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Review Article

The Pharmacologic Basis for the Successful Treatment of Persistent Lyme Disease

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Abstract

Lyme Disease is an infectious disease that may become a persistent illness. The causative organisms are sensitive *in vitro* to many antibiotics, but there are numerous patients with persisting symptoms that have had difficulty resolving those symptoms with standardly recommended antibiotic treatments. Herein is described the pharmacologic basis for the successful treatment of persistent Lyme disease, using known pharmacokinetic properties.

Introduction

Lyme disease is caused by the spirochete *Borrelia burgdorferi*, and may present with various clinical manifestations. Infection may be asymptomatic, it may produce a localized erythematous reaction at the site of the tick bite, it may produce acute systemic disease, and it may result in later or persistent disease manifestations involving the musculoskeletal and nervous systems [1]. Treatment of the earliest symptoms and signs of infection is generally successful [2], but treatment of recurring or persisting symptoms using standardly recommended antibiotic protocols has often not been successful [3,4]. The reasons for failure of antibiotic treatment in patients with persistent or recurring symptoms are not known but include these possibilities:

a) There is no longer any infectious process,

b) There is an autoimmune process that is now responsible for the symptoms,

c) The infection is still present, but needs more specific antibiotic regimens and longer durations of treatment.

After the initial bacteremia that occurs in patients inoculated with *B. Burgdorferi* by the Ixodes tick that may last for up to two months, the organisms can no longer be reliably found or otherwise detected in blood, urine, cerebrospinal fluid, or tissues, despite ongoing symptoms or signs. Current serologic tests can be useful when positive in supporting the clinical diagnosis, but they are indirect tests based on the immune system's recognition of specific antigens, and are not reliably positive in patients with continuing symptoms of Lyme disease [5,6].

In evaluating the possible explanations for the persistence of symptoms and failures of antibiotic treatments in patients with persistent Lyme disease, the most compelling evidence is for persistent infection, that evidence from animal models including non-human primates, documenting the recovery of persisting, non-replicating, but metabolically active spirochetes, inducing expression of host genes following experimental infection and standard treatment protocols [7-10].

In this report, evidence derived from patient experience with various unsuccessful and successful antibiotic regimens is reviewed. Using the pharmacologic properties of various antibiotic regimens, a logical explanation is provided for the antibiotic regimens that have been successful in resolving Lyme disease in several thousand patients seen over a 30-year period of time.

Pharmacologic and Pathophysiologic Considerations

After the bite of an Ixodes sp competent for carriage of sufficient numbers of *B. Burgdorferi*, the organisms enter the subcutaneous tissues and can become localized there, but also enter the blood and lymphatic systems. Whether they enter or are engulfed by dendritic cells of the nervous system is uncertain, but in the course of illness, the sensory nervous system becomes involved in the disease process. In certain animal models, the bacteria can target and persist in cartilaginous tissues, but it is not clear that this is the case in non-human primate models or in the human disease. There is evidence that the neurologic system is the primary locus in non-human primates [11], and is likely the case in human disease, based on the ongoing neurologically based symptomatology. Rheumatologic symptoms and signs might also be due to neurologic involvement of a specific joint, as in the case of syphilis. Whether there is intracellular localization of the spirochetes in neuronal or other types of cells, or they continue their presence in some extracellular milieu has not been firmly established.

Regardless of the locus of persisting infection, the spirochetes do not appear to multiply to any great extent following the initial infection, as patients with ongoing illness do not appear to worsen with or without additional antibiotic treatment, this observation consistent with findings in animal models [8,9,12]. Hence, antibiotics that target bacterial multiplication processes are not as likely as those antibiotics that target metabolic processes to be successful treatment regimens. Observations using intravenous ceftriaxone or other beta-lactam antibiotic treatments over a number of months in such patients

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without consistent improvement is supportive of this assumption [13].

B. Burgdorferi is sensitive *in vitro* to numerous antibiotics of varying antibacterial actions. Clinically, however, there are known treatment failures using certain classes of antibiotics. Beta-lactam antibiotics have no consistent efficacy in patients with persistent symptoms, results consistent with an intracellular locus for the bacteria, as beta-lactam antibiotics have little or no intracellular penetration.

Macrolide antibiotics are highly active *in vitro* against *B. Burgdorferi*, but are not very effective in the treatment of either early or later Lyme disease [14], despite their known good tissue and intracellular penetration. In considering the possible reasons for this discrepancy, the findings by Raoult, et al. [15] appear to be relevant. They found that the use of agents that increase intracellular pH enhanced the effectiveness of doxycycline in a tissue culture model of intracellular rickettsia infection, results that could explain the lack of efficacy of macrolide antibiotics, which are of limited efficacy in an acidic milieu [16]. Hence, if persistent *B. Burgdorferi* reside in an intracellular acidic compartment or in an acidic extracellular space, macrolide antibiotics would not be effective unless the acidic milieu were alkalinized. Possibly relevant to this issue is whether *B. Burgdorferi* can alter the pH of their environment, as happens with numerous other pathogens (eg mycobacteria, both typical and atypical, brucella, histoplasma, leishmania, legionella, toxoplasma, and cryptococcus) that block phagosome acidification or phagosome-lysosome fusion.

These antibiotic pharmacologic properties would help explain the results obtained in patients with known or suspected Lyme disease treated with a macrolide antibiotic. Patients being treated with hydroxychloroquine itself for presumptive systemic lupus erythematosus without obvious improvement and who were subsequently found to have positive serologic tests for Lyme disease and were treated with the addition of a macrolide antibiotic, successful clinical responses were observed [14]. And this successful response has been replicated in the subsequent twenty plus years of treatment experience involving several thousand patients. Additional observations in patients who were using vitamin C supplementation (an acidifying agent) and were not improving with this combination treatment regimen, but did subsequently improve on discontinuation of this supplementation, results again supporting the importance of pH optimization in treatment considerations. Further evidence in this regard is that the addition of hydroxychloroquine to the tetracycline treatment of persistent Lyme disease was without any additional benefit to the use of tetracycline alone, tetracycline being active in an acidic milieu.

The question arises is how could macrolide antibiotics be effective against *B. Burgdorferi* central nervous system infection if this class of antibiotics does not obviously cross the blood-brain barrier. The fact that macrolide antibiotics are effective in patients with apparent central nervous infection by *B. Burgdorferi* is supported by resolution of brain SPECT scan abnormalities concurrent with clinical improvement [17]. In the absence of data that would support the possibility that the combination of a macrolide antibiotic and hydroxychloroquine allows for penetration of the blood-brain barrier, it is probable that *B. Burgdorferi* reside in one of the three elements of the blood-barrier, and that macrolide antibiotics need not cross the blood-barrier to be effective in the treatment of central nervous infection. There is little evidence that *B. Burgdorferi* is present in brain tissue itself, results supporting the hypothesis that its effects on central nervous system function are not mediated by encephalitic processes, but by some yet to be discovered pathogenetic events.

Doxycycline is effective both *in vitro* and *in vivo* in patients with early Lyme disease. But it's effectiveness in patients with relapsing or persisting symptoms is poor. As doxycycline can penetrate tissues and cells, and is relatively active in an acidic milieu, the probable explanation for its failure in treatment of patients with continuing symptoms is that insufficient concentrations of the antibiotic are achieved at the site of infection. This is likely the case because doxycycline is highly protein bound in serum, and too little antibiotic diffuses to the site of infection. In contrast, tetracycline, which is not highly protein-bound, was found to be more effective than doxycycline in treating patients with persisting disease [13]. The higher dose of tetracycline, ie 1500-2000 mg/day, might also be a factor in its greater effectiveness compared to doxycycline. It is possible that higher doses of doxycycline, ie 300-400 mg/day, would be effective in the treatment of such patients, and the clinical experience of a number of practitioners would support that possibility.

Another likely key variable in the treatment of patients with persistent Lyme disease is the duration of treatment. The results of two controlled treatment trials of three months showed no difference in improvement between antibiotic treated and placebo treated patients. cannot be used to conclude that further antibiotic treatment would not be successful, as neither the duration of treatment necessary to resolve the presumptive infection is known, nor was there a consideration that differing antibiotic regimens might be successful in resolving the illness [3,4]. In support of the concept of longer duration treatment are examples from other infectious processes involving several months or years, such as tuberculosis, leprosy, Q fever, certain fungal infections, certain parasitic infections, and several viral infections. Similar to tuberculosis and other chronic infections, the multiplication time of *B. Burgdorferi in vitro* is much slower than other bacteria that cause acute disease, a factor that might also allow the spirochete to survive for longer periods of time.

Recent *in vitro* studies have noted that persistent *B. Burgdorferi* cells may take various shapes and may not be affected by antibiotics that are otherwise active against the organisms in standard cultures [18]. Whether it is the shape of the bacterium, whether there are bacterial aggregates (sometimes referred to as biofilms), and whether these occur *in vivo* to any degree are questions remaining to be answered. These *in vitro* studies have noted that there are some antibiotics, and some combinations of antibiotics, that are more effective than others in killing persister cells [19]. Re-treatment of persisting cells also appeared to be effective. There is also a suggestion that administering the antibiotic or antibiotics in a pulse-dosing scheme might prove more effective in the killing of persister cells [20].

Of additional possible importance for the explanation of persistent infection despite antibiotic treatments is the potential role of antibiotic tolerance in limiting the curative ability of antibiotic treatment. In a number of other bacterial systems, antibiotic tolerance has been shown to be the basis of successful persistence of these bacteria. This system has been described as a toxin-antitoxin system, based on the involvement of certain metabolic processes and ribonucleases [21]. Whether this type of system exists in *B. Burgdorgeri* remains to be determined, but it would seem a reasonable probability, given similarities in metabolic systems. BB0755 has been annotated as a ribonuclease, and in our studies, the purified protein has unique

cytotoxic activity on glial and neural cells in tissue culture [22]. Additional studies will be needed to determine the further relevance of these observations to the phenomenon of bacterial persistence and antibiotic tolerance.

Discussion

The diagnosis of persistent Lyme disease continues to be based on the clinical history and symptomatology. That these symptoms are primarily subjective in nature has created difficulties in affirming the diagnosis and distinguishing persistent Lyme disease from other multi-symptom disorders referred to as "Chronic Fatigue Syndrome", "Fibromyalgia", and "Gulf War Veterans' Illnesses". Most of these patients have as their major symptoms fatigue, musculoskeletal pain or stiffness, and abnormalities of cognitive function, especially short-term memory deficits and inability to concentrate. Numerous additional symptoms are usually also present.

The pathogenesis of the later and chronic manifestations of Lyme disease requires additional study. The spirochetes appear to have an affinity for the nervous system, and clinical observations support the involvement of sensory nerve roots in addition to other central nervous system manifestations [11,12]. *B. Burgdorferi* have been shown to bind to glycolipids of the nervous system and produce antibodies to gangliosides [23-25]. These bacteria have also been shown to generate T-cell independent B-cell immunologic responses characterized primarily by IgM, and not IgG reactivity [8,9]. Consistent with these observations are the overall weak immunologic responses, as measured by antibody titers, of patients with persistent Lyme disease [12]. The observations reported here, expanding on previous reports, affirm that patients with the persistent form of Lyme disease have primarily IgM responses, which responses dissipate, and frequently disappear, with successful antibiotic treatments [13].

Previous reports of the immunologic responses of patients with late Lyme disease have focused primarily on patients with arthritis, such patients demonstrating robust IgG responses. These patients, primarily males, seem to be less ill and less incapacitated than are patients with chronic, more subjective symptomatology, who have weaker immunologic responses, primarily of the IgM type. In such patients with persistent symptoms, the lack of a more robust IgG response may be an indication of the host failure to adequately resolve the infection, similar to observations made in animal models. Collectively, then, information derived from various experimental sources and clinical observations provides strong support for the validity of IgM responses as an indicator of chronic infection, and of ongoing active infection, in patients with the chronic, persistent form of Lyme disease.

In previous published placebo-controlled studies of various antibiotic regimens for the treatment of patients with persisting or relapsing symptoms of Lyme disease, there has been no benefit found between the antibiotic treated and placebo treated regimens [3,4]. One study employed a month of intravenous ceftriaxone, followed by two months of doxycycline [3]. The possible antibiotic-related explanations for failure of this regimen to improve patients with persisting symptoms are a) one month of intravenous ceftriaxone is insufficient duration of treatment, b) two months of doxycycline are insufficient duration of treatment, c) the differing mechanisms of action of the two antibiotics (ie ceftriaxone reliance on active bacterial multiplication, which apparently is not the case in persistent disease, and doxycycline dosage and protein binding properties limiting the amount of effective drug reaching the target organisms, and d) the duration of treatment of the antibiotic combination is insufficient to eradicate the infection. There were criticisms of this trial regarding difficulties recruiting sufficient numbers of patients-the study was both initiated and prematurely ended because of time limitations, and the resultant low numbers of patients weakening the statistical evaluations and conclusions. There were also no controls for severity and duration of symptomatology.

The other major placebo-controlled trial examined the combination of clarithromycin and hydroxychloroquine in patients with persistent Lyme disease given for three months [4]. The possible explanations for failure of this regimen are a) there was an initial two-week period of treatment of all patients with intravenous ceftriaxone, which might have allowed the subsequent placebo group to improve sufficiently to obscure any benefit from the three-month treatment trial, b) there was no controlling for duration of illness, as this has observationally been an apparent factor in outcome of treatment, c) there was no controlling for taking supplements, especially vitamin C, which can interfere with the alkalinizing efficacy of hydroxychloroquine, and d) the duration of treatment was insufficient, as it appears that resolution of symptoms in patients with illness greater than 1-2 years requires 4-6 months or more of treatment.

Based on the consideration of the pharmacologic properties of the two antibiotic regimens that have apparently been successful in the treatment of patients with persisting symptoms of Lyme disease, including duration of treatment, and likely explanations of the failure of similar and differing regimens in the treatment of such patients, a logical and rationale approach to the successful treatment of patients with persistent Lyme disease is presented. What is needed, however, to validate these observations and explanations, is a specific direct detection test that can determine if the continuing symptoms of patients with persistent Lyme disease are due to active infection, along with additional controlled treatment trials based on the described pharmacologic principles. If, and until there is such a specific test, clinicians have to exercise their judgment as to how to best manage patients with persistent Lyme disease, including treatment with one of the apparent successful regimens.

The following Tables and caveats can serve as guidelines to the treatment of persistent Lyme disease (Table 1-3).

Table 1: Treatment of Persistent Lyme Disease.

Tetracycline: 500 mg tid (20 min before or after meals) or
750 mg bid (eg 20 min before or 1hr after breakfast and supper)
Macrolide antibiotic:
clarithromycin-500 mg bid or
erythromycin-500 mg bid or
azithromycin-500 mg qd
plus
Hydroxychloroquine 200 mg bid with food

Table 2: The Role of Supplements.

No supplemental B vitamins: the bacteria do not synthesize B vitamins and supplementation might assist their survival
No supplemental C vitamins: vitamin C will diminish the effectiveness of the macrolide antibiotic
No supplemental antioxidants (eg vitamin E, CoQ10): antioxidants antagonize the effects of the body's attempts to oxidize the bacteria, which produce antioxidants.
There need be no changes or restrictions in diets themselves.

Table 3: The Duration of Treatment.

The total treatment duration for persistent or recurrent symptoms may vary from a few weeks to several months or more, depending on the clinical response. In patients with symptoms for less than 1-2 years, 3-6 months of treatment with one of the regimens in Table 1 is usually sufficient to result in apparent cure. In patients with ongoing or severe symptoms for more than 2-3 years, 12-18 months, sometime longer, of treatment may need to resolve most, if not all symptoms. In these cases, it is useful to alternate the two antibiotic regimens every 6 months or so, the tetracycline regimen usually in the non-sunny months.

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