Published in final edited form as:

Sex Transm Dis. 2012 August ; 39(8): 645–647. doi:10.1097/OLQ.0b013e3182536574.

RPR Titer Variation in the Two Weeks Following Syphilis Therapy

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Abstract

Background—Serologic tests for syphilis (STS) results at time of diagnosis are the basis for evaluating response to syphilis therapy. Following treatment, however, STS titers may continue to increase for several weeks. We evaluated RPR titer variation over the 14 days following therapy using data from a recent large, prospective RCT.

Methods—Prospectively enrolled participants in North America and Madagascar with primary, secondary or early latent syphilis were randomly assigned to penicillin, doxycycline (in the case of penicillin allergy) or azithromycin treatment. Blood for RPR analysis was drawn at days 0, 7, and 14 post-treatment. All RPR titers were determined simultaneously at a central laboratory.

Results—470 patients had data available for at least 2 of 3 RPR measurements. Overall, 20% of patients showed a titer increase of at least one dilution in the 14 days following therapy. The greatest proportion of titer increases following therapy was seen in patients with primary syphilis. Comparing outcome of therapy using the initial (day 0) RPR titer vs. the maximal RPR titer (over 14 days), resulted in outcome reclassification in 2.98% of participants.

Conclusions—Despite the fact that about 20% of early syphilis patients had increases in RPR titers immediately following treatment, these changes rarely influenced assessment of therapeutic outcome. Only 3% of patients treated would have been reclassified.

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Potential Conflicts of Interest: K.H.- No conflict. M.W.- No conflict. A.S.- No conflict. D.M. is a share holder in Merck and has been a consultant to Cempira Pharma. F.B. – No conflict. K.V.D- No conflict. P.L. has received research funding from GSK, Abbott Diagnostics, Norvartis and Trinity Diagnostics and has been on the speakers' bureaus for GSK, Norvartis and Abbott Diagnostics. L.M.- No conflict. M.G. –No conflict. E.W. has received research funding from GenProbe, Becton-Dickinson, Roche Molecular Diagnostics, Siemens Diagnostics, and has been on the speakers' bureaus for GSK, Norvartis and Abbott Diagnostics.

Keywords

Syphilis testing; RPR; Syphilis Treatment Outcome

Introduction

Syphilis is a relatively common, chronic infectious disease of public health importance. In addition to direct morbidity associated with infection, syphilis may be transmitted to sexual partners and to unborn children of infected mothers. Syphilis also is associated with increased risk for HIV transmission.[1] U.S. syphilis rates have risen steadily through the last decade.[2]

Serological testing for antibodies against *Treponema pallidum* is the most widely used means for syphilis diagnosis. Repeated determination of non-treponemal (i.e. RPR, VDRL) serologic test for syphilis (STS) titers is recommended to evaluate response, with a four-fold (2 dilution) decrease from baseline and/or seroreversion in 12 months following treatment representing an appropriate response to therapy/serologic cure.[3] In most settings, the non-treponemal STS titer present at treatment is used to evaluate subsequent therapeutic response. However, it is possible that anti-treponemal antibody concentrations may continue to increase for a period of time following effective therapy.[4] To evaluate the frequency with which STS titers increased following early syphilis therapy, we analyzed weekly serologic test results obtained on three occasions from over 400 patients in a recent therapeutic trial that compared benzathine penicillin G to azithromycin for early syphilis therapy.

Methods

Data collected as part of an open-label, randomized controlled trial conducted from June 2000-March 2009 at five sexually transmitted disease clinics in North America and three clinics in Madagascar were analyzed. Methods, including details regarding recruitment, therapeutic intervention, and clinical assessment, were previously described.[5] The protocol was approved by the Institutional Review Board (IRB) at the University of Alabama at Birmingham (UAB) and at each participating site.

Briefly, participants with primary, secondary or early latent syphilis were randomized to treatment with single doses of benzathine penicillin 2.4 million units intramuscularly or azithromycin 2.0 grams. Participants with reported penicillin allergy were randomized to doxycycline 100 milligrams orally twice daily for fourteen days or azithromycin 2.0 grams orally. Follow up visits for RPR testing were scheduled at 7 and 14 days, and 3 and 6 months following treatment. Sera to determine study-defined treatment outcomes were stored frozen and all RPR testing was performed same day at the UAB central laboratory according to accepted methods.[6]

The primary outcome of the trial was serological response to therapy at 6 months. To evaluate response to treatment, the maximal RPR titer during three visits occurring in the 14 days following therapy (i.e. day of treatment, 7 days and 14 days) was used as the baseline for analysis. Serological cure was defined as either negative RPR or 4-fold (2 dilutions) decrease in titer (no participants had recurrent signs of infection); treatment failure was defined as 4-fold increase in RPR titer without clear history of re-exposure. Serological non-response or serofast status was defined as no more than a 2-fold (1 dilution) increase or decrease from baseline. As specified in the protocol, those participants defined as treatment failure or serological non-response were retreated at 6 months with benzathine penicillin or doxycycline, if penicillin allergic.

The study population for this report is participants with serological data at the 6 months visit post treatment and without a change in eligibility status prior to the 6 month visit. Statistical analysis was performed using SAS Software Version 9.2.[7] P-values are based on chi-square tests obtained from relevant contingency tables. We determined the proportions of participants with an increase in RPR titer during the 14 days following syphilis therapy.

Results

A total of 470/517 (90.9%) patients had data for at least 2 of 3 RPR measurements during their first two weeks of study participation and completed the six-month follow up without a change in protocol status. Selected demographic characteristics are presented in Table 1. Median RPRs at diagnosis, stratified by stage, were Primary 1:16, Secondary 1:64, and Early Latent 1:32.(Figure 1) Overall, 20.2% (95) of patients showed a titer increase in the 14 days following therapy.(Table 2) Of these, 88.2% (84) demonstrated an increase of 1 dilution, while in 11.8% (11) RPR titers increased 2 dilutions. Persons with the earliest stages of syphilis were more likely to experience RPR increases in the two weeks following therapy, with 30.5% of participants treated for primary syphilis experiencing an increase in RPR titers, while the proportion of secondary and early latent syphilis patients was about 17% and 16%, respectively.(p=0.005)

We compared the outcome of therapy (i.e. cure, serofast, failure) at 6 months using both a “clinical definition,” the initial titer at the time of treatment, and a “research definition,” the maximal titer obtained during the 14 days following treatment. When the two definitions were compared, the outcome changed in only 14 participants (2.98%). Thirteen changed from serofast (clinical) to cure (research) and one changed from failure (clinical) to serofast (research). (Table 3) Increased RPR titers in the two weeks following therapy did not occur in all patients with treatment failure. Of the five participants classified as serological treatment failures[5], only one had a single dilution rise in RPR titer in the 14 days following therapy. However at the time of defined treatment failure, this patient’s RPR titer had increased by 3 dilutions from the initial titer.

Selected characteristics of participants with a rise in RPR titer following treatment were compared to those without a rise in titer. Earlier syphilis stage was the only variable significantly associated with an increase in RPR titer following therapy.(Table 1) Age, gender, treatment regimen, ethnicity (Malagasy vs. non-Malagasy), prior syphilis and Jarisch-Herxheimer reaction were not significantly associated with an increase in RPR titer during the 14 days following treatment.

Discussion

To our knowledge, these data represent the first systematic analyses of RPR increases in humans immediately following therapy of early syphilis. We found that initial RPR titers underestimate the maximal RPR titer in about 20% of early syphilis patients following therapy. In particular, earlier stage is associated with an increase in RPR titer, while age, gender, ethnicity, treatment regimen, prior syphilis, or a Jarisch-Herxheimer reaction were not significantly associated. Using the RPR titer measured at the time of treatment as the baseline to assess serologic response resulted in re-classification of ~3% of patients, slightly underestimating cures and overestimating failures.

While we acknowledge the relatively limited clinical implications, our study quantifies the frequency of increase in RPR titers in the weeks immediately following early syphilis therapy. While the CDC STD Treatment Guidelines recommend follow up of non-treponemal serologic tests of syphilis patients at 6 and 12 months following therapy[3], from

time to time patients have repeat syphilis testing prior to these specified times. In our experience, this situation can result in confusion about the appropriate next step. Our data suggest that a rise in RPR titer within the 14 days following early syphilis therapy is not indicative of increased risk of treatment failure and does not require additional therapy or change in management.

We acknowledge several study limitations. Combining the azithromycin and penicillin treatment arms raises concern for possible effects; however, our analysis did not reveal a significant effect on RPR titer increase. We also acknowledge that in clinical settings where syphilis patients are tested repeatedly, RPR or VDRL titers may vary +/- 1 dilution. We sought to minimize variability by testing all serum simultaneously in a single laboratory. Nonetheless, some of the observed variations may reflect the acknowledged error of the test. We also excluded pregnant or HIV positive patients, limiting the generalizability to these groups. We collected data regarding treatment response up to 6 months; it is conceivable that outcomes may have differed if additional data was collected past that time point. Finally, as only patients with early syphilis were enrolled, these findings are not applicable for patients with late stages of syphilis.

These data also have implications for the research setting. Given that RPR titers increase in about 20% of participants with early syphilis, testing several times over the two weeks immediately following therapy will provide the most accurate peak titer for subsequent assessment of response to therapy. Had the initial RPR at time of treatment been used as the baseline for therapeutic response at 6 months, ~3% of patients treated would not have met criteria for serologic cure.

Acknowledgments

We gratefully acknowledge the following: Carolyn Deal, Ph.D., Nancy Padian, Ph.D., and Peter Wolff, MHA, Sexually Transmitted Infections Clinical Trials Group Executive Committee; Willard Cates, M.D., M.P.H., Myron Cohen, MD., and Walter E. Stamm, M.D., Sexually Transmitted Diseases Clinical Trials Unit Executive Committee; Emil Gotschlich, M.D., Kenyon Burke, Ed.D., Helen Lee, Ph.D., Larry Moulton, Ph.D., and Peter Rice, M.D., Data Safety and Monitoring Board; Lihan Yan, Melinda Tibbals, Robin Cessna, Carol Smith and Jamie Winestone, EMMES Corporation; Nincoshka Acevedo, B.S., Florence Carayon, M.A., and Jill Stanton, B.A., Family Health International; Carol Langley, M.D., Janet N. Arno, M.D., Indiana University School of Medicine; Tomay Mroczkowski, M.D., Stephanie Taylor, M.D., Barbara Smith, R.N., Louisiana State University; Carolyn Deal, Ph.D., Penny Hitchcock, DVM, Barbara Saverese, R.N., Peter Wolff, MHA, National Institutes of Allergy and Infectious Disease; Joan Stephens, R.N., Anna Lee Hughes, R.N., Tracey Burkett, CRNP, Connie Lenderman, MT (ASCP), MBA, Paula B. Dixon, Grace Daniels, and Sharron Hagy, University of Alabama at Birmingham/Jefferson County Department of Health; Heidi Swygard, M.D., Karen Lau, F.N.P., Christopher Bernart, P. A., University of North Carolina at Chapel Hill; Bodo Sahondra Randrianasolo, M.D., Mbolatiana Soanirina, M.D., Michèle Raharinivo, Felaosa Noroseheno Ramiandrisoa, M.D., Ny Lovaniaina Rabenja, M.D., Herinjaka Andrianasolo, Roméo Rakotomanga, Tahiana Rasolomahefa, Norbert Ratsimbazafy, M.D., Zo Fanantenana Raharimanana, M.D., Verolanto Ramaniraka, M.D., Marina Rakotonirina, Tiana Ravelohanitra, Andrianiseta Rakotomihanta, Jacqueline Hortensia Rajaonarison, Lucienne Rasoamanana, Elyse Rasoanijannahary, Charlotte Razanasolonambinina, Olivier Claret Raelina, M.D., Naina Ranaivo, M.D., Angele Zanatsoa, Claire Fety, Cynthia Mamy, Bruno Raelina, Esther Solovavy, Justine, Julianne Rasoamarovavy, Diana Ratsiambakaina, M.D., Agnè Ramaroson, M.D., Theodosie Tombo, David Noelimanana, Florence Raeliarisoa, Gilbert Razaka Sadiry, Bacar Soumaely, Bernard, Justin Ranjalahy Rasolofomanana, Lala Rakotondramasy, Falimanantsoa Sylvain Ramandiarivony, Hobitiana Rakotoarimanana, Lucie Razanamandrisoa, University of North Carolina-Madagascar; Jocelyne Andriamiadana, M.D., USAID Madagascar; and Institut Pasteur de Madagascar, The Ministry of Health, Madagascar.

Sources of Support: This work was supported by the National Institute of Allergy and Infectious Diseases at the National Institutes of Health [grant number N01 A1 75329, Myron Cohen, MD, PI] and the STI Clinical Trials Group [grant number HHSN 26620040073C, Edward W. Hook, III, MD, PI].

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Figure 1.
Distribution of RPR Titers at Day of Treatment (Visit 1) by Stage

Table 1

Characteristics of Patients With and Without RPR Titer Increase In the 14 Days Following Early Syphilis Treatment

Characteristic	No RPR Titer Increase (N=375), n(%)	RPR Titer Increase (N=95), n(%)	OR (95%CI)
Gender			
Male	226 (77.9)	64 (22.1)	1.36 (0.85, 2.19)
Female	149 (82.8)	31 (17.2)	1
Age (years)			
<=24	180 (77.9)	51 (22.1)	1.39 (0.63, 3.03)
25-29	78 (76.5)	24 (23.5)	1.50 (0.64, 3.52)
30-39	73 (86.9)	11 (13.1)	0.74 (0.28, 1.92)
>=40	44 (83.0)	9 (17.0)	1
Race/ ethnicity			
Black	56 (87.5)	8 (12.5)	1
White + other	10 (71.4)	4 (28.6)	2.80 (0.71, 11.1)
Malagasy	309 (78.8)	83 (21.2)	1.88 (0.86, 4.10)
Prior history of syphilis			
No	65 (84.4)	12 (15.6)	1
Yes	27 (84.4)	5 (15.6)	1.00 (0.32, 3.12)
Unknown/ Test not performed	283 (78.4)	78 (21.6)	1.49 (0.77, 2.90)
Syphilis Stage			
Primary	82 (69.5)	36 (30.5)	1
Secondary	181 (82.7)	38 (17.3)	0.48 (0.28, 0.81)
Early Latent	112 (84.2)	21 (15.8)	0.43 (0.23, 0.79)
Jarisch-Herxheimer Reaction			
No	231 (79.4)	60 (20.6)	1
Yes	143 (80.3)	35 (19.7)	0.94 (0.59, 1.50)

Table 2

By Stage, Percentage of Patients with an Increase in RPR Titers in the 14 Days Following Therapy of Early Syphilis.

Stage	N	Median RPR at diagnosis	% with increased titers within 14 days following treatment (95% CI)	% with titers increased by 2 dilutions following therapy (95% CI)
Primary	118	1:16	30.5 (22.4-39.7)	5.9 (2.4-11.8)
Secondary	219	1:64	17.4 (12.6-23.0)	0.5 (0.0-2.5)
Early Latent	133	1:32	15.8 (10.0-23.1)	2.3 (0.5-6.5)
Total	470	1:64	20.2 (16.7-24.1)	2.3 (1.2-4.1)

Table 3
Comparison of Treatment Response Using Clinical or Research Definitions of Baseline RPR Titer

Clinical Definition: Initial RPR titer at visit 1	Research Definition: Maximal RPR titer during 14 days (visits 1-3)				
	Frequency	Cure	Failure	Serofast	Total
	Cure	357	0	0	357
	Failure	0	5	1	6
	Serofast	13	0	94	107
	Total	370	5	95	470