Is There a Role for Minocycline in Neurodegenerative Disease Treatment?

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By Claire Sowerbutt [2]

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During the past decade, a great deal of research has been undertaken to better understand the pathogenesis of neurodegenerative diseases. Data from stroke models has shown that the semisynthetic tetracycline antibiotic minocycline can mediate neuroprotection in neurodegenerative diseases by inhibiting caspase-1 and inducible nitric oxide synthase (iNOS) activity. These 2 enzymes are involved in neurodegeneration in amyotrophic lateral sclerosis (ALS), Huntington disease (HD), and Parkinson disease (PD). Today, animal data together with results from small studies of minocycline in humans look promising.

CELL DEATH INHIBITOR
The evidence for using minocycline in neurodegenerative diseases stems from work done in 1996, when the caspase family of proteases were identified as mediators of cell death. A finding for which Sydney Brenner, H. Robert Horvitz, and John E. Sulston received the Nobel Prize for Medicine in 2002.

Subsequent studies by Robert M. Friedlander, assistant professor of surgery at Brigham and Women's Hospital in Boston, has shown that caspase-1 plays a role in ALS-mediated pathogenesis and ALS-mediated cell death. "We were able to show that these proteins were activated within the brain. That research was published in Nature in 1997. That's one piece of the puzzle," he said. Friedlander and colleagues then discovered that caspase-1 induces inflammation by activating interleukin (IL)-1b. Coincidentally, investigators involved in a number of randomized, placebo-controlled clinical trials of minocycline in rheumatoid arthritis (RA) found that minocycline mediated protection in RA, in part by blocking IL-1b production and iNOS production. iNOS is up-regulated in microglia, which regulates apoptosis. "So now we have a drug that blocks IL-1b production and iNOS production," Friedlander said. This was the second piece to the puzzle.

"A group in Finland tested minocycline in a stroke model, putting the pieces of the puzzle together, and they showed very nice protection in the stroke model," Friedlander continued. "They looked at the expression of the caspase-1 gene that we'd been working on for so many years and showed—as we had shown earlier—that it is increased in stroke, and that minocycline blocked the increase in caspase-1 and the increase of iNOS in the stroke study," Friedlander explained. "We then tested minocycline in a brain trauma model to confirm the findings from the Finnish group, and found it to be protective."

Friedlander and his colleagues then tested minocycline in mouse models of both HD and ALS. "We also had shown in 1999 that caspase-1 is important in Huntington disease. So we treated mice affected by either HD or ALS with minocycline. Both models lived longer," Friedlander said. Further investigation into the mechanism of action of minocycline in the ALS mouse model revealed that minocycline is concentrated in mitochondria. "This is very important," Friedlander said. Mitochondrial dysfunction is one of the pathways proposed to play a role in HD. "The mitochondria is the trigger for some of the cell death pathways. Minocycline concentrates in the mitochondria and blocks the release of the trigger factors. So it's acting at a very elemental level and is a key step in triggering cell death. That's one direct function of minocycline," he said.

These data, combined with the pharmacodynamic profile of minocycline, makes it a good target for further study in neurodegenerative disorders. Minocycline is highly lipophilic and capable of crossing the blood-brain barrier. Furthermore, it more readily penetrates the cerebrospinal fluid in humans than other tetracyclines. And, importantly, minocycline has a safety profile that covers 30 years of clinical use. It is a molecule that can be taken over a prolonged period—months—without the
MINOCYCLINE AND HD
In 2004, the Huntington Study Group reported that minocycline, 100 and 200 mg/d administered over an 8-week period, demonstrated good tolerability in 60 patients with HD. The randomized, double-blind, placebo-controlled tolerability study was conducted at 8 sites in the United States. Compliance was good, with means between the active and placebo arms of 98% and 99%. No effect was seen on the Unified Huntington's Disease Rating Scale (UHDRS) scores during the short study; however, there was a slight change in the overall Stroop Interference score—a worsening among minocycline-treated patients. The authors suggest that this was "likely a chance finding due to the large number of statistical comparisons. The magnitude of change is not sufficient to suggest a meaningful clinical change."

However, another small study of 14 patients with genetically confirmed HD, showed that minocycline was effective in treating HD. Study participants received 24 months of treatment. Evaluations were done at baseline and at months 6 and 24 using the UHDRS and a neuropsychological test battery. Although only 11 patients were available for assessment at 24 months, the data revealed an initial improvement at month 6, followed by a stabilization of general motor and neuropsychological function. The authors also noted a "significant amelioration of psychiatric symptoms that was not apparent after the first 6 months." Measurements in relation to HD symptoms quantified on the Mini-Mental State Examination, the Total Motor Score, the Total Functional Capacity Scale, and the Independence Scale stabilized after 3 years of treatment, the authors added, concluding that their findings warrant further, long-term investigation through controlled clinical trials.

In 2006, Stack and colleagues reported findings from the R6/2 mouse model, in which minocycline was used in conjunction with coenzyme Q10. This study, which Friedlander coauthored, found that the 2 agents used in combination provided greater efficacy in ameliorating behavioral and neuropathological alterations than either agent used alone. The team reported significantly extended survival and improved rotarod performance in the R6/2 mouse model. Furthermore, "combined therapy attenuated gross brain atrophy, striatal neuron atrophy, and huntingtin aggregation in the R6/2 mice, relative to individual treatment," they reported.

PLUS CREATINE IN PD
Minocycline also is being studied in combination with creatine in PD. The most recent data come from a randomized, double-blind, futility trial, funded by the National Institute of Neurological Disorders and Stroke. The results are encouraging in that they failed to show futility for minocycline. The study included 200 eligible patients screened through 45 sites across the United States. They were randomized in a 1:1:1 fashion to 10 g/d of creatine, 200 mg/d of minocycline, or placebo for 12 months. The futility threshold was set at a 30% reduction in the Unified Parkinson's Disease Rating Scale progression.

The sensitivity analysis determined that neither agent could be dismissed as futile. Furthermore, the results showed 91% tolerability in the creatine group and 77% in the minocycline arm. Common adverse events included nausea (17%), joint pain (19%), and upper respiratory tract symptoms (26%).

"Overall, minocycline passed the official threshold so much that it appeared to be nonfutile," said Bernard Ravina, MD, MS, chief of the movement and inherited neurological disorders unit, and associate professor in the Department of Neurology at the University of Rochester School of Medicine and Dentistry in New York.

However, he explained, while minocycline demonstrated potential to slow the progression of PD, it did not look as good as creatine. "We're moving forward with 10 grams of creatine—because it appeared to be the more promising of the 2 agents," Ravina said. "That's not to say that minocycline isn't worth studying further; we just decided that creatine looked a little better. And, it was better tolerated," he said.

Creatine, which comes mostly from meat or flesh products, can be synthesized in the body. "It's a very active entity in energy metabolism. In the brain, creatine is involved in energy metabolism of neuronal cells, and brain cells more broadly than neurons," said Karl Kieburtz, MD, MPH, director of the Clinical Trials Coordination Center and professor in the departments of Neurology and Community and Preventative Medicine, also at the University of Rochester School of Medicine and Dentistry.

The role of creatine, however, is different from that of minocycline. "Unlike minocycline, where the role is not to act as an antibiotic but as an interference to cell death signaling pathways, creatine intervenes indirectly by helping cells do better regarding their energy production," Kieburtz
explained. Part of the programmed cell death mechanism occurs when the cells are failing energetically. "The idea behind creatine in neurodegenerative diseases—and this is being studied in Parkinson and Huntington disease currently—is that it helps cells that may be injured or in the process of dying by bolstering their energetic reserves," he said. There is a phase 3 study under way, and it is one of the largest clinical trials for PD to date, enrolling 1720 patients with early-stage disease at 51 medical centers in the United States and Canada.

Begun in January 2006, DOMINO (a multicenter, double-blind, pilot study of minocycline in Huntington disease) has enrolled 100 patients. This study randomly assigns participants (3:1) to minocycline (100 mg PO bid) or placebo. Enrollment will take place over 6 months, and participants will remain on a blinded study drug for 18 months. The study is designed to establish a preliminary estimate of minocycline impact on the progression of HD and the futility of further study of minocycline. "The last subject enrolled will be followed for a minimum of 5 years. The article about the results will likely be published a decade from now," Kieburtz said.

HOW PROMISING IS MINOCYCLINE?
"It's clinical utility is unproven," said Kieburtz. Whether or not it's promising depends on how that term is defined. "Drug development's an interesting research activity. There are some fairly obviously big bugaboos in drug development—one of which is safety—and many drugs fall down because of safety," he said.

Citing the recent example of rofecoxib (Vioxx), Kieburtz explained that "drugs can be in use for a long time before people recognize that they're not completely safe. So there's difficulty in identifying truly safe drugs. Minocycline is very safe. It has been around for decades. Its adverse-effect profile is well known. It causes dizziness, nausea, skin sensitivity—a handful of problems, none of which are typically lethal, but neither are they entirely innocuous."

From a safety perspective, minocycline appears to be a good candidate for further evaluation in neurodegenerative diseases, particularly because any agent that will treat PD or ALS will be taken for 5 to 10 years. "So safety is very important, knowing a lot about the safety of minocycline makes it an appealing compound. But that is not what most people mean by 'promising.' Rather, most people understand the term as meaning 'it looks like it works,'" Kieburtz said.

This presents a conflict. "On one hand, we have a drug that appears fairly safe; on the other, we have an illness for which we have no treatments to slow disease progression. So, we think what's the harm in trying minocycline? But, in fact, there could be harm," Kieburtz said. Citing the example of vitamin E in heart disease, Kieburtz explained that for many years, the general belief was that because it was a vitamin, it couldn't really cause that much harm. "Now there are several meta-analyses showing that the vitamin increases the risk for cardiovascular death. A similar story is the case with hormone replacement therapy," he said.

While testing in animal models has yielded good results thus far, there are simply not enough data to make the statement that minocycline will improve outcomes in neurodegenerative diseases.

THE FUTURE
Commenting on the data overall, Friedlander explained that therapeutic cocktails for the treatment of neurodegenerative diseases will likely be necessary. "My thought all along has been that to treat complex diseases such as ALS or HD, we're going to have to do the same thing that has been done in AIDS and cancer. That is, while one drug doesn't really do very much, when you add the effects of concomitant therapy, provided the agents used act via different mechanisms, you have an additive effect," he said.

"That was our hypothesis when we used creatine and minocycline," Friedlander said, referring to a study done in 2003 in animal models of ALS. "Both creatine and minocycline seem to be acting at the level of the mitochondria, but the mechanism of action must be different," he said. "We combined them and the effect was surprising, because it was perfectly additive. In other words, minocycline extended the life of the mice by 13%, creatine extended it by 12%, and when added together, survival increased by 25%, giving us more hints that it's going to be critical to evaluate some of these drugs in combination," he said.

"What I'm worried about with respect to the human clinical trials is that the effect of many of these drugs might be small. When we do our tests in transgenic mice, we take 20 mice with the same genetic background, the same age, the same exact mutation, and we see these small effects. In humans, everyone is different," Friedlander said.

Although the data must inform clinical practice, generating those data will likely remain tricky. "There are pluses and minuses," said Friedlander. "The beauty of minocycline is that it's very cheap and safe and has been used in humans for many, many years. But in part, that's also negative:
industry is not interested in minocycline because it's off patent and generic, so funding and developing the clinical trials will really be up to government sources," he said.

References: REFERENCES

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