Survival of *Naegleria fowleri* primary amebic meningoencephalitis (PAM) could be improved with an intensive multi-route chemo- and biotherapeutic regimen

Joseph Martin Alisky*

*Marshfield Clinic Research Foundation, 1000 Oak Avenue, Marshfield, WI 54449, United States
Marshfield Clinic Thorp Center, 704 South Clark, Thorp, WI 54771, United States*

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**Summary** *Background*: *Naegleria fowleri* primary amebic meningoencephalitis (PAM) has a very high mortality rate, probably exceeding 95%. A few people have survived after getting intravenous and intrathecal amphotericin, variably coupled with other agents that include dexamethasone, diflucan, chloramphenicol and rifampin, but even with prompt initiation of therapy, it is still a very uphill battle.

**Presentation of the hypothesis**: Survival could be improved by combined intrathecal, intranasal and intravenous amphotericin, diflucan and rifampin, with adjuvant intravenous chloramphenicol, azithromycin, minocycline and linezolid, intramuscular trifluoperazine, intranasal Cry1C protoxin and intrathecal anti-*Naegleria* immune globulin and dexamethasone.

**Hypothesis rationale**: Instilling medications intranasally, intravenously and intrathecally would target the primary reservoir of infection and its common sites of spread. Intrathecal dexamethasone should attenuate cerebral edema, a primary cause of death in PAM. Azithromycin and minocycline appear to have synergy with amphotericin in killing *N. fowleri* in animal models, and the other agents, which also showed efficacy in animal models, should also be additive or synergistic as well. In essence one would approach PAM in the manner of chemotherapy for tuberculosis and cancer, with multidrug therapy to assure complete eradication.

**Testing the hypothesis**: The hypothesis could be validated using murine and bovine models of *N. fowleri* PAM.

**Implications of the hypothesis**: PAM may be emerging as a significant public health threat, underscoring the need for effective therapeutic regimens.

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in vitro testing with cultured water, the ameba invades the central nervous system through the cribiform plate, usually producing fulminant illness within a week [1–5]. There have only been a total of nine known cases where people have survived PAM, out of about two hundred published cases in the literature [1]. In these nine survivors, infection was recognized promptly and the patients were given intravenous and intrathecal amphotericin, variably coupled with other agents that include dexamethasone, diflucan, chloramphenicol and rifampin [1–5]. But even using drugs known to be capable of killing N. fowleri, survival is by no means assured, and the odds are still definitely in favor of the pathogen, not the patient [6]. I propose here combating PAM with an aggressive regimen combining multiple drugs and biologically based therapeutics.

Presentation of the hypothesis

Mortality from PAM could be reduced by prompt intrathecal and intranasal administration of amphotericin, diflucan and rifampin, followed by intravenous dosing to treat systemic spread of N. fowleri beyond the central nervous system, with intravenous chloramphenicol as well. Based on in vitro data and animal models, intravenous muramyl dipeptide (a strong immune activator), intravenous azithromycin, minocycline and linezolid, intramuscular trifluoperazine, intranasal Cry1C protoxin (another strongly immunogenic molecule, produced by Bacillus thuringiensis) and intrathecal anti-Naegleria immune globulin should further boost survival [7–16]. Finally, cerebral edema, a major cause of death in PAM [6], should be reduced by the intrathecal dexamethasone without interfering with Cry1C- and muramyl dipeptide-stimulated immune response. Targeting to different physiological compartments (intrathecal, intranasal and intravenous) is expected to produce higher bioavailability of drugs directly at the site of the pathogens. Chances of successful eradication would be increased, and killing of the N. fowleri should be further enhanced by attacking it with several agents simultaneously, similar to the approach taken with chemotherapy for cancer and tuberculosis. With luck, there may also be synergy between some of these different agents, as was the case when in animal models azithromycin and minocycline were given in combination with amphotericin [9,10].

Testing the hypothesis

In vitro testing with cultured N. fowleri could establish the basic outline of a combination regimen, testing the above agents to make sure the premise that anti-Naegleria activity is enhanced rather than diminished. Subsequently, more definitive proof of principle could be established using with animal models, of which three exist — mice, rabbits and cows. Mice and rabbits have already been used in testing new therapeutics for PAM [8,9,11,14–17], and there are case reports of cows that died from clinical PAM that appears to be identical to the disease in humans, affording an experimental system where brain weights and biodistribution volumes would be more comparable to humans than would be had with the smaller animals [18–20]. Once the hypothesis was validated in animal models, an international consortium could be established for clinical trials. For ethical reasons, it would be impossible to have a true placebo controlled randomized study; the best one could do is look at mortality from the new approach and compare it to a previous baseline mortality rate approaching 100%.

Significance

PAM is a growing public health concern. A cluster of six cases of PAM in the southwestern United States (Arizona) was recently in the news world-wide [21]. Contamination of water sources from an expanding population is a concern in many parts of the world, and global warming may increase the number of locations where ambient conditions favor N. fowleri. New molecularly targeted drugs for N. fowleri are under development that may eventually be superior to anything today, but it may be some time before these agents are ready for clinical testing [22,23], and novel approaches such as using RNA interference are most likely a few years in the future at the very least [24]. Intensive combination chemotherapy with existing drugs and biological preparations, on the other hand, could be available quickly to meet the new threat posed by PAM. The idea is thus put forward here in the hopes someone will pick up on this idea and do further investigation.

References


