a combination of anti-HIV protease inhibitors (PI) lopinavir/ritonavir (Kaletra) with ribavirin (9). Consequently, the use of anti-HIV drugs has been suggested for patients with SARS and in the prophylaxis of patients' close contacts (7). However, if the case of the only HIV patient reported with SARS infection is considered, the patient was in treatment with PI before SARS infection. As the authors comment: "it could be argued that if Kaletra was active against Coronavirus, it should have prevented the infection in the first place" (52). In our opinion, the positive role of HIV PI in SARS could be attributed not only to an antiviral activity but also to an immunomodulatory activity. Nuclear factor–kappa B (NF-kB) is an ubiquitous transcriptional factor and a pleiotropic regulator of many genes involved in inflammatory responses and immuno-regulatory activities. In most cell types, NF-kB is associated with the inhibitor IkB in the cytoplasm. The NF-kB activation follows this sequence of events: in response to external sig-

nals, IkB binds to NF-kB factor. Activation requires IkB phosphorylation at serine residues, followed by phosphorylation-dependent multi-ubiquitination at lysine residues, degradation of IkB by an ubiquitin-dependent proteasome and, finally, the release of free NF-kB transcription factor. Free NF-kB moves to the nucleus and induces expression of certain genes. kB degradation is an efficient process that can be inhibited by serine protease inhibitors, suggesting that it is an obligatory step in NF-kB activation (17). Monini et al. have reported that IP are capable of inhibiting inflammatory cytokine production and modulating antigen presentation and T-cell responses (37). In particular, ritonavir has recently been shown to inhibit the expression of adhesion molecules and the production or release of inflammatory cytokines or chemokines, including tumour necrosis factor (TNF) alpha, IL-6 or IL-8 by endothelial cells (44). HIV PIs, used at therapeutic concentrations, affect pathways involved in cell invasion and matrix metallo-proteases (MMP) activity, particularly MMP-2 proteolytic activation (37). MMPs are known to be involved in several immune and immunomodulatory functions. Specifically, MMPs are required for leucocyte transmigration and tissue infiltration by inflammatory cells. In this context, ritonavir has been shown to abolish cytotoxic T lymphocyte (CTL)–dependent inflammatory responses in a murine model of lymphocytic choriomeningitis virus infection (1). André et al. found that ritonavir appeared to inhibit the chymotrypsin-like activity of isolated 20S proteasomes in vitro, being able to reduce proteasome cellular functions such as the degradation of ubiquitin conjugates and IkB (1). In addition, Tovo has reported a study on two HIV-uninfected subjects in prophylaxis with HAART including indinavir. At the end of prophylaxis in both subjects, who did not acquire HIV, the percentage of peripheral blood mononuclear cells expressing TNF-alpha, IL-2 and IFN-gamma was reduced when compared with simultaneously tested normal controls (51). All these studies attempt to examine the role that the immunomodulatory properties of IP could play in SARS.

Corticoids in the treatment. In general, the use of steroids for SARS seems to be beneficial. The differences encountered in the clinical results with corticoids are probably explained by the fact that the optimal timing, dosage, and duration of treatment have not been determined yet (15). However, as discussed in the second part of this article, the adverse effects of systemic corticoids are themselves a cause of mortality and morbidity (Fig. 1).

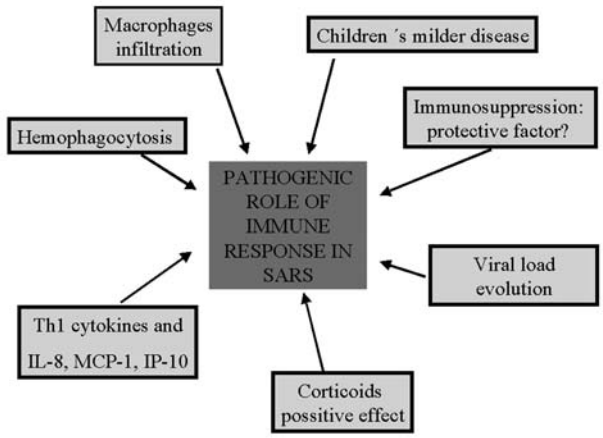

FIG. 1. Evidence of the immune implication in SARS.

ANALYSIS

The evidences recovered here could contribute to a better understanding of the disease. On the basis of these evidences, the responsibility of an abnormal immune response in the pathogenesis of respiratory distress appears to be clear. This conclusion could lead to the development of better treatment approaches. It also affects vaccine design, epidemiological control of the disease and prevention of spreading.

Relevance for therapy strategies. An important question to be answer for SARS treatment is the degree of viral pathogenicity. If a direct viral cytopathic effect were the principal cause of the lung damage in SARS, then young children would be the most affected patients, due to their immune system's immaturity (4). The same rational could be applied to immuno-suppressed hosts. However, the reality is that children under 12 years old do not develop respiratory distress, with no need of oxigenotherapy. Additionally, immunosuppressed hosts are not reported to show an increased mortality. Even more, it seems to represent a protective factor. Pharmacological research (screening of drugs with antiviral activity against the new Coronavirus and design of new ones) is undoubtedly necessary in SARS. However, perhaps we currently have drugs in our pharmacies that could prevent respiratory distress. The role that immunomodulators could play in SARS therapy acquires more relevance; we have previously proposed phosphodiesterase (PDE) inhibitors as drugs to be considered because of their activity in decreasing proinflammatory cytokines. They present other interesting pharmacological properties, for example their ability to decrease the in vitro replication of several kinds of viruses (3). In addition, we propose here other alternative immunomodulators: inhaled corticoids, teophylline, cromolyn sodium, ketotifen, and nedocromil sodium.

PDE inhibitors

a) Non-specific PDE inhibitors. Pentoxifylline (PTX). PTX is able to decrease the secretion of TNF, IL-1 and IL-6, as well as IP-10 (CXCL10), modulating neutrophil

and macrophage activation (6,27,29,40,46). By blocking the inflammatory action of IL-1 and TNF on neutrophils, PTX may reduce the tissue damage caused by neutrophils in conditions such as septic shock, adult respiratory distress syndrome, cardiopulmonary bypass lung damage and myocardial reperfusion injury (47). Other proof or its efficacy modulating inflammation is that PTX can inhibit cytokine release from alveolar macrophages in pulmonary sarcoidosis (49) (a NIH clinical trial to test PTX in this disease is currently ongoing). Additionally, PTX can inhibit ICAM-1 expression and chemokine production (IL-8 and MCP-1) induced by proinflammatory cytokines in human pulmonary epithelial cells (28). In a previous study, our group examined the in vitro activity of PTX on cell proliferation, cytokine production, viral replication and $CD4^+$ depletion in acutely HIV-1–infected human T-cells. PTX was able to inhibit with similar potency IFN-gamma, TNF-alpha and cell proliferation (38). PTX also has an additional advantage. Evidence on its down-modulating effect on proinflammatory cytokines does not come only from in vitro assays. It has also been tested in patients, patients with other diseases with an important inflammatory component. In this context, PTX administration provides clinical benefit. Examples of this are HTLV-I-associated myelopathy/tropical spastic paraparesis, asthma, acute respiratory distress syndrome in oncological patients or mucosal leishmaniasis (3). It has also been tested successfully in animal models for *P. carinii* lung infection and experimental bleomycin-induced fibrosing alveolitis (two other inflammatory conditions) (3). In relation to the mechanism of action of PTX, we showed in another work that PTX and Rolipram, (a specific PDE IV inhibitor discussed later), decreased transcription of IL-2 and TNF-alpha promoters in transiently transfected normal T-cells. Moreover, they inhibited the activation of NF-kB and nuclear factor of activated T cells (NFAT), and stimulated activator protein–1 (AP-1) and cAMP response element-binding proteins (CREBs). These data indicate that blockade of PDE IV regulates transcription of inflammatory cytokines through inhibition of NF-kB and NFAT, and stimulation of AP-1 and CREB (23). But the complete mechanisms of action of PTX remain to be elucidated. Haddad et al concluded in their elegant work with primary cultures of alveolar epithelia that, taken together, the potent anti-inflammatory potential of PTX points to a multifaceted mechanism of action (21): "It is possible that this non-selective PDE inhibitor regulates an inflammatory signal by counteracting intracellular reactive nitrogen species/reactive oxygen species and up-regulating a feedforward/feedback loop via amplification of IL-10. However, the possibility that PTX suppresses IL-6 via direct inhibition of TNF-alpha cannot be excluded." PTX is an inexpensive drug, with very low toxicity and minimal side effects associated with chronic use (dizziness, headache, nausea or vomiting, stomach discomfort).

b) Specific PDE IV inhibitors such as Rolipram, Roflumilast and Cilomilast: they act exclusively on the isoenzyme IV of PDE, being able to decrease proinflammatory cytokines just as PTX does (16). PDE IV is abundant and the major regulator of cAMP metabolism in almost every proinflammatory and immune cell. Because of that, these drugs are being investigated for possible applications in respiratory inflammatory diseases such as chronic obstructive pulmonary disease (COPD). However, the specific PDE isoenzymes regulate differentially the inflammatory cytokine biosynthesis (21). Since other isotypes of the enzyme are also present in the lung (isoenzymes I, II, III, V, VII), we postulate that a non-specific phosphodiesterase inhibitor such as PTX could perform a wider spectrum of activity in SARS than the specific ones.

Inhaled corticoids. With less immuno-suppressor activity than those administered orally or intravenously, inhaled corticoids would be aimed at exerting a local immunomodulation in the lung. Misuse of systemic glucocorticoids and antibiotics in SARS has lead to secondary infections, pathological fractures and avascular necrosis. These adverse effects have represented an important cause of mortality (32). Perhaps, given in time, inhaled corticoids could prevent distress arrival with minimal adverse effects.

Other xanthines (such as teophylline). This drug not only induces bronchodilation, but also inhibits inflammatory cell activation and infiltration in the airways.

Cromolyn sodium, ketotifen, and nedocromil sodium. They are anti-allergic drugs used prophylactically in the treatment of bronchial asthma. Cromolyn and nedocromil sodium are active by inhalation. Ketotifen is orally active. The mechanisms of action of these prophylactic drugs are not clearly understood, but cromolyn sodium was originally thought to be a "mast cell stabilizer," preventing the release of histamine and other inflammatory mediators. It is now clear that this action is not the only effect of these prophylactic drugs. They are capable of affecting many inflammatory cell types, including alveolar macrophages, thereby preventing inflammatory cell recruitment into the airway wall.

Specific TNF-alpha inhibitors (drugs such as Etanercept or Infliximab). These drugs have demonstrated to provide clinical benefit in the context of inflammatory diseases such as rheumatoid arthritis or inflammatory intestinal disease. In our opinion, it would be more useful to target a wider range of proinflammatory cytokines,

other than TNF, which could be implicated in the disease pathogenesis. PTX would represent a better option in this regard. Moreover, these specific anti-TNF drugs have been reported to be associated with the appearance of some infections such as tuberculosis reactivations (26). Finally, these kinds of drugs are really expensive.

In our opinion, an early immunomodulatory therapy based on the levels of proinflammatory cytokines such as TNF and IFN-gamma could prevent the appearance of respiratory distress or improve the patient's clinical condition once it is established. In conclusion, immunomodulators, in combination or not with antivirals, seem to be a good option. We emphasize that young children, as shown by the reports previously described, seem to need no antivirals or immunomodulators to overcome the disease.

Relevance for vaccine development. As is the case with viral diseases, obtaining an effective vaccine is a current priority in SARS research. However, considering our previous comments, it is important to think once again about the role that the immune system plays in the pathogenesis. Vaccine design should avoid those SARS coronavirus antigens and vaccinal strategies that could lead to immune-mediated inflammatory damage, as happens in the natural disease. First of all, we need a good animal model. Present alternatives are not fully satisfying (35). The animal model's pathology has to resemble that of the human disease (35); even more importantly, the animals used to test any vaccines have to be mature. If the animals used to test the vaccine are too young, it could be more probable not to find adverse effects, judging by SARS clinical behaviour in young children. Researchers have to be very careful in vaccine development for this disease, as they could paradoxically develop a vaccine that, instead of conferring protection, would induce damage. There is a clear precedent. Several vaccines designed to protect cats from feline infectious peritonitis virus, also a coronavirus, predispose them to accelerated disease and death from the virus. Something similar happened with vaccines for measles and respiratory syncytial virus during trials in the 1960s. Even today, people who received that measles vaccine can develop serious disease when they encounter the measles virus (35). Of course, attenuated vaccines with living virus, although more immunogenic, would represent a higher risk in relation with inducing a possible inflammatory response than the ones based on isolated viral antigens. In our view, the development of vaccines capable of stimulating the production of antibodies with the ability to block viral cell entry should be the main objective in SARS, rather than the development of ones that could elicit a strong cellular response in the host. Management of this infectious disease could benefit from the development of this kind of vaccines for prevention of the infection, along with the use of immunomodulators (combined or not with antivirals) in the treatment.

Moreover, it would be interesting to study the prevalence of antibodies against other more common coronaviruses in SARS patients, and the correlation with their clinical course. Human coronaviruses 229E and OC43 cause 30% of colds (39); antibody prevalence should therefore be high in the general population. Has the presence of antibodies against other common coronaviruses any influence in the final outcome of SARS patients? On the other hand, patients having previous contacts with ordinary coronaviruses will develop a secondary immune response (stronger and more specific) in further encounters. Is there any cross-reaction between this secondary immune response to other common coronaviruses and the immune response to SARS coronavirus? Children under 12 years of age are probably having initial contacts with common coronaviruses, and thus developing primary immune responses. Adolescents and adults have been exposed to a wider range of coronaviruses, and have the ability to develop a powerful secondary immune response to them. Does this secondary immune response play any role in SARS (protective or deleterious)?

Relevance for epidemiological control of the disease. According to the exposed in the introduction, immunodeficiency state could be a protective factor against the development of respiratory distress. Patients with an immature or a depressed immune response could show a sub-clinical form of the disease. The existence of mild-symptomatic pediatric infected patients, with symptoms similar to those of influenza, could lead to undiagnosed cases. These children will become unadvertised hosts for the virus, with the possibility of transmitting the disease to adults (patients who develop a more severe course). The same could be true for immunosuppressed hosts, so physicians working in affected countries should be aware of any kind of subclinical condition suspicious of SARS, and confirm when possible by serology to SARS coronavirus or by molecular biology technologies. These precautions can be extremely useful to control virus spreading.

The specific case of HIV patients under HAART therapy. HAART leads to immune reconstitution in HIV patients, decreasing the risk of infections. However, if a competent immune response seems to be fundamental in the evolution to distress in SARS, what would be the consequences of immune reconstitution in HIV patients regarding risk for distress? Will it be increased, or will they be protected by the use of protease inhibitors? Knowing more about SARS physiopathology appears to be essential for dealing better with a new outburst of SARS.

Additional tests to be implemented in SARS. In our view, current reports usually focus on virus but somehow leave aside the cohort of events triggered by the immune system. In the event of a new outburst of SARS, it seems

necessary to include additional immunological tests to perform on SARS patient samples and on autopsy tissues. Regarding cytokine measurements, as said by Openshaw (43), the site of sampling, the exact time after infection, and the methods used to measure cytokines are critical determinants with fundamental affects on the interpretation of such studies. Cytokine release is often a very local phenomenon. Additionally, the differences existent among different authors in regard to the cytokine profile in SARS could be attributed to the moment of sample collection and the kind of treatment that patients were then receiving (pulsed or high doses of corticoids, for example). Peripheral measurements of cytokines levels might not reflect local pathogenic events well. Cytokine levels in serum samples (coming from peripheral blood) may not be the most accurate samples to use in deciding about the kind of treatment or when to begin therapy. Cytokine measurements from sputum, nasopharyngeal or oropharyngeal specimens, tracheal or bronchoalveolar lavage (BAL) could be more representative of the local events in the lung. Arterial oxygen saturation by pulse oximetry, oxygen pressure in arterial blood (Pao_2) and the ratio of Pao_2 to fraction of inspired oxygen (Pao_2/Fio_2) could complement the information provided by the cytokine measurements. Both parameters (laboratory and clinical) could help choose the best moment to start treatment with immunomodulators. The objective is to achieve a correct balance in the immune response, which has to be able to eliminate the virus while avoiding inflammation-mediated damage. In this way it might be possible to avoid acute lung injury (Pao_2 200–300) or respiratory distress ($Pao_2 < 200$). Thus, these immunological markers could be useful in disease monitoring and for prognosis. Another important tests to know more about SARS pathogeny should include immuno-histochemistry for Th1 and Th2 cytokines and complement deposit in pulmonary tissue coming from autopsies, study of white blood cells patterns of activation by flow cytometry (immunophenotype) along with intracellular staining for TNF and IFN. Finally, SARS courses with T CD4 and CD8 lymphopenia along with neutrophilia (55). The possibility of an apoptotic mechanism in T cells in response to cytokines such as TNF should be studied further (Fig. 2).

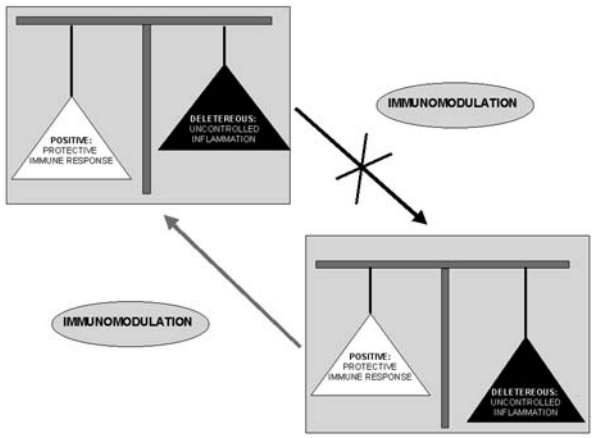

FIG. 2. Rationale for the use of immunomodulators in SARS. Starting immunomodulatory therapy early could prevent the exacerbated inflammatory response that leads to respiratory distress. Once distress is established, immunomodulatory therapy would be aimed at down-modulating inflammation.

CONCLUSION

There is strong evidence supporting the important role that an abnormal immune response (rather than a direct viral cytopathic effect) could play in SARS pathogenesis. Such evidence comes from autopsies, studies on patient's serum samples (showing elevation of proinflammatory cytokines), along with the revelation of immunodeficiency state and immune system immaturity as protective factors against evolution to respiratory distress. Differences encountered in the clinical severity of the disease in adult patients are probably based on genetic differences (41) and on age (regulation of inflammatory-immune response could be worse in older people). Additionally, the influence of the previous personal history of contact with more common coronaviruses should be studied. The importance of the immune implication in respiratory distress affects therapy approaches; immunomodulatory drugs could be as good an option (or even better) as antivirals. The immunomodulatory drugs we propose are cheap, with no important adverse effects as demonstrated by their extended use in common daily medical praxis, representing an opportunity not only for Occidental countries but also for the ones with a lesser degree of development. Other drugs that could perform a positive role in SARS are PI, not only for their antiviral activity but also for their immunomodulatory properties. The monitoring of proinflammatory cytokines levels in appropriate samples (sputum, bronchoalveolar lavage) along with clinical parameters to evaluate the respiratory function, could be of use in choosing the best moment to start immunomodulatory therapy. The immune implication in distress pathogenesis in SARS shows additional consequences for the design of vaccines, epidemiological control of the disease and election of prognosis markers.

In conclusion, close interaction among immunologists and virologists would yield better results in understanding and managing the disease, as well as producing more efficient therapies. SARS constitutes a lesson for future emergent viral diseases. Pondering adequately the possibility of immune-related pathogenic factors could be dramatically relevant in the future.

The easiest explanation for a complicated problem is usually the one closest to reality.

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