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Treatment of Covid-19 with Minocycline and a Guanosine-Restricted Diet: Case Report

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Abstract

We report the treatment of a 21-year-old female Covid-19 patient by a novel combination of minocycline and a guanosine-restricted diet. Minocycline is an antibiotic with well documented broad spectrum anti-viral effects, including evidence of activity against SARS-CoV-2. Deprivation of guanosine has been documented as an effective anti-viral modality in vitro and in animal models, and specific in vitro activity against CoV-SARS-2 has been reported. The patient's symptoms resolved rapidly.

Keywords

Covid-19, SARS-CoV-2, drug repurposing

Introduction

Minocycline, and a related drug, doxycycline, are antibiotics which have been demonstrated to have broad spectrum anti-viral, anti-inflammatory, and neuroprotective activity [1-8]. Minocycline crosses the blood brain barrier and has been demonstrated to reduce brain viral load in an animal model of West Nile virus [5], which, like SARS-CoV-2, is neurotropic. Both minocycline and doxycycline have been identified as inhibitors of SARS-CoV-2 [9], and clinical trials evaluating their efficacy to treat Covid-19 have been advocated [10,11].

Guanosine is a nucleoside which when phosphorylated becomes a nucleotide that viruses incorporate into their RNA (or DNA) to replicate. Viruses are unable to replicate in the absence of guanosine. The body pool of guanosine has, fundamentally, two sources. One is the diet [12]. The second source is comprised of enzymatic pathways which produce guanosine [13]. Anti-viral effects of low guanosine diets have been demonstrated in vitro and in animal models [14,15]. Reduction of the body pool of guanosine in vitro or in animal models by administering mycophenolic acid or its prodrug mycophenolate have been shown to have broad antiviral effects [14-17] when administered in very low doses (considerably lower than the doses used for clinical immunosuppression).

This patient showed rapid resolution of fever and bodyaches, as well as reduction of other symptoms when treated by a 24-hour food fast followed by low guanosine diets, prepared by a registered dietician. As discussed below, the addition of low-dose minocycline likely further benefited the patient.

Case Presentation

A 21-year-old white female university student was told that her roommate tested positive for Covid, and two days later she developed fever and bodyaches. The patient took a PCR Covid test on that day and the positive results were reported to her four days later. Her medical history was unremarkable except for polycystic ovary disease for which she was had been prescribed a birth control pill. She was familiar with the research of one of the authors (SAB) regarding the antiviral effects of low guanosine diets. Accordingly, she started on a 24 hour fast, in which no food was permitted but she was able to drink either water or milk (which is a protein; commercial milks are thought to contain no nucleic acids). She kept a food diary and a symptom diary. After 24 hours, she began a very low guanosine diet (called the Urgent diet). A few days later she was moved to a diet with somewhat more guanosine and which is more palatable (called the Phase I diet). On day 4, she was started on minocycline 50 mg BID. About 36 hours after starting the minocycline she was asked how she felt, and she responded, "I feel great!" Upon further questioning, she indicated that her fever and bodyaches were gone and she had about

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90% of her normal energy back. See Fig. 1. On day 5, she developed what she described as "swollen glands" on the neck and said that she always, her whole life, developed such signs when she had a cold. From her description it appears these were submandibular and superficial cervical lymph nodes. She said she typically takes acetaminophen and that the condition usually resolved in a few days. The "swollen glands" resolved by day 8. A summary of her history of symptoms is as follows: sore throat (days 1-3), fever (days 1-5), chills (days 1-2), body aches (days 1-5), headache (days 2-5), cough (days 2-4), fatigue (days 1-6), sinus congestion (days 1-8), "swollen glands" (days 5-8). The patient did not experience: loss of taste or smell, shortness of breath, nausea or vomiting. She continued on the Phase 1 diet and minocycline to day 14. We note that the patient took acetaminophen on days 1-5 (650 mg Q4H on days 1 and 2; 650 mg BID on days 3 and 4; 650 mg once on Day 5), and only disclosed this to the treating physician after two weeks. We estimate that the patient's dietary intake of guanosine was about zero during the first day (the food fast), and about 15-35 mg/day for days 2-4 (the "Urgent" diet) and about 35-75 mg/day for days 5-14 (the "Phase 1" diet). For comparison, generally Americans take in about 2,000 mg/day of nucleotides [18], and we estimate therefore that they take in about 500mg/day of guanosine. Thus, on any day of treatment, the patient took in 15% or less of the guanosine in a typical diet.

The patient had dramatic resolution of her fever and bodyaches, and the other symptoms quickly dissipated. She had no further symptoms at all after day 8. It seems likely that the guanosine-restricted diet was responsible for this quick improvement. We believe that the acetaminophen she took may have reduced the height of her fever, but is unlikely to have caused the rapid decline and resolution of it and the other symptoms. The documented anti-viral, anti-inflammatory, and neuroprotective properties of minocycline likely contributed to her quick recovery.

Discussion

This Covid-19 patient responded with rapid resolution of her fever and symptoms to a low-guanosine diet, which is believed to have inhibited replication of the virus, and she also appears to have benefited from the addition of treatment with minocycline.

Reduction of the pool of guanosine in cell and animal models of viral infection has been effective in mitigating signs and mortality from viral diseases [14,15,19]. Evidence of reduction both by dietary means and by inhibiting enzymatic pathways that produce guanosine has been reported by these authors. Enzymatic pathway inhibition was specifically effective in treatment of SARS-CoV-2 in both in vitro [17] and in animal models [20]. We believe that the current case report indicates that dietary restriction of guanosine intake may also contribute to mitigation of Covid-19 replication and resolution of symptoms. As can be seen from Figure 1, the rapid defervescence of the patient occurred when she was on low guanosine diet and before minocycline was started. Interestingly, a small group of MERS coronavirus patients treated with mycophenolate mofetil, an inhibitor of guanosine synthesis, did well, with no mortality [21].

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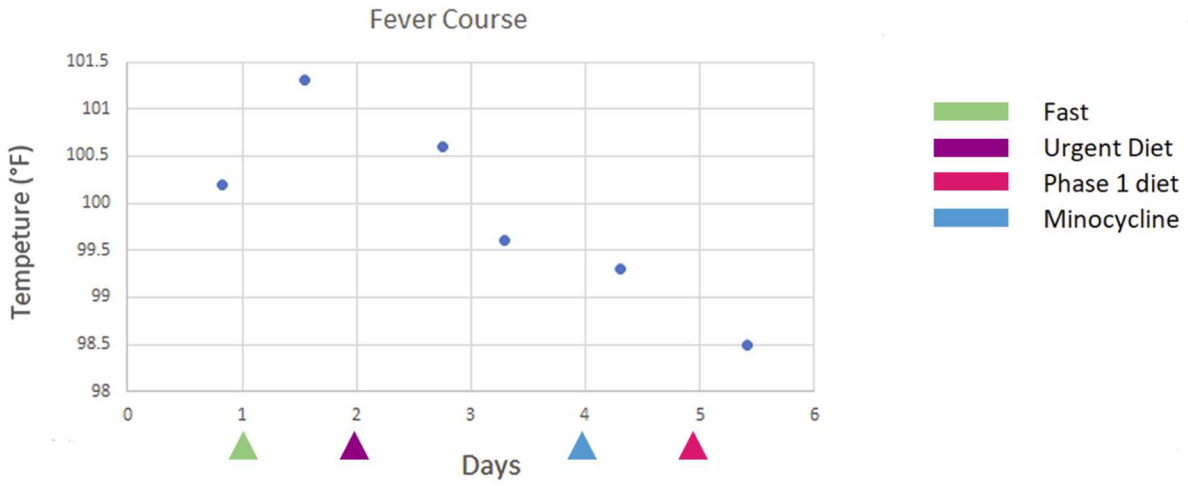

Figure 1. Fever course with markers of each treatment initiation. (Note: 98.6º F=normal=37º C)

Minocycline and doxycycline have each been documented to be effective inhibitors of many viruses including specifically SARS-CoV-2 [9], the causative agent of Covid-19. Several mechanisms of anti-viral activity have been documented for these drugs (see references above). Additionally, both doxycycline and minocycline have been demonstrated to have anti-inflammatory activity, which should mitigate cytokine storm due to Covid. Notably, doxycycline has been shown clinically to reduce cytokine storm in Dengue [22]. A small case series of doxycycline's effectiveness against Covid has been published already [23], in which symptoms resolved within 3 days. Quite a few publications have recently emerged in the literature providing rationales for clinical trials using these drugs for treatment (and prevention) of Covid [11,24,25]. Published research supports that they are effective as antiviral therapeutics at doses lower than the typical doses for their approved uses. It was for that reason that the dose of minocycline prescribed was 50mg BID, rather than the standard antibiotic dose of 100mg BID. We suspect that the anti-viral, anti-inflammatory, and neuroprotective properties of minocycline (see citations above) benefited the patient's recovery.

A substantial body of literature now exists supporting the use of both guanosine-lowering treatments and minocycline or doxycycline for treatment of SARS-CoV-2 and other viral diseases. The authors encourage the development of clinical trials to rigorously test the effectiveness of these novel approaches.

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Potential Conflict of Interest Statement
SAB has intellectual property which may relate to some of the treatments reported.

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