SCRUB TYPHUS EMERGING THREAT

NEW HORIZONS

Scrub Typhus In HIV Patients-A Ray of Hope

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Introduction

Scrub typhus is caused by an obligate intracellular bacterium, *Orientia tsutsugamushi* (1), transmitted by trombiculid mites (Leptotrombidium deliense) (2,3,4).

It is an established fact that in HIV-1-infected individuals, viral load rises transiently in presence of any acute infection with another organism. Transient rises in HIV viral load have also been reported following immune activation by intercurrent infection, immunization, and even tuberculin skin testing. But many studies especially over the last decade were prompted by the unexpected finding that HIV-1 copy number fell instead of rising during an acute infection with *Orientia tsutsugamushi*, thus causing a suppressive action on viral replication in HIV-1 individuals not receiving antiretroviral drugs. This finding paved the way for future research of development of vaccines in HIV-1 infected patients.From all parts of the world, there are emerging data on specific infectious agents that may attenuate HIV-1 infection. New literature suggests that certain pathogens are capable of inhibiting HIV-1 replication. These include GB virus C, measles virus, *Orientia tsutsugamushi* and human T lymphotropic virus types 1 and 2. In addition, there are conflicting data on the effects of Mycobacterium tuberculosis on the replication of HIV-1, with some suggesting that this organism may also inhibit HIV-1 replication. In this review, we summarize and critically discuss the body of emerging literature concerning scrub typhus infection that may have the ability to attenuate HIV-1 infection (5). Hence, HIV-1-suppressive factors that are produced during scrub-typhus infection should be investigated further in the search for novel strategies for the treatment and prevention of AIDS.

Evidence and Mechanism

The idea for the study began about a decade ago, when George Watt, a tropical disease specialist in Bangkok, became intrigued by one HIV-1 infected patient who developed scrub typhus. It was surprising to him that this one patient's HIV level or "viral load" dropped coincident with an acute case of scrub typhus. Watt began systematically hunting for HIV-infected people who also had acute cases of scrub typhus in order to evaluate their response to the disease. After a massive, extensive and yearlong screening program in Thailand, Watt uncovered 10 people who clearly had both infections and no others. First, the Thai team compared viral loads in these patients to a control group of five HIV-infected people who did not have scrub typhus but did have either malaria or leptospirosis. Over the 28-day study, the investigators found that the patients with scrub typhus had significantly lower HIV viral loads than those with the other diseases. In two of these people, in fact, the levels fell so low that the most sensitive tests could not detect HIV. Median viral load 3 days after admission was significantly lower in the scrub-typhus group than in patients with other infections (193% vs. 376% of day 28 values, p=0·03). In four *O tsutsugamushi*-infected patients HIV-1 RNA copy number fell by three-fold or more compared with day 28 values (*Fig. 1*), and HIV-1 copy numbers were below the assay threshold in two patients with scrub typhus. The new findings were an absolutely fascinating example of how one infection ameliorates the effect of another (6). As HIV disease progresses usually, the virus typically evolves to a form more adept at destroying immune system cells. Specifically these HIV infected cells fuse with other cells to form clumps called "syncytia," which serves as an efficient means of transmitting the virus and speeding the course of disease. But when an HIV patient develops acute scrub typhus infection, synctia formation is impeded. Evidence came from second study, a comparison of viral variants in the same 10 scrub typhus patients and another control group whose CD4 counts were more closely matched. It was found that none of the 10 patients with scrub typhus had a syncytia-inducing HIV variant, whereas five of the seven controls did. Watt and his co-workers attempted to tease out how *O. tsutsugamushi* might thwart HIV. Preliminary data in both mouse and test tube experiments with human sera point to antibodies against scrub, which for some unknown reason seem also to bind HIV and blunt its progression.

In 2001, Watt and his colleagues examined the HIV-inhibitory effects previously found to be associated with scrub typhus infection. Individual 500 ml units of plasma from donors with mild scrub typhus were safety-tested, subjected to virucidal heat treatment, and administered to 10 HIV-1-infected recipients who were not receiving

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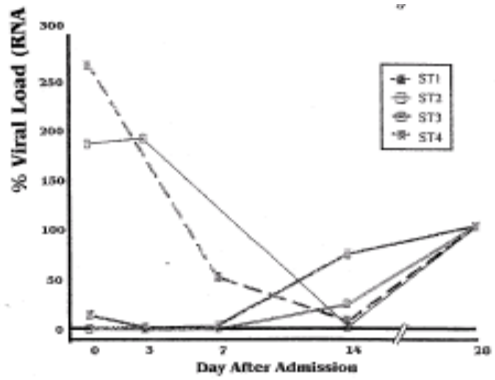

Fig 1. Shows Sequential HIV-RNA Concentration in Plasma [Rna/Ml] of 4 Patients Coinfected with HIV and Scrub Typhus

antiretroviral drugs. HIV-1 copy number fell three-fold or more in two recipients, and virus burden was reduced for 8 weeks in 70% (7/10) of recipients of a single plasma infusion, compared with the mean of three pre-infusion measurements. Thus establishing the fact that scrub typhus donor plasma inhibited HIV-1 in vitro compared with normal human plasma and media controls. In the clearest *in vivo* response, reduction in viral load was accompanied by clinical improvement, a switchback from the syncytia-inducing to the non-syncytia-inducing phenotype, and decreases in CD8 cells and IL-6 levels. Scrub typhus infections generated heat-stable, transferable plasma factors that exerted prolonged and evident anti-HIV effects (7).

As far as the mechanism of this phenomenon is concerned, many host and microbial factors have been shown to modulate HIV-1 infection. Among anti-HIV host factors are natural ligands or natural antibodies to HIV co-receptors, anti-inflammatory cytokines, interferons and several body fluid components such as lactoferrin and prostaglandins. Microbial pathogens/factors that may suppress HIV-1 infection include lipopolysaccharide, scrub-typhus rickettsia, human herpesviruses-6 or -7, and GB virus C (8, 9).

It has already been proven that CC subfamily Chemokines, MCP-1 and RANTES play a key role in modulating HIV-1 replication in mononuclear phagocytes in the blood and lung, thus having therapeutic implications for prevention and/or treatment of HIV disease (10, 11). So, *O. tsutsugamushi* induces the expression of these anti-HIV chemokine genes, encoding MCP-1, IL-8, and RANTES, in human endothelial cells. Chemokines belonging to the CC chemokine subfamily (potent attractants for monocytes and lymphocytes) are also induced (12). In view of this observation, and the relative increase in CD8+ T lymphocytes during HIV-1 disease, particularly in the lung, it is suggested that C-C chemokines might play a key role in suppressing HIV-1 replication and delaying the progression of the disease

Conclusion

Keeping in view the increasing scientific evidence establishing the role of scrub typhus as HIV suppressive factor with the fact that anti retroviral drugs are expensive, poorly tolerated and fewer than 10% of HIV patients can afford the antiviral combinations, antibodies to scrub typhus could potentially be generated as a very safe and inexpensive modality of treatment in our country. While just a simple application of these HIV-suppressive factors for HIV-infected individuals is not still realistic, further investigation of mechanisms involved may lead to a better understanding of HIV pathogenesis and help establish a standard and novel anti-HIV strategy in the country.

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