UNIVERSITY OF CALGARY

Facts and Figures

What is minocycline?
Minocycline belongs to a class of second generation tetracycline oral antibiotics. It is used to treat bacterial infections including acne; pneumonia and other respiratory tract infections; and infections of the skin, genital, and urinary systems. It is sometimes used to treat mild rheumatoid arthritis.

Minocycline has an established and relatively safe clinical track record since its introduction in 1971 as an acne medication. It comes in capsule form in a variety of formulations to control its **bioavailability** and release into the body.

In addition to its antibiotic effects, minocycline appears to dampen detrimental immune responses. Laboratory studies also suggest that minocycline protects neurons from injury in models of neurological diseases. The combined anti-inflammatory and neuroprotective effects have incited MS researchers to investigate this drug as a potential therapeutic for people living with MS.

How does minocycline work?
Minocycline's antibacterial effects are exerted through the molecule's ability to pass through the membrane of vulnerable strains of pathogenic (disease-causing) bacteria. Once inside, minocycline binds to a specific coding region in the bacterium's genetic machinery and prevents protein synthesis, thus effectively killing the pathogen.

Unrelated to its antibacterial activity, minocycline also boasts anti-inflammatory properties that make it an option for certain chronic inflammatory conditions like rheumatoid arthritis and, importantly, render it a potential candidate for the treatment of MS. Although its anti-inflammatory mode of action is not fully understood, minocycline is believed to prevent the migration of disease-causing white blood cells called T-cells into the central nervous system, by suppressing certain compounds that disrupt the **blood-brain barrier**. Finally, minocycline suppresses the activity of various pro-inflammatory cells and molecules, including **microglia** and certain **cytokines** and **chemokines**.

In addition to its anti-inflammatory properties, minocycline has recently drawn considerable research attention for its ability to promote **neuroprotection** in models of neurological diseases, which makes it a promising candidate for the treatment of several neurodegenerative disorders, including MS. Minocycline has been shown to exert its neuroprotective effects primarily through at least three mechanisms. The first is the inhibition of a process of cell death called **apoptosis**, which affects myelin-producing cells in MS that

normally mediate myelin repair. Secondly, minocycline has antioxidant activity that reduces cellular damage caused by **oxidative stress** that can cause damage to nerve fibres. Lastly, minocycline protects against **excitotoxicity**, which can lead to cell death and inflammation. It is not clear whether minocycline acts through one or a combination of these neuroprotective or inflammatory mechanisms to potentially alleviate the MS disease process.

What research has been done on minocycline and MS?
Early studies were conducted in animals with an MS-like disease to provide preliminary evidence of its potential as an MS therapeutic and to examine its mechanisms of action. Pioneering research conducted by Drs. V. Wee Yong and Luanne Metz and their teams was funded by the MS Society of Canada. They demonstrated that minocycline targeted an enzyme that is involved in stimulating inflammatory cell infiltration into the brain. When minocycline was given to mice with both mild and severe forms of MS-like disease, symptom severity was significantly reduced and symptom onset was delayed.

Several clinical studies have since been conducted that have tested the efficacy and safety of minocycline in persons living with MS. Two pilot studies, also conducted by Drs. Metz and Yong, have shown that minocycline was safe and well tolerated by people living with MS. The first study of 10 people with relapsing-remitting MS revealed preliminary evidence of reduced inflammatory activity on MRI scans, compared to the baseline period pre-treatment; the benefit held for up to three years.

A larger phase II, multi-centre, double-blind, placebo-controlled trial led by Dr. Metz compared the efficacy of minocycline administered in combination with glatiramer acetate (Copaxone®) to glatiramer acetate and placebo in 44 participants with relapsing-remitting MS. The combination of minocycline and glatiramer acetate reduced the total number of T1 gadolinium-enhanced lesions on brain MRI by 63% and the total number of new and enlarging T2 lesions by 65% over 9 months. The results, although not statistically significant, were encouraging enough to warrant further study.

Most recently, Dr. Metz led an MS Scientific Research Foundation-funded, phase III clinical trial to determine if minocycline, taken orally at a dose of 100mg twice daily, is better than placebo at reducing the proportion of participants with **clinically-isolated syndrome (CIS)** who convert to MS over 6-months. The study was a double-blind, randomized, placebo-controlled clinical trial carried out in 142 participants after they experienced their first demyelinating event. Dr. Metz presented preliminary results of the trial at the 31st European Committee for Treatment and Research in MS (ECTRIMS) Congress in 2015.

The study was carried at MS clinics in Vancouver, Burnaby, Calgary, Edmonton, Winnipeg, London, Toronto, Ottawa, Montreal, Greenfield Park, Quebec City, and Halifax. Results published on <<insert date>> in the *New England Journal of Medicine* demonstrated that minocycline reduced conversion to MS by 27.6% (p=0.001) within 6 months. While 61% of placebo-treated participants reached MS within 6 months only 33.4% of minocycline-treated participants did.

Glossary

- **Apoptosis:** A process of programmed cell death; although this is a naturally-occurring and beneficial process in the body, abnormal levels of apoptosis can lead to tissue injury.
- **Bioavailability:** How quickly and how much of the drug reaches its target of action.
- **Blood-Brain Barrier:** A barrier formed by a continuous layer of tightly connected endothelial cells; prevents most large molecules and cells found in the blood from entering the brain tissue.

- **Chemokines:** A protein beacon that attracts white blood cells bearing a receptor for the chemokine.
- **Clinically-isolated syndrome (CIS):** single episode of neurological symptoms suggestive of multiple sclerosis.
- **Cytokines:** A small messenger molecule that influences the actions of immune system cells. There are many different cytokines, each acting only on cells that have receptors for that cytokine.
- **Excitotoxicity:** The process by which nerve cells are damaged or destroyed by excessive stimulation by certain brain chemicals, or neurotransmitters,
- **Neuroprotection:** The preservation of the structural and functional integrity of nerve cells.
- **Oxidative Stress:** An imbalance between the levels of free radicals – highly reactive molecules resulting from energy production – in cells and the body's ability to counteract them with antioxidants, resulting in damaging effects.

References

1. Brandula V, Rewcastle NB, Metz LM, Bernard CC and Yong VW. Targeting leukocyte MMPs and transmigration: minocycline as a potential therapy for multiple sclerosis. *Brain*. 2002; 125(Pt 6):1297-308.
2. Plane JM, Shen Y, Pleasure DE and Deng W. Prospects for minocycline neuroprotection. *Arch Neurol*. 2010; 67(12):1442-8.
3. Yong WV. Prospects for neuroprotection in multiple sclerosis. *Front Biosci*. 2004; 9:864-72.
4. Yong VW, Wells J, Giuliani F, Casha S, Power C, Metz LM. The promise of minocycline in neurology. *Lancet Neurol.* 2004; 3:744-51.
5. Metz LM, Zhang Y, Yeung M, Patry DG, Bell RB, Stoian CS, Yong VW, Patten SB, Duquette P, Antel JP, Mitchell JR. Minocycline Reduces Gadolinium-enhancing MRI Lesions in Multiple Sclerosis. Ann Neurol. 2004 May; 55(5):756.
6. Zabad RK, Metz LM, Todoruk TR, Zhang Y, Mitchell JR, Yeung M, Patry DG, Bell RB and Yong VW. The clinical response to minocycline in multiple sclerosis is accompanied by beneficial immune changes: a pilot study. *Mult Scler*. 2007; 13(4):517-26.
7. Zhang Y, Metz LM, Yong VW, Bell RB, Yeung M, Patry DG and Mitchell JR. Pilot study of minocycline in relapsing-remitting multiple sclerosis. Can J Neurol Sci. 2008; 35(2):185-91.
8. Metz, LM, Li D, Traboulsee A, Myles ML, Duquette P, Godin J, Constantin M, Yong VW, GA/minocycline study investigators. Glatiramer acetate in combination with minocycline in patients with relapsing--remitting multiple sclerosis: results of a Canadian, multicenter, double-blind, placebo-controlled trial. Mult Scler. 2009; 15(10):1183-94.