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Are Long-Term Antibiotic Treatments Safe And Effective In Treating Patients 16 And Older With Disseminated Lyme Disease?

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Are Long-Term Antibiotic Treatments Safe And Effective In Treating Patients 16 And Older With Disseminated Lyme Disease?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not long-term antibiotic treatments are safe and effective in treating patients 16 and older with disseminated Lyme disease?

Study Design: Systematic review of three randomized controlled trials (RCTs) published in peer reviewed journals between 2010-2014, all English language.

Data Sources: The three randomized controlled trials were found using PubMed.

Outcomes Measured:

Two of the studies measured quality of life using RAND-36 Health Status Inventory. The third study measured patients' symptoms using a visual analogue scale.

Results: All three studies found no significant change in the quality of life or in patients' symptoms when comparing extended antibiotic courses to placebo when treating persistent disseminated Lyme. Two studies had relatively low numbers needed to harm when looking at adverse events.

Conclusions: Based on the information provided by these three RCTs, it can be concluded that long-term antibiotic treatments are not safe or effective in treating patients 16 and older with disseminated Lyme disease. Both antibiotic treatments studied had adverse events and increasing duration did not improve quality of life or reduce symptoms any more than the placebo

Key Words: Lyme disease, Anti-bacterial agents

INTRODUCTION

Lyme disease is the most common tick-bourne infection in the United States as well as in Europe. It is a spirochetal disease caused by Borrelia burgdorferi that is transmitted by the Ixodes tick family.[1,2] Lyme disease has three stages that starts with a localized infection and progresses to early dissemination and late persistent stage.[1,2] When patients continue to have early disseminated or late persistent symptoms after their course of antibiotics it is referred to as Post Treatment Lyme Disease Syndrome (PTLDS) or chronic Lyme.[3]

Although Lyme disease is the most prevalent vector-borne illness reported in the United States, it predominately affects the northeastern coast and upper midwest with 96% of cases occurring in 14 states.[4] Over 30,000 cases of Lyme disease are reported yearly but studies suggest that over 376,000 people are diagnosed yearly.[2,4] Of those diagnosed, roughly 10-20% of patients have remaining symptoms.[1,4] Discrepancies between the number of cases reported and diagnosed could be caused by inconsistent reporting practices from state to state. Due to the high prevalence of Lyme disease it is estimated that anywhere from 712 million to 1.3 billion dollars are spent yearly on Lyme disease and PTLDS.[4] It is unknown how many office visits are contributed to Lyme disease but research shows that having one chronic Lyme symptom increases outpatient visits by 66% over a one year period.[4]

Localized infection occurs after the tick-bite and classically begins with erythema migrans and flu-like symptoms before disseminating hematogenously causing musculoskeletal, neurologic, cardiac complications. Lyme disease can continue to spread in late persistent stage initiating arthritis and chronic neurologic deficits. The exact cause of PTLDS is still unknown. Evidence suggest that it is not caused by a current infection and is liken to some auto-immune conditions.[1,2,3] Localized and early disseminated infections are commonly treated with doxycycline 100mg PO

bid or alternatively with amoxicillin 500mg PO TID for 2-3 weeks.[1,2,5,6,7] For patients with Lyme arthritis the antibiotic course should be for 30 days. With neurologic or cardiac involvement ceftriaxone IV for 2-3 weeks is recommended.[1]

Patients can continue to have Lyme disease symptoms even after being treated with the above antibiotic regimens. There is controversy on the proper treatment for persistent disseminated Lyme symptoms. This paper explores the safety and efficacy of extending antibiotic treatment in the hopes of reducing disseminated Lyme and persistent symptoms.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not long-term antibiotic treatments are safe and effective in treating patients 16 and older with disseminated Lyme disease?

METHODS

The studies used in this systematic review included three randomized, double-blind, placebo controlled clinical trials (RCT). The population studied included patients over 16 years old with disseminated Lyme disease. The intervention used in each of the studies was extended antibiotic treatments. The population was compared to a placebo group who only received a placebo. The outcomes measured in the studies included quality of life, symptoms, and safety. All articles were published in English language in peer-reviewed journals. All studies were discovered using the keywords “Lyme disease” and “anti-bacterial agents” using the PubMed database. The studies were chosen based on their relevance to the clinical question and had patient oriented outcomes (POEMS). Inclusion criteria for the sources were randomized, controlled, and double-blind studies that measured POEMS for patients with Lyme disease.

Articles were excluded if they were written over 10 years ago, involved patients under the age of 16, and were meta-analyses. The statistics used in this review includes p values, mean change from baseline, relative risk increase (RRI), absolute risk increase (ARI), numbers needed to harm (NNH), relative benefit increase (RBI), absolute benefit increase (ABI), and numbers needed to treat (NNT). The specific studies demographics and characteristics can be found in Table 1.

Table 1 - Demographics & Characteristics of Included RCTs

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Berende (2016)[5]	RCT	280	48.7± 11.8	16 years or older Complaints of musculoskeletal pain, sensory disturbances, neuropsych disorders, or cognitive disorders related to erythema migrans or proven Lyme borreliosis Written informed consent form	Pregnancy; Allergic to antibiotics, recent therapy < 4 wks ago; Dx of neuroborreliosis, immune disorders, spirochetal ds, liver ds, or co-morbidities; Taking cisapride, astemizole, terfenadine, barbiturates, phenytoin, carbamazepine, or OCP; Enrolled in other trial	45	Doxycycline 100 mg PO BID X 12 weeks
Cameron (2008)[6]	RCT	86	18-82	At least 16 years old Recurrent Lyme disease symptoms after previous successful treatment	Inadequate initial antibiotic tx or amoxicillin allergy; Newly positive ELISA, IgM western blot or new infection; Other dx contributing to symptoms	38	Amoxicillin 3 g PO q X 3 months
Oksi (2007)[7]	RCT	145	19-87	Clinical Lyme dx confirmed by microbiological tests Intent-to-treat	Penicillin or cephalosporin allergy; < 16 years old; Pregnancy; Antibiotic tx within 1 month	7	Amoxicillin 1g BID x 100 days

OUTCOMES

Two of the studies measured quality of life using RAND-36 Health Status Inventory. The third study, Oksi et al., measured patients' symptoms using a visual analogue scale (VAS) completed by the participants. The VAS valued from 0 to 100 where 0 meant symptom free, 50 represented baseline before any invention, and 100 showing worsen in symptoms.

RESULTS

All three RCTs used extended antibiotic treatment compared to placebo. Two studies used amoxicillin as their antibiotic and the third used doxycycline. Berende et al. and Oksi et al. both initially treated with 2g of IV ceftriaxone for 2 and 3 weeks respectively before introducing the intervention.[5,7] While Cameron population consisted of patients who were already treated for Lyme disease but had a recurrence of symptoms.[6] The three studies were similar in that they all included participants 16 years and older that presented with arthralgia, cardiac, or neurologic involvement with confirmed Lyme disease. The RCTs also excluded patients with allergies to antibiotics, recent antibiotic use, and pregnancy to avoid further complications and encourage compliance. Cameron conducted the study in a primary care internal medicine practice in New York and Oksi et al. was conducted in 3 different hospitals in Finland. Berende et al. was performed at two medical centers in Netherlands.

Oksi et al. further categorized their participants into definite and possible cases for disseminated Lyme borreliosis. This was based on symptoms, signs, and laboratory signs by the end of the trial. Patients categorized with a possible diagnosis had a clinical picture of disseminated Lyme but either had no microbiological confirmation or had microbiological confirmation but symptoms could be contributed to another cause or condition. This paper reviews the results of the cases labeled definite. Oksi et al. enrolled 145 participants, 73 receive

amoxicillin and 72 received the placebo. Of those, 54 in the amoxicillin group were definite and 52 in the placebo group. The study had a total of 7 withdraws due to lack of compliance or another diagnosis contributing to symptoms was discovered.

In the Berende et al. trial, 86 patients started in the doxycycline group and only 65 (75%) were included in the per-protocol analysis. The placebo group started with 98 people and ended with 74 (75%) in their analysis for a total of 45 dropouts (24.5%) between the two groups.

Cameron had started with a small sample population of 86 Lyme disease patients in which 52 were assigned to the amoxicillin group. At the end of the study only 31 amoxicillin-assigned and 17 placebo- assigned patients were evaluated with 38 withdrew.

The outcomes in all three articles did not differ significantly from their ($p > .05$) baseline for either patient's quality of life or symptoms (Table 2). Berende et al. measured patient's physical quality of life (QOL) using SF-36 physical component score and compared the mean change from baseline of those treated with doxycycline to those on the placebo. The difference was .2 with a 95% CI (-2.1 to 2.8) and a p-value of .69. Cameron also measured the same outcome and had a difference of 1.5 with a non-significant p-value when comparing change in baseline of amoxicillin to the placebo. Oksi et al. on the other hand measure patient's symptoms by using VAS and report 0 difference and p-value of .37 in mean change from baseline when comparing amoxicillin and placebo. Oski et al. also reported that 92.5% of patients with definite Lyme borreliosis had reported an excellent or good outcome with amoxicillin treatment compared 87% of the placebo group with a p-value of .49. Excellent and good outcomes were defined as a VAS less than 30. This data was converted into a dichotomous format to evaluate efficacy by getting a value of 19 for the number needed to treat (NNT) as shown in Table 3.

Table 2: Comparison of Efficacy through Mean Change from Outcome Baseline

Study	Outcome	Mean change from baseline	95% CI	P-value
Berende [5]	Physical QOL	.2	(-2.1 to 2.8)	.69
Cameron[6]	Physical QOL	1.5	N/A	Non-significant
Oski[7]	Symptoms	0	N/A	.37

Table 3: Statistical Analysis of Oksi et al[7] Efficacy in Improving Symptoms

CER	EER	RBI	ABI	NNT
.870	.925	.063	.055	18.18 → 19

Adverse events data from two trials (Table 4) was reported as continuous data and was later converted into dichotomous format to evaluate safety of treatment. Berende et al. reported adverse events in 54.7% of those taking Doxycycline and 42.9%% of those taking placebo, resulting in a number needed to harm (NNH) of 8 with a p-value of 0.27. A NNH of 8 means that for every 8 people treated with doxycycline, 1 adverse event will occur in an additional patient that would not have occurred using the placebo. The most common adverse reactions reported during this trial for doxycycline were photosensitivity, nausea, diarrhea, and rash. Cameron reported adverse events occurring in 39% of those taking amoxicillin compared to 35% taking the placebo with a non-significant p-value. The calculated NNH came out to 25. Diarrhea, yeast infections, and nausea were the highest reported adverse events on amoxicillin.

Table 4: Comparison of Adverse Events and Tolerability

Study	CER (Placebo)	EER	RRI	ARI	NNH
Berende[5]	.429	.547 (doxycycline)	.275	.118	8.47 → 8
Cameron[6]	.35	.39 (amoxicillin)	.114	.04	25

DISCUSSION

There are several limitations among these three trials. The first is that the duration of the patient's symptoms varied before receiving the treatment or be influenced by an undiagnosed

active infection. The three studies also had small population sizes which reduces the validity of the studies. Cameron trial experienced a high drop- out rate with over 55% of the enrollees withdrew from the trial. Berende et al. also had a notable withdraw rate of 24.5%. This lowers sample size and reduces validity. These high drop-out rates and non-compliance could be contributed to adverse events to the antibiotics and the extend course. What might have been tolerable for a short course, such as diarrhea and nausea may not be so when extended to 60-100 days.

Both Berende et al. and Oksi et al. had similar limitations within their trials and in application to other populations. Participants in these two studies did not have any previous treatment for Lyme disease. It would have been unethical to not initially treat them with ceftriaxone, and thus only explored extended adjunctive therapy. It is also unknown if this data correlates to patients in the United States, as both trials were performed only in Europe. The genospecies of Borrelia burgdorferi may vary from continent to continent. The Cameron Trial, although performed in New York, was only conducted at a single location and therefore has a lower generalizability than the multi-site trials. Although these trials have their own limitations, collectively they support each other with similar findings.

The two interventional antibiotics used in these three studies, amoxicillin and doxycycline, are both generic antibiotics that are readily available in the United States with a prescription. They are both relatively inexpensive, and insurance should provide some coverage. Amoxicillin has both gram positive and negative coverage, and is also used commonly in ear, nose, and throat infections, eradication of H. pylori in PUD, and used in pregnancy to treat urinary tract infections.[8] Amoxicillin is used in pregnancy and breast feeding but there is conflicting data on teratogenicity risk.[8] Patients can have anaphylactic or hypersensitivity

reactions to this antibiotic especially in those who have a penicillin allergy. Doxycycline is used for a variety of different conditions ranging from acne, to sexual transmitted infections, malaria prophylaxis, and rocky mountain spotted fever.[9] Doxycycline, however is less tolerable and has more adverse events such as GI inflammation and upset, hypersensitivities such as Stevens-Johnson syndrome or toxic epidermal necrosis, and photosensitivity.[9] Doxycycline is contraindicated in pregnancy, breast feeding, and children under the age of 8 for potential teratogenic risks, and accumulation in developing teeth and long bones.[9]

There are other various treatments that have been provided for patients with persistent disseminate Lyme disease. These various treatments, including long courses of antibiotics, do not having supporting data and have left some patients with harmful complications such as septic shock, osteomyelitis, Clostridium difficile colitis, and paraspinal abscesses.[10]

CONCLUSIONS

Based on the information provided by these three RCTs, it can be concluded that long-term antibiotic treatments are not safe or effective in treating patients 16 and older with disseminated Lyme disease. Both antibiotic treatments studied, doxycycline and amoxicillin had adverse events such photosensitivity, rash, nausea, and most commonly diarrhea. The three RCTs showed that extending the duration of antibiotics in treating Lyme disease did not improve quality of life or reduce symptoms any more than the placebo. These studies however did not consider other antibiotics or expanded the initial use of ceftriaxone. Nor did these studies investigate treating patients with local Lyme disease with a longer duration of antibiotic reduces the prevalence of disseminated or chronic Lyme disease. It might be beneficial to explore these topics in future studies.

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