Clinical Potential of Minocycline for Depression with Psychotic Features

Tsuyoshi Miyaoka
Department of Psychiatry
Shimane University School of Medicine
Minocycline

1. Second-generation tetracycline which exerts anti-inflammatory effects that appear to be completely separate and distinct from its anti-microbial action.

2. One of the most brain-penetrable of the tetracyclines.

3. It has been shown to have neuroprotective effects.

4. The capacity of minocycline to alleviate disease for several neuropsychiatric disorders is increasingly being recognized.
The potential of minocycline in neurology

1. Ischemic and haemorrhagic stroke
2. Multiple sclerosis
3. Spinal-cord injury
4. Parkinson’s disease
5. Huntington’s disease
6. Amyotrophic lateral sclerosis

Yong et al. Lancet Neurol 2004
Mechanisms of minocycline’s effects

1. Inhibition of microglial activation
2. Attenuation of apoptosis
3. Suppression of free-radical production
4. Inhibition of matrixmetalloproteinases
5. Changes in leucocyte function
6. Others
Clinical trials of Minocycline in neurology

<table>
<thead>
<tr>
<th>Disease</th>
<th>Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huntington’s Disease</td>
<td># Open-label</td>
</tr>
<tr>
<td></td>
<td># Randomized,</td>
</tr>
<tr>
<td></td>
<td>double-blind,</td>
</tr>
<tr>
<td></td>
<td>placebo-controlled</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td># Randomized,</td>
</tr>
<tr>
<td></td>
<td>double-blind,</td>
</tr>
<tr>
<td></td>
<td>placebo-controlled</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td># Cross-over trial</td>
</tr>
</tbody>
</table>
Minocycline in Huntington’s disease
Case report

“The patient, a 39-year-old female,........ After 5 weeks of minocycline administration, there was mild improvement in abnormal movements and psychiatric symptoms,........ Minocycline was discontinued, which was followed by significant worsening of her clinical state, movements and psychiatric symptoms,........”

Denovan-Wright EM et al. J Psychopharmacol 2002
Case Report

Possible Antipsychotic Effects of Minocycline in Patients with Schizophrenia

Miyaoka T et al. Prog in NP & BP 2007
Possible antipsychotic effects of minocycline in patients with schizophrenia

“The patient, a 23-year-old male, was diagnosed with “catatonic schizophrenia.” Physical and neurological examination revealed no marked abnormalities or anomalies. Laboratory examinations of serum and urine were normal. EEG, CT, and MRI of brain showed no abnormal results. Haloperidol (HPD) was started........”

Miyaoka T et al. Prog in NP & BP 2007
Possible antipsychotic effects of minocycline in patients with schizophrenia

Figure 1

Haloperidol (mg/day)

Minocycline

150 mg/day

150 mg/day

Miyaoka T et al. Prog in NP & BP 2007
Minocycline as Adjunctive Therapy for Schizophrenia:
An Open-Label Study

Subjects

1. 22 patients with schizophrenia (determined by DSM-IV) were recruited.

2. Psychiatric symptoms were rated using the Positive and Negative Syndrome Scale (PANSS).

3. The mean age of onset of illness was 23.5 years (SD = 9.7), and the mean number of psychiatric hospitalization was 2.2.

4. This study was approved by Helsinki Committee of in Shimane University School of Medicine.

5. All subjects gave informed consent according to institutional guidelines and the recommendations from the Declaration of Helsinki.
1. All patients were taking a stable dose of antipsychotic medication for at least 1 month before baseline screening and entry into this study.

2. Minocycline treatment was initiated according to following schedule: 100 mg orally daily for the first week, and 150 mg orally daily from weeks 2. The total duration of minocycline treatment was 4 weeks.

3. The clinical ratings were performed a total of three times: (i) at baseline before minocycline initiation, (ii) at the end of open-label minocycline treatment, and (iii) 4 weeks after minocycline treatment was discontinued.
Results
PANSS (positive)

Baseline: 40.8
4 weeks: 16.3
Follow up: 14.2

PANSS (negative)

PANSS (general)

Clinical Potential of Minocycline for Depression with Psychotic Features

Miyaoka et al. (in preparation)
Subjects

1. 25 patients with unipolar psychotic depression (determined by DSM-IV) were recruited.

2. The primary efficacy endpoint was change from baseline to Week 6 on the Hamilton Depression Rating Scale (HAM-D-17).

3. Secondary efficacy variables were the change from baseline in Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impressions-Severity of illness Scale (CGI-S).

4. This study was approved by Helsinki Committee in Shimane University School of Medicine.

5. All subjects gave informed consent according to institutional guidelines and the recommendations from the Declaration of Helsinki.

Miyaoka et al. (in preparation)
Minocycline treatment phase of the study

1. All patients were taking a stable dose of antidepressants medication for at least 1 month before baseline screening and entry into this study.

2. Minocycline treatment was initiated according to following schedule: 100 mg orally daily for the first week, and 150 mg orally daily from weeks 2. The total duration of minocycline was 6 weeks.

3. The clinical ratings were performed a total of four times: (i) at baseline before minocycline initiation, (ii) at the open-label minocycline treatment (2, 4, and 6 week).

Miyaoka et al. (in preparation)
Results
HAM-D-17

Miyaoka et al. (in preparation)
BPRS (total)

Miyaoka et al. (in preparation)
CGI-S

Miyaoka et al. (in preparation)
1. Minocycline is a potent inhibitor of microglial activation and the apoptotic pathway.

2. Studies that have examined markers of apoptosis and levels of apoptotic regulatory proteins in postmortem schizophrenia and depression brain tissue indicated a dysfunction of apoptosis in several cortical regions, including evidence that the apoptotic vulnerability is increased.
Neuroinflammation in Schizophrenia-Related Psychosis: A PET Study

Janine Doorduin\textsuperscript{1}, Erik F.J. de Vries\textsuperscript{1}, Antoon T.M. Willemsen\textsuperscript{1}, Jan Cees de Groot\textsuperscript{2}, Rudi A. Dierckx\textsuperscript{1}, and Hans C. Klein\textsuperscript{1,3}

\textbf{TABLE 2. Binding Potentials of $^{11}$C-(R)-PK11195}

<table>
<thead>
<tr>
<th>Region</th>
<th>Healthy volunteers</th>
<th>Patients</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal lobe</td>
<td>1.78 $\pm$ 0.75</td>
<td>2.08 $\pm$ 0.76</td>
<td>0.459</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>1.83 $\pm$ 1.20</td>
<td>1.93 $\pm$ 0.74</td>
<td>0.892</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>1.28 $\pm$ 0.34</td>
<td>1.04 $\pm$ 0.56</td>
<td>0.079</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>1.77 $\pm$ 0.93</td>
<td>2.28 $\pm$ 1.22</td>
<td>0.720</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>1.39 $\pm$ 0.28</td>
<td>1.82 $\pm$ 0.59</td>
<td>0.017</td>
</tr>
<tr>
<td>Thalamus</td>
<td>1.61 $\pm$ 1.44</td>
<td>1.49 $\pm$ 0.35</td>
<td>0.742</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>1.37 $\pm$ 0.30</td>
<td>2.07 $\pm$ 0.42</td>
<td>0.004*</td>
</tr>
<tr>
<td>Midbrain</td>
<td>1.68 $\pm$ 0.60</td>
<td>2.63 $\pm$ 0.40</td>
<td>0.014</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>1.11 $\pm$ 0.22</td>
<td>1.45 $\pm$ 0.48</td>
<td>0.040</td>
</tr>
<tr>
<td>Pons</td>
<td>1.54 $\pm$ 0.32</td>
<td>2.85 $\pm$ 1.42</td>
<td>0.027</td>
</tr>
</tbody>
</table>

*\(P < 0.005\).

Statistical analysis was performed using multivariate general linear model, with whole-brain gray matter as covariate. Data are average $\pm$ SD.
1. Pae et al. described that minocycline may exert antidepressant effects based on its known physiological properties of neuroprotection and anti-inflammation.

2. In vitro and in vivo animal studies are important to further clarify the physiological properties of minocycline in an effort to better understand the pathophysiology of depression.

3. Clinical studies should be conducted to elucidate whether minocycline has clinical efficacy as an antidepressant.
1. Further research with additional subjects is clearly necessary because the mechanisms of both psychosis and the effects of minocycline on the CNS are still poorly understood.

2. The present data need to be confirmed in larger, randomized, double-blind, and longer term trials.
Minocycline has demonstrated efficacy in treatment of patients with schizophrenia and psychotic depression in open-label study.

The mechanism of action of minocycline that might be related to its antipsychotic potential appears to involve inhibition of apoptosis and inflammation.