Full Title: Lyme Vaccination and Arthritic Conditions in the U.S. Adult Population: An Analysis of the Vaccine Adverse Events Reporting System (VAERS) Database from December 1998 through October 2000

Short Title: Lyme Vaccination

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Abstract

Objectives: The purpose of this analysis was to examine arthritic adverse reactions following recombinant Lyme vaccination in the adult population of the United States.

Methods: A certified copy of the VAERS database was obtained and analyzed from December 1998 through October 2000 using Microsoft Access. The arthritic reactions identified were: arthritis, arthrosis, arthralgia and joint disease. The chi-square statistical method was used to determine whether the noted elevated incidence rates of arthritic reactions in Lyme vaccine recipients achieved statistical significance over those reported following Tetanus-diphtheria (Td) and rubella vaccinations received by adults.

Results: Arthritic reactions were reported for patients in the age group 35-62 year-olds within four to six days after vaccination. Arthritic reactions were fairly evenly reported for men and women. Because of the molecular design of the recombinant form of Lyme vaccine, it was assumed that this vaccine would be well-tolerated and result in few serious adverse reactions. This prediction was not bone out by our analysis of the VAERS database. Rather, our analyses showed a statistically significant increase in arthritic reactions over those reported following Td or rubella vaccination in adults.

Conclusion: Our results indicate a less reactogenic Lyme disease vaccine is needed. The withdrawal of Lyme vaccine in early 2002 seems well justified based upon the results of this study and Lyme vaccine probably should not be used until processes have been developed to produce a safer vaccine.

Introduction

Lyme disease is a bacterial infectious disease of considerable importance. In the United States, Lyme disease is caused by the spirochete *Borrelia burgdorferi* sensu lato; in Europe *B. afzelii* and *B. garinii* have also been identified as causes of Lyme disease.[1] Ticks of the Ixodes ricinus complex-*I. Scapularis* and *I. Ricinus* in Europe-transmit spirochetes after feeding for 36-72 h.[1-3] The most important reservoir for *B. burgdorfei* is the white-footed mouse, in North America, where both adult and nymph forms of the tick can transmit infection.[4]

The most commonly reported vector-borne infection in the United States is Lyme disease. Lyme disease is most prevalent in the northeast, north central and western costal regions of the United States, although cases of it have been reported in all 50 states. Those that are most often affected by the disease are children from 5-14 years old and adults between 30-55 years old. In the United States from 1982 to 1996 a 30-fold increase in the number of cases of Lyme disease has been observed.[5]

In Europe and the United States, case definitions for Lyme disease have been developed.[6,7] The initial symptoms of the disease are characterized by erythema migrans and flu-like illness, followed by neurologic, cardiac, or musculoskeletal manifestations which follow weeks or months after exposure.[4]

The early attempts to develop a vaccine against Lyme disease involved making whole-cell preparations of *B. burgdorferi*.[8,9] The observed reactogenicity/toxicity of the whole-cell preparations caused the pursuit of a recombinant vaccine.[10] The outer surface protein A (OspA) of *B. burgdorferi* was selected and proved to be immunogenic in animal models.[11-13] OspA expression occurs primarily in the tick and is upregulated after passage from the vertebrate host

to the tick.[14] In addition, *Borrelia* OspA is primarily found in the United States, although this is not true in Europe.[15]

The OspA-based Lyme vaccine confers protection in a unique way. Bactericidal antibodies generated against OspA eliminate *B. burgdorferi* from this vector during feeding, preventing infectious spirochetes from entering the host.[16,17] To be effective, a seroprotective level of antibody must be obtained before exposure to infected ticks, and a bactericidal antibody can be achieved through vaccination or infection.[18-20]

The Food and Drug Administration (FDA) of the United States in 1998 licensed an adjuvanted vaccine (LYMErix™, SmithKline Beecham Pharmaceuticals) containing 30 micrograms of lipidated recombinant OspA for the prevention of Lyme disease and asymptomatic infection in persons 15-70 years old.

In a multi-center double-blind trial of 10,936 participants, this vaccine was administered in a 0-, 1-, and 12-month (0, 1, 12) schedule, demonstrating efficacy after two to three doses. Antibody titers one month after dose 2 were determined to be 1,227 IU/mL and one month after dose 3 were determined to be 6,006 IU/mL. These levels of antibody were achieved in 90 and 95 percent of recipients, respectively. Efficacy in preventing symptomatic Lyme disease was 76 percent after three doses of vaccine and 49 percent after two doses. Efficacy for preventing asymptomatic disease was 100 percent after the third dose and 83 percent after the first two doses. LYMErix vaccine was described as well-tolerated in the trials.[21] Two studies were published, one by Steere and colleagues and another large clinical trial by Sigal and colleagues that were unable to substantiate inflammatory arthritis as a complication of Lyme vaccination.[21,22]

The purpose of this analysis was to examine arthritic adverse reactions reported to the

Vaccine Adverse Events Reporting System (VAERS) database following recombinant Lyme vaccination in the adult population of the United States. The VAERS database has been maintained by the Centers for Disease Control and Prevention (CDC) since 1990. All adverse reactions following vaccination are to be reported to this database as mandated by US law. The protocol for reporting of all serious reactions to VAERS requires written and telephonic confirmation by the CDC. The CDC also follows up all serious reactions one year after they occur to determine whether or not the patients had fully recovered from their reaction. The VAERS Working Group of the CDC analyzes the VAERS database. A recent study by the VAERS Working Group of the CDC has stated that VAERS is simple for reporters to use, flexible by design and that its data are available in a timely fashion.[23] We and other authors have found that the massive size of the VAERS database makes it a unique and useful tool to analyze adverse reactions to vaccines. Our recent studies have shown an association between hepatitis B vaccination and arthritic, immunological and gastrointestinal symptoms based upon our analysis of the VAERS database.[24-30] We have also reported on the incidence of adverse reactions in the state of Texas, arthritic symptoms following rubella vaccination and joint-related adverse reactions following anthrax vaccination in light of biological warfare scenarios based upon analysis of the VAERS database.[31-33] It was our aim in this study that by examining the VAERS database we would gain a broad perspective of the effects of Lyme vaccination in the United States population based upon many millions of doses of vaccine that is virtually unattainable by any other methods of analysis.

Patients and Methods

In order to further examine arthritic adverse reactions reported following Lyme

vaccination, we made a retrospective examination of the information reported to the VAERS database from December 1998 through October 2000 using Microsoft Access. Our analysis was limited to only those arthritic reactions reported in the adult population for which the FDA has approved Lyme vaccine. The arthritic adverse reactions reported to the VAERS database examined in this study were as follows: arthritis, arthrosis, arthralgia and joint disease. We also examined the number of reaction reports, emergency room (ER) visits, life threatening reactions, hospitalizations, disabilities and deaths reported to the VAERS database following vaccination. These categories for adverse reactions were based upon descriptions of adverse reactions by those reporting them and by defined reporting fields contained in the VAERS database. The incidence rates calculated in this study were based upon the estimates of the Biological Surveillance Summaries that we obtained from the CDC for the number of doses administered during the period examined. The use of these numbers to calculate the incidence of adverse reactions reported to the VAERS database has been validated in several of our recent publications.[27-33] The CDC estimates indicated that 1,400,000 Lyme vaccinations were administered during this study period. Additionally, as a control, tetanus-diphtheria (Td) vaccine adverse reactions reported to VAERS from 1991 through 1999 in adults were analyzed, so as to maximize the background reporting rates of adverse reactions reported to the VAERS database. The CDC estimates indicated that 129,293,354 Td vaccination were administered from 1991 through 1999 to adults. The incidence rates of adult adverse reactions in Td vaccine recipients provided a background rate to compare against the incidence rates of adverse reactions in Lyme vaccine recipients.

We believe an unbiased search of the incidence rate of a specific adverse reaction to one

vaccine would be expected to be similar to the incidence rate following another vaccine administered to a similar aged population because whatever the inherent limitations in the accuracy of reported adverse reactions to the VAERS database, they should be expected to equally effect the reports of both vaccines under study. Similarly, the number of doses of a type of vaccine administered based on the Biological Surveillance Summaries of the CDC should be unbiased because whatever the inherent limitations of the Biological Surveillance Summaries, they should apply equally to each vaccine under study. In performing our statistical analyses, the assumption of equal reactogencity between vaccines forms the basis of our null hypothesis. In performing our statistical analysis we used a 2x2 chi-square contingency table where we assume that the total number of an adverse reaction following our control vaccine and the number of doses administered based upon our Biological Surveillance Summaries for the time period examined are the expected values and the total number of an adverse reaction following our vaccine under study and the number of doses administered based upon our Biological Surveillance Summaries for the time period examined are the observed values. The use of vaccine control groups to determine if there was a statistical relationship between a vaccine and specific types of reactions using chi-square statistical analysis has been validated in several of our recent publications.[27-33] We used the statistical package contained in Corel's Quattro Pro and accepted a p value of 0.05 as statistically significant.

We have also used the incidence rate of an adverse reaction following our vaccine under study in comparison to the incidence rate of an adverse reaction following our control vaccine group to determine the relative risk of the adverse reaction and the percent association of the adverse reaction following our vaccine under study. The relative risk value is obtained by

dividing the incidence rate of the adverse reaction following our vaccine under study by the incidence rate of the adverse reaction following our vaccine control group. The percent association value is calculated by dividing the relative risk value by the relative risk value plus one and multiplying this computed value by 100.

Results

(Table 1) summarized the incidence per million vaccinations of total reaction reports, ER visits, life threatening reactions, hospitalizations, disabilities and deaths reported to the VAERS database following Lyme and adult Td vaccinations among those residing in the United States. This table showed that there was a statistical increase in the incidence of total reaction reports, ER visits, life threatening reactions, hospitalizations and disabilities reported to the VAERS database following Lyme vaccination in comparison to our adult vaccine control group. (Table 2) summarized the number of male and female reaction reports, mean age in years, mean onset in days and the incidence per million vaccinations of arthritic reactions reported following Lyme vaccination among those residing in the United States. This table showed that most of the arthritic reactions reported to the VAERS database following Lyme vaccination occurred in patients about 50 years-old within four to six days after vaccination. The data further showed that the number of arthritic reactions reported following Lyme vaccination were evenly divided between men and women(approximate female/male ratio = 0.82). (Table 3) compared the reactivity of adult Td vaccine and Lyme vaccine administration among those residing in the United States. This table showed a statistical increase in arthritic reactions reported to the VAERS database following Lyme vaccine in comparison to our adult Td vaccine control group.

Discussion

The prediction, both from the vaccine design and early clinical trials on Lyme vaccine, that this type of vaccine would be well-tolerated and result in few adverse reactions is not borne out by our analysis of the VAERS database. Our analysis showed a statistically significant increase in numerous adverse reactions reported to occur in adults after Lyme vaccination when compared with our adult Td vaccine control group.

We also compared the incidence of arthritic reactions reported following Lyme vaccination with those reported following adult rubella vaccination to the VAERS database. We have previously reported on arthritic conditions reported to the VAERS database following adult rubella vaccination.[31] In our previous paper, we found that arthritic reactions were reported following adult rubella vaccination as follows: 78/million rubella vaccinations for arthralgia adverse reactions, 24/million rubella vaccinations for arthrosis adverse reactions, 19/million rubella vaccinations for arthritis adverse reactions and 5.0/million rubella vaccinations for joint disease adverse reactions. The Institute of Medicine (IOM), of the U.S. National Academy of Sciences, reported in 1991, that the evidence indicated a causal relationship between the currently used rubella vaccine and acute and chronic arthritis.[34] In comparing the incidence rate per million vaccinations of arthritic reactions reported to VAERS following Lyme vaccination to rubella vaccination, a statistical increase in the incidence of arthralgia, joint disease and arthritis ($p < 0.01$) and arthrosis ($p < 0.05$) adverse reactions was observed. However, it should be noted that there is the potential that some of the cases of arthritic reactions we analyzed following Lyme vaccine may be, acute self-limited reactions that did not lead to chronic serious problems. In order to address this problem we, again, compared the incidence of adverse reactions classified as arthritis following Lyme vaccine to those following rubella vaccine. Specifically, we

compared the incidence of arthritis adverse reactions where the patients were considered to be disabled and where the patients were considered not have recovered from their adverse reaction as reported to the VAERS database based upon a one year followup. We found that the incidence of arthritis adverse reactions following Lyme vaccine where the patient was considered to be disabled was 11/million Lyme vaccinations and where the patient was considered not to have recovered was 25/million Lyme vaccinations and following adult rubella vaccination where the patient was considered to be disabled was 0.41/million adult rubella vaccinations and where the patient was considered not to have recovered was 3.7/million adult rubella vaccinations. The incidence rates were statistically increased ($p < 0.01$) over the incidence rate of arthritis reactions following adult rubella vaccine.

The overall rate of developing an arthritic reaction, based upon our numbers, as an adult was 300/million doses of Lyme vaccine. However, since arthritic reactions following Lyme vaccine were unexpected, the arthritic adverse reactions reported to VAERS undoubtably are under reported. Doctors need to become aware of these reactions and should they occur following Lyme vaccinations they should be reported to VAERS.

Our results confirmed the work of Croke and colleagues who provided direct evidence that OspA can induce arthritis in Hamster animal model systems.[35] They showed hamsters vaccinated with 30, 60, or 120 micrograms of recombinant OspA and challenged with *B. burgdorferi* developed swelling of the hind paws which was detected in 100, 100 and 50 percent, respectively. The authors stated that their findings suggested recombinant OspA vaccines should be modified to eliminate epitopes of OspA responsible for the induction of arthritis, especially considering the FDA has approved recombinant OspA vaccine for use in humans.

The mechanism by which Lyme vaccine may be associated with arthritic conditions may involve the histocompatibility type HLA-DR4. This histocompatibility group has demonstrated an increased frequency of migratory arthritis following natural infection with *B. burgdorferi*.[36] Additionally, an epitope of OspA, when bound to transgenic mouse HLA-DRB1*0401, is cross-reactive with human leukocyte function-associated antigen-1, prompting speculation that so-called 'treatment-resistant' Lyme arthritis is an autoimmune phenomena. Evidence for the role of a cross-reactive T-cell response in the pathogenesis of Lyme arthritis remains theoretical.[37,38]

A recent study by Lathrop and colleagues concluded that following the first 19 months of Lyme vaccination, based upon analysis of the VAERS database, there were no unexpected or unusual patterns of reported adverse events following Lyme vaccination, other than hypersensitivity reactions, compared with adverse events observed in clinical trials.[39] It is interesting to note that the early clinical trials reported that Lyme vaccine was generally well-tolerated and that apparently these clinical trials, as reported by Lathrop and colleagues, observed similar rates of reactivity as we observed in this study in making their decision that Lyme vaccine was generally well-tolerated. Our data does not support the observation that Lyme vaccine was generally well-tolerated.

Conclusion

Our study showed that there was a statistical increase in the incidence rate of arthritis, arthrosis, arthralgia and joint disease reported to the VAERS database following Lyme vaccine in comparison to our adult vaccine control group. Even more remarkable, our analysis showed Lyme vaccination to have a statistical increase in the incidence rate of both acute and chronic arthritic reactions in comparison to adult rubella vaccination, which has been determined, by the

IOM, to have a causal relationship with acute and chronic arthritis. The observed arthritic reactions were totally unexpected based upon the Lyme vaccine design as a single antigen, genetically engineered, purified vaccine. Our results indicate that additional study is necessary into Lyme disease to allow for the production of a safer vaccine. The withdrawal of Lyme vaccine in early 2002 seems well justified based upon the results of this study and Lyme vaccine probably should not be used until processes have been developed to produce a safer vaccine.

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Table 1. Adverse reactions reported following vaccination

Type of Vaccine	Incidence per Million Vaccines of Reaction Reports	Incidence per Million Vaccines of ER Visits	Incidence per Million Vaccines of Life Threatening Reactions	Incidence per Million Vaccines of Hospitalizations	Incidence per Million Vaccines of Disabilities	Incidence per Million Vaccines of Deaths
Lyme	629	216	13	29	31	2.1
Td Vaccine	56	24	0.49	2.1	0.32	0.10

This table showed that there was a statistically significant ($p < 0.01$) increase in the incidence of total reaction reports, ER visits, life threatening reactions, hospitalizations and disabilities reported to the VAERS database following Lyme vaccination in comparison to our adult Td vaccine control group.

Table 2. Lyme vaccination adverse reactions

Type of Reaction	Number of Female Reports	Number of Male Reports	Mean Age (years)	Mean Onset (days)	Incidence per Million Vaccinations
Arthralgia	122	142	47.7 ± 12.4	4.8 ± 7.3	196
Arthrosis	20	31	49.1 ± 15.2	6.6 ± 8.8	36
Arthritis	33	26	50.4 ± 13.8	6.3 ± 8.8	42
Joint Disease	13	23	52.0 ± 11.3	5.2 ± 7.9	26

Table 3. A comparison between adult Td and Lyme vaccination

Type of Adverse Reaction	Incidence of Associated Adverse Reaction per Million Td Vaccinations	Incidence of Associated Adverse Reaction per Million Lyme Vaccinations	Relative Risk of the Adverse Reaction Following Lyme Vaccination	Percent Association Between Lyme Vaccination and the Associated Adverse Reaction	Chi-Square Association Between Lyme Vaccination and the Associated Adverse Reaction
Arthralgia	2.7	196	73	99	$p < 0.01$
Arthrosis	0.39	36	92	99	$p < 0.01$
Arthritis	0.24	42	175	99	$p < 0.01$
Joint Disease	0.22	26	118	99	$p < 0.01$