

## Failure of Azithromycin in Treatment of Brill-Zinsser Disease

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Received 12 June 1998/Returned for modification 13 March 1999/Accepted 24 March 2000

**Two patients suffering from Brill-Zinsser disease were treated with azithromycin, which did not prove effective. *Rickettsia prowazekii*, the agent causing Brill-Zinsser disease, cannot be treated with azithromycin. Both patients had epidemiological features consistent with and a clinical course typical of the disease. The diagnosis of Brill-Zinsser disease was serologically confirmed.**

Brill-Zinsser disease occurs as a late recrudescence of epidemic typhus. The clinical effect of a newly developed azalide, called azithromycin, against *Rickettsia prowazekii* has not yet been determined. No clinical studies have been published regarding the effect of this treatment.

Two patients were admitted to the University Hospital for Infectious Diseases, Zagreb, Croatia, because they were suffering from a high fever of undetermined cause. After serological tests using Weil-Felix agglutination and complement-fixing reaction (CFR) for epidemic typhus were conducted, Brill-Zinsser disease was diagnosed. What follows is an illustration of the diagnostic procedures as divided into two case reports.

**Case 1.** A 59-year-old male developed a febrile illness on 22 June 1992. He was admitted to the hospital after 5 days of suffering from a high fever. This man was a refugee from Brčko in Bosnia, which he had fled during the Bosnian War in 1992. In his childhood during World War II, he had been infested with lice. He told us that, although he had suffered from some type of febrile illness of unknown cause, some of his neighbors had been diagnosed with epidemic typhus. This led us to suspect that he had also suffered a mild form of typhus in his childhood, which gave us a starting point.

Upon physical examination, a fever of 40°C, chills, shivering, severe frontal headache with photophobia, and meningeal irritation were revealed. A papular rash on the chest, arms, and legs was observed. A spinal tap was performed, and a pleocytosis of 256/mm<sup>3</sup>, predominantly mononuclear cells with 480 mg of proteins per liter, showed rickettsial meningitis. During the first 6 days of hospitalization, the patient suffered from a fever of up to 39°C. He was treated on the first day of hospitalization with azithromycin at doses of 500 mg a day for a total of 3 days, which proved ineffective. The Weil-Felix test was administered, and a rise in titer count from 1:20 to 1:160 was observed. The CFR test for determining typhus exanthematicus was performed, and a rise in titer count from 1:8 to 1:128 helped to confirm a diagnosis of Brill-Zinsser disease. A new therapy was administered on the seventh day of hospitalization, using doxycycline at doses of 100 mg twice a day. Within 24 h of starting therapy, the patient's temperature dropped and he became symptom free.

**Case 2.** A 62-year-old male developed a febrile illness on 22 January 1996 and was hospitalized 8 days later. He was from the village of Sinac in Croatia. He told us that he was infested with lice in his childhood during World War II. He also told us

that a few of his neighbors had suffered from epidemic typhus at that time, again giving us starting point. In this case, we also had reason to believe that he had suffered a mild form of typhus during his childhood.

A physical examination revealed a fever of 39°C, chills, shivering, headache, pharyngitis, enlarged and painful cervical lymph nodes, and pain in the muscles and joints. A papular rash appeared on his legs and back. Physical and radiographic examination of the chest revealed atypical pneumonia. Despite treatment with azithromycin at doses of 500 mg a day for 3 days, the patient continued to suffer from high fevers for 6 more days, showing the ineffectiveness of azithromycin therapy. On the 10th day of hospitalization, a spinal tap was performed that revealed a pleocytosis of 45/mm<sup>3</sup>, predominantly mononuclear cells and 900 mg of protein per liter. Upon performance of the Weil-Felix test, the titer count of 1:80 remained unchanged. However, the CFR test showed a titer count change of 1:8 to 1:128, thus revealing Brill-Zinsser disease. On the 12th day of hospitalization, doxycycline therapy was administered at doses of 100 mg twice a day. The patient became afebrile and symptom free within 24 h of starting therapy.

Epidemic typhus has been a serious problem in Croatia, Bosnia, and Herzegovina in the past. In Croatia, large outbreaks occurred during and immediately after World War II, but epidemic typhus was never endemic.

The Weil-Felix test of patients who are suffering from Brill-Zinsser disease may show a negative or low titer count (7) or a change. This test is not always accurate for such a diagnosis. However, the CFR tests, developed later to obtain more accurate titer counts, help to establish and confirm the diagnosis of Brill-Zinsser disease. Our research team is aware that other tests have been developed, but in the aforementioned cases, we had only the CFR test at our disposal.

Tetracycline and chloramphenicol are effective antibiotics against *R. prowazekii* infection but not suitable for children and pregnant women. A single dose of doxycycline, 100 mg orally, is curative (2, 4, 6). Azithromycin is efficient in the treatment of intracellular bacterial infections and can be a potential alternative to tetracycline and chloramphenicol in the treatment of *Rickettsia* infections (3). Some authors agree that azithromycin shows good activity against *Rickettsia akari*, *Rickettsia conori*, *R. prowazekii*, *Rickettsia rickettsii*, and *Rickettsia typhi* in vitro (3). Azithromycin proved more efficient than doxycycline against some *Rickettsia tsutsugamushi* isolates (9).

Our clinical experience, based on only two cases, demonstrates the failure of standard-dose azithromycin in the treatment of Brill-Zinsser disease. The azithromycin (Sumamed) was locally made (Pliva d.d., Zagreb, Croatia).

Both cases were diagnosed as rickettsial meningitis, which

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resulted from an infection of the endothelial cells that caused vasculitis and thrombosis of capillaries, small arteries, and veins (5, 7). Meningitis shows an increase in permeability across the blood-brain barrier and an influx of mononuclear cells. Very low concentrations of azithromycin are found in the cerebrospinal fluid in patients without meningitis (8), but very high concentrations are found in macrophages (1). This could account for the failure of the drug in the above-mentioned two cases. Studies show that doxycycline is also present in only small amounts in the cerebrospinal fluid (10) after therapy.

Azithromycin is given in doses of 500 mg a day for 3 days because significant antibacterial activity against many intracellular pathogens persists in the tissues for more than 5 days after completion of the therapy.

Both patients were effectively cured with doxycycline, although the second patient could have recovered without specific therapy. Therefore, our results need to be reproduced by other investigators, in order to clarify the potential of azithromycin in the treatment of Brill-Zinsser disease.

#### REFERENCES

1. **Ballow, C. H., and G. W. Amsden.** 1992. Azithromycin: the first azalide antibiotic. *Ann. Pharmacother.* **26**:1253-1261.
2. **Huys, J., P. Freyens, J. Kayihigi, and G. Berghe.** 1973. Treatment of epidemic typhus: a comparative study of chloramphenicol, trimethoprim-sulphamethoxazole and doxycycline. *Trans. R. Soc. Trop. Med. Hyg.* **67**:718-721.
3. **Ives, T. J., P. Manzwitsch, R. L. Regnery, J. D. Butts, and M. Kebede.** 1997. In vitro susceptibilities of *Bartonella henselae*, *B. quintana*, *B. elizabethae*, *Rickettsia rickettsii*, *R. conorii*, *R. akari*, and *R. prowazekii* to macrolide antibiotics as determined by immunofluorescent-antibody analysis of infected Vero cell monolayers. *Antimicrob. Agents Chemother.* **41**:578-582.
4. **Krause, D. W., P. L. Perine, J. E. McDade, and S. Awoke.** 1975. Treatment of louse-borne typhus fever with chloramphenicol, tetracycline or doxycycline. *East Afr. Med. J.* **52**:421-427.
5. **Perine, P. L., P. C. Chandler, D. K. Krause, P. McCardle, S. Awoke, E. Habte-Gabr, C. L. Wisseman, and J. E. McDade.** 1992. A clinico-epidemiological study of epidemic typhus in Africa. *Clin. Infect. Dis.* **14**:1149-1158.
6. **Perine, P. L., D. W. Krause, A. Awoke, and J. E. McDade.** 1974. Single-dose doxycycline treatment of louse-borne relapsing fever and epidemic typhus. *Lancet* **ii**:742-744.
7. **Saah, A. J.** 1995. *Rickettsia Prowazekii* (epidemic or louse-borne typhus), p. 1735-1737. In G. L. Mandell, J. E. Bennett, and R. Dolin (ed.), *Mandell, Douglas and Bennett's principles and practice of infectious diseases*, 4th ed. Churchill Livingstone, New York, N.Y.
8. **Steigbigel, N. H.** 1995. Macrolides and clindamycin, p. 334-336. In G. L. Mandell, J. E. Bennett, and R. Dolin (ed.), *Mandell, Douglas and Bennett's principles and practice of infectious diseases*, 4th ed. Churchill Livingstone, New York, N.Y.
9. **Strickman, D., T. Sheer, K. Salata, J. Hershey, G. Dasch, D. Kelly, and R. Kuschner.** 1995. In vitro effectiveness of azithromycin against doxycycline-resistant and susceptible strains of *Rickettsia tsutsugamushi*, etiologic agents of scrub typhus. *Antimicrob. Agents Chemother.* **39**:2406-2410.
10. **Yim, C. W., N. M. Flynn, and F. T. Fitzgerald.** 1985. Penetration of oral doxycycline into the cerebrospinal fluid of patients with latent or neurosyphilis. *Antimicrob. Agents Chemother.* **28**:347-348.