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Commentary

Is minocycline useful for therapy of acute viral encephalitis?

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ABSTRACT

Minocycline is a tetracycline derivative with anti-inflammatory, anti-apoptotic, and anti-oxidant properties. Therapy has proved useful in some experimental models of both noninfectious and infectious neurological diseases and also in clinical trials in humans, including acute traumatic cervical spinal cord injury. In models of viral encephalitis, treatment has shown both beneficial and deleterious effects. In reovirus infection in mice, minocycline delayed the disease, but did not improve either the morbidity or mortality of the disease. In neuroadapted Sindbis virus infection of mice, minocycline prevented disease, but therapy needed to be given before clinical signs were present in most of the animals. In experimental rabies in neonatal mice minocycline aggravated the disease, likely related to anti-inflammatory effects. Minocycline has also been shown to aggravate disease in a mouse model of Huntington disease, in a monkey model of Parkinson disease, and in a mouse model of hypoxic-ischemic brain injury. Hence, there is experimental evidence of benefit of minocycline in both infectious and noninfectious neurological diseases, but there is a lack of benefit and harmful effects in other diseases. This may reflect multiple mechanisms of actions that cannot be predicted in a new disease or in an infection caused by a specific viral agent. Minocycline therapy is a double-edged sword and this drug should not be given empirically to patients with acute viral encephalitis for anticipated neuroprotective effects. Much more work needs to be done in experimental models in animals as well as in clinical trials. Because patient enrollment in clinical trials on acute viral encephalitis has proven to be difficult, funding will be a challenge.

New therapeutic agents are desperately needed for the therapy of acute viral encephalitis in humans. For the most part, therapy is supportive and effective antiviral therapy is only available for a minority of encephalitic diseases, including intravenous acyclovir for herpes simplex encephalitis. Reversal of immunosuppression may be useful in certain opportunistic infections such as progressive multifocal leukoencephalopathy (e.g., associated with human immunodeficiency viral infection). In addition, the usefulness of therapy with corticosteroids requires further study except in situations with threatened brain herniation. An effective novel therapy such as a neuroprotective agent would be an exciting advance in the therapy of acute viral encephalitis in humans. In this article I consider the evidence that minocycline, which has been evaluated in a number of neurological conditions in laboratory animals and humans, is beneficial for viral encephalitis.

Minocycline is a tetracycline-derivative with broad-spectrum antimicrobial activity with anti-inflammatory, anti-apoptotic, and anti-oxidant properties. Minocycline effectively penetrates the blood–brain barrier and the drug has a good safety record (Seukeran et al., 1997). In 1998 Yrjanheikki et al. (1998) recognized that inflammation is an important contributing mechanism in cerebral ischemia and, because minocycline had been known have anti-inflammatory properties with benefits in rheumatoid arthritis and other inflammatory diseases, they evaluated and first demonstrated that minocycline was neuroprotective in global brain ischemia in gerbils. We have subsequently learned that the major potential targets for neuroprotection include the complex signaling network linking mitochondria, oxidative stress, excitotoxicity, poly (ADP [adenosine diphosphate]-ribose) polymerase-1 (PARP-1), and apoptosis (Plane et al., 2010). Minocycline might therefore have beneficial effects in a variety of neurological disorders, including stroke, hypoxia-ischemic brain injury, Parkinson disease, Huntington disease, Alzheimer disease, multiple sclerosis, spinal cord injury, and amyotrophic lateral sclerosis (Plane et al., 2010; Yong et al., 2004). Many studies have now been published on therapy of noninfectious neurological diseases with minocycline. Some studies have shown neuroprotective effects, whereas it was ineffective or deleterious in others (Plane et al., 2010). For example, minocycline was shown to have a harmful effect on patients with amyotrophic lateral sclerosis in a phase 3 randomized clinical trial (Gordon et al., 2007). On a more positive note, a recent phase 2 randomized clinical trial in patients with acute traumatic cervical (but not thoracic) spinal cord injury showed greater motor recovery in patients who had

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received 7 days of intravenous minocycline than those receiving placebo (Casha et al., 2012).

The drug has also been evaluated in animals for a number of infectious conditions. Therapeutic benefits have been reported in a variety of experimental viral infections, including neuroadapted Sindbis virus infection of mice (Darman et al., 2004), reovirus infection of mice (Richardson-Burns and Tyler, 2005) and simian immunodeficiency virus (SIV) infection of pigtailed macaques (Zink et al., 2005) and rhesus macaques (Ratai et al., 2010) (Table 1). In a neonatal mouse model of reovirus infection, minocycline therapy (35 mg/kg intraperitoneally daily beginning 2 days post-infection) delayed the onset, progression, and mortality of the encephalitis by 4 days, and there was less apoptosis and reductions in viral titer and viral antigen expression in treated mice compared with controls (Richardson-Burns and Tyler, 2005). In this model minocycline delayed, but did not prevent of the development of fatal encephalitis. Hence, there was no long-term neuroprotective effect.

In neuroadapted Sindbis virus infection, minocycline (50 mg/kg intraperitoneally daily beginning at the start of infection) protected mice from the development of hindlimb weakness and from viral-induced motor neuron death without effects on viral replication or spread (Darman et al., 2004). Further studies by Irani and Prow (2007) showed that although therapy initiated at the time of viral inoculation was highly effective in preventing neurological disease and death, a delay in initiating therapy resulted in progressively less efficacy until protection failed when therapy was initiated four days after viral inoculation, which was still prior to the time of onset of clinical disease in most of the mice (Irani and Prow, 2007). Hence, from a translational point of view, this benefit would not be expected to be clinically useful in managing humans who present with neurological symptoms and signs caused by their infections.

Although SIV encephalitis is a subacute or chronic encephalitis, the rationale for using minocycline is the same as in more acute infections. In SIV infection of juvenile pigtailed macaques, minocycline therapy (4 mg/kg/day orally beginning 21 days after viral inoculation prior to the development of clinical signs) reduced the severity of the encephalitis, suppressed the viral load in the brain, and decreased the expression of inflammatory markers in the brain over the 12-week period of the study after viral inoculation (Zink et al., 2005). Unfortunately, this was exclusively a pathological study, with no reported assessment of clinical disease in the treated and untreated animals. Another group of investigators showed that therapy with oral minocycline administered beginning 4 weeks after SIV inoculation of rhesus macaques with antibody-targeted depletion of CD8 T-lymphocytes resulted in neuroprotection, as determined with proton magnetic resonance spectroscopy and postmortem immunohistochemical studies (Ratai et al., 2010). Therapy prevented the progressive decline in neuronal integrity and reduced neuronal counts over 8 weeks post-inoculation, although clinical endpoints were also not evaluated in this study. Minocycline was also studied in a phase 3 clinical trial of human immunodeficiency virus (HIV)-associated cognitive impairment and no cognitive improvement was demonstrated (Sacktor et al., 2011). Although the pathogenesis of HIV-associated cognitive impairment is different than that of acute viral encephalitis, some of same neuroprotective benefits might be anticipated. It should be emphasized that in all of the above experimental studies in which there were beneficial effects of minocycline therapy, treatment was initiated prior to the onset of clinical encephalitis, which is not the clinical setting for therapeutic intervention in humans.

Because a neuroprotective agent would be highly desirable for rabies, minocycline has been evaluated for its potential benefit. In rabies virus-infected cultured mouse embryonic neurons Jackson et al. (2007) showed that minocycline did not improve the viability of the infected neurons. In experimental infection of neonatal mice with an attenuated rabies virus strain, minocycline treatment of rabies virus-infected mice, in which subcutaneous administration of 50 mg/kg daily was begun on the day of viral inoculation, was associated with more severe neurological disease and a higher mortality rate than treatment with vehicle. The number of infected neurons in regional brain areas of moribund mice treated with minocycline was greater than in those treated with vehicle. There were less CD3-positive cells in the brain parenchyma of minocycline-treated than in vehicle-treated mice, indicating an anti-inflammatory effect that may have also affected immune effectors and impaired the host's ability to control the infection, resulting in aggravation of the rabies encephalomyelitis with a higher mortality rate. This could reflect impaired host defenses due to anti-inflammatory and/or anti-apoptotic effects of minocycline.

Minocycline therapy has also aggravated the underlying neurological process in other studies. In the 3-nitropropionic acid mouse model of Huntington's disease, minocycline treatment was associated with a worse mean motor score, impaired general activity, and significantly deteriorated performances on the rotarod, pole test, and beam-traversing tasks and was associated with more severe neuronal cell loss in the dorsal striatum in comparison with untreated mice (Diguet et al., 2004). In minocycline-treated monkeys in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of Parkinson's disease, the same investigators also found more severe clinical features of parkinsonism and greater loss of putaminal dopaminergic nerve endings vs. untreated animals (Diguet et al., 2004). Minocycline was also found to increase MPTP-induced damage to dopaminergic neurons in mice (Yang et al., 2003). Although minocycline has been found to protect against cerebral ischemia in a rat model of transient middle

Table 1
Studies evaluating minocycline in studies of viral encephalitis in animal models and in humans.

Virus	Host/condition	Results	References
Beneficial effects			
Neuroadapted Sindbis virus	4 to 5-week old mice	Reduced clinical signs and neuronal death	Darman et al. (2004)
Neuroadapted Sindbis virus	4 to 5-week old mice	Reduced neurological disease and death	Irani and Prow (2007)
Simian immunodeficiency virus	Juvenile pigtailed macaques	Reduced severity of encephalitis	Zink et al. (2005)
Simian immunodeficiency virus	Rhesus macaques	Prevented decline in neuronal integrity and reduced neuronal counts	Ratai et al. (2010)
Japanese encephalitis virus	4 to 6-week old mice	Reduced mortality	Mishra and Basu (2008)
Lack of beneficial effects			
Reovirus	Neonatal mice	Delayed progression of disease	Richardson-Burns and Tyler (2005)
Human immunodeficiency virus (HIV)	Human clinical trial/cognitive impairment	No improvement in HIV-associated cognitive impairment	Sacktor et al. (2011)
Harmful effects			
Rabies virus	Neonatal mice	Higher mortality and morbidity	Jackson et al. (2007)

cerebral artery occlusion (Yrjanheikki et al., 1999), the opposite effect has been observed in a mouse model of hypoxic-ischemic brain injury (Tsuji et al., 2004). In another inflammatory disease of the CNS, experimental allergic encephalomyelitis, beneficial effects of minocycline therapy have been reported. Therapy has improved clinical scores and reduced T-cell infiltration (Chen et al., 2011; Nikodemova et al., 2010). These studies have suggested that there may also be benefit in multiple sclerosis, and small clinical trials have shown promise in a pilot study (Metz et al., 2009) and also in a study in which the combination of minocycline with glatiramer acetate was compared with glatiramer acetate/placebo treatment (Zhang et al., 2008). In general, benefits of minocycline therapy may be anticipated when inflammatory responses target the host, whereas detrimental effects may occur in diseases in which inflammatory responses limit disease progression. However, this is an oversimplification because of multiple mechanisms of action. Hence, there is experimental evidence of benefit of minocycline in both infectious and noninfectious neurological diseases, but there is a lack of benefit and harmful effects in others that likely reflect multiple mechanisms of actions, which cannot be predicted in a new disease.

Therapy of a neurological disease with minocycline is a double-edged sword because benefits and adverse effects cannot be determined without careful experimentation and clinical trials in humans. Because of a complex interplay of anti-inflammatory and anti-apoptotic effects as well as other effects, a dominant neuroprotective effect can never be assumed and there always is a potential for aggravation of the underlying condition. Although it may be very tempting to add minocycline therapy to cocktail of experimental drugs for its potential neuroprotective benefits, especially in rabies, because the disease is virtually always fatal (Jackson, 2011), this approach should be strongly discouraged until there are data from experimental studies in animal models that have been followed by safety studies and efficacy trials in humans. It will likely be necessary to evaluate minocycline therapy in acute viral encephalitis caused by different viruses because there are diverse pathogenetic mechanisms and therapy could aggravate encephalitis caused by one virus and have a beneficial effect for another virus. For example, the efficacy in Japanese encephalitis could be very different than in herpes simplex encephalitis. Hence, laboratory confirmation of the causative virus will be essential in the experimental design. It is of interest to note that in India preparations for initiation of a phase 2 randomized double blind control trial of minocycline for Japanese encephalitis have already begun (Dutta and Basu, 2011).

Although minocycline is presently on the market and available for use, much work needs to be done to determine whether the drug will be useful for therapy of acute viral encephalitis. Securing funding for the appropriate studies will be a considerable challenge. Recent efforts on multicenter clinical trials on the therapy of acute viral encephalitis, including herpes simplex encephalitis by the Collaborative Antiviral Study Group (ClinicalTrials.gov identifier NCT00031486) and also in Europe (Martinez-Torres et al., 2008) and on West Nile virus infection by MacroGenics (ClinicalTrials.gov identifier NCT01206504), have shown substantial difficulties in enrollment of patients. The evaluation of outcomes requires large numbers of patients enrolled at multiple sites with follow-up over a period of a year or more. However, enrollment is difficult because viral encephalitis is uncommon and is difficult to diagnose with certainty in its early stages, when treatment is most likely to be beneficial. In the case of arboviral encephalitis there is also uncertainty where the disease will occur from year to year. For minocycline, the patent on the drug has already expired. In addition, the market is relatively small for therapeutic agents for neglected tropical diseases such as rabies and Japanese encephalitis. Hence, sponsorship of clinical trials by the pharmaceutical industry is not a viable option. There is uncertainty whether many millions of dollars will be invested in the near future on clinical trials on minocycline for use in acute viral encephalitis.

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