

Rectal Lymphogranuloma venereum among Men who Have Sex with Men: 7 versus 21 Days Doxycycline Effectiveness

Angelo Roberto Raccagni, MD¹, Alessia Siribelli, MD¹, Sara Diotallevi, Ms², Michela Sampaolo, MD², Elena Bruzzesi, MD¹, Nicola Clementi, Prof^{1,2}, Riccardo Lolatto, Ms², Roberto Burioni, Prof^{1,2}, Antonella Castagna, Prof^{1,2}, Silvia Nozza, MD^{1,2}

Vita-Salute San Raffaele University, Milan, Italy (A.R. Raccagni, A. Siribelli, E. Bruzzesi, N. Clementi, R. Burioni, A. Castagna, S. Nozza)

IRCCS San Raffaele Scientific Institute, Milan, Italy (S. Diotallevi, M. Sampaolo, N. Clementi, R. Burioni, A. Castagna, S. Nozza)

Corresponding author: Angelo Roberto Raccagni, MD; <https://orcid.org/0000-0001-7811-6255> Via Stamira D'Ancona 20 Milano, 20127, Italy

Phone +390226437953; Fax +390226437903; E-mail: raccagni.angelo@hsr.it

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Summary Line. Among MSM with rectal LGV, comparable clinical and microbiologic cure were found after 7- or 21- doxycycline days, regardless of symptoms.

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Abstract

This is a retrospective study on MSM diagnosed with rectal LGV, treated with 7 or 21 days of doxycycline between 2015-2022. Overall, 143 MSM were included: 58 (41%) had LGV. 100% microbiologic cure was found among MSM with symptomatic or asymptomatic LGV treated with 7 and 21 days of doxycycline.

Keywords: Lymphogranuloma venereum; Chlamydia; Doxycycline; MSM

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Background

Lymphogranuloma venereum (LGV) is a sexually transmitted infection (STI) caused by *Chlamydia trachomatis* (Ct) serovars L1-3. CDC guidelines recommend treatment of LGV genotypes with 21-days of doxycycline (DOXY), compared to 7-days DOXY treatment of non-LGV.[1] Preliminary findings suggest that shorter courses of DOXY may be effective for treatment of LGV.[2-4]

Aim is to evaluate the clinical and microbiologic cure of LGV after 7- or 21-days of DOXY among MSM with symptomatic or asymptomatic rectal LGV genotypes.

Methods

This is a retrospective study based on chart review on MSM in care for HIV infection or PrEP at the Infectious Diseases Unit of San Raffaele Hospital, Milan, Italy. We included people diagnosed between 2015 (start of genotype determination) and 2022 (freezing date) with rectal Ct, detected by nucleic acid amplification test (NAAT) on rectal swabs with Cobas CT/NG test on Cobas 6800 system (Roche). Rectal swabs were collected by clinicians or self-collected. Sequencing genotype determination applied to all positive samples to distinguish between LGV and non-LGV cases and to establish specific genotypes. LGV positive samples were amplified by nested Omp1 PCR and sequenced with an ABI-3730 genetic analyzer (Applied Biosystems).[5] The consensus sequences were compared with known LGV strains with Basic Local Alignment Search Tool (BLAST) search tool to identify specific genotypes.[6] Occasionally, genotypes determination was not feasible due to non-amplifiable sequencing results. All people with an available rectal chlamydia test after the end of DOXY treatment (next Ct test) were included.

People were treated with 7- or 21-days of DOXY depending on timing of available sequencing results. For example, during the SARS-CoV-2 outbreak, sequencing results were available long after the completion of the 7 DOXY days of treatment, and no further treatment was prescribed due to resolution of symptoms.

Symptomatic LGV infection was defined by reported symptoms: discharge, pain, tenesmus, constipation, diarrhea, or bleeding.

Clinical cure was defined as resolution of symptoms after DOXY treatment. Microbiologic cure (MC) after DOXY treatment was defined by means of next Ct test results, considering eradication in case of negative or positive next Ct test with a different Ct genotype (re-infection).

Date of Ct diagnosis was considered as baseline. Data were reported as median (interquartile, IQR) or frequency (%). Mann-Whitney test was used to compare baseline characteristics of individuals. Proportions of MC according to presence of symptoms and treatment durations were compared using exact binomial test. Clinical data, individuals' characteristics and microbiologic results were retrieved from electronic health records. Analyses were conducted using the aforementioned two-sided test at 0.05 alpha level of significance with R Statistical Software, v.4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Overall, 143 MSM were included in the study: 58 (41%) had LGV genotypes, 63 (44%) non-LGV Ct genotypes and 22 (15%) Ct infection with non-amplifiable sequencing results. Detected LGV genotypes were 3 (5%) L1, 23 (40%) L2, 10 (17%) L2b and 22 (38%) L2c.

People with symptomatic LGV were 44 (76%). Among people with LGV, median age at baseline was 39.5 (33.7-47.1) years; 55 (95%) MSM were Caucasian. PLWH were 52 (90%), with 760 cells/ μ L (623-9344) median CD4⁺ lymphocytes; 6 (10%) were PrEP users [Table 1]. Overall, 22 (38%) MSM received 7-days (12 symptomatic) and 36 (62%) 21-days (32 symptomatic) of DOXY for LGV treatment, according to physician choice and depending on the timing of sequencing results.

Median time to next Ct test since LGV diagnosis was 7.37 (3.04-16.9) months, with no significant difference between the 7-days and 21-days DOXY treatment groups, across both symptomatic [8.87 (6.05-13.6) vs 11.7 (3.14-21.6); p=0.98] and asymptomatic [3.14 (2.11-3.48) vs 15.2 (4.12-24.9); p=0.20] LGV cases.

All MSM with symptomatic LGV were clinically cured, with observed resolution of symptoms after treatment with DOXY regardless of duration.

Microbiologic cure (MC) occurred in 57 (98%) people: 52 (90%) had a negative next Ct test and 5 (9%) had non-LGV Ct re-infection at time of next test (all genotypes D). One person had a positive next Ct test after LGV treatment with a non-amplifiable sequencing result (next Ct test at 10.2 months and with >30 sexual partners reported between rectal LGV and next Ct test). This could indicate a low bacterial load, which is unlikely to represent persistent LGV infection and was therefore excluded from subsequent analyses in the absence of complete sequencing results.

Proportions of MC among MSM with LGV, according to presence or absence of symptoms, who received 7- or 21-days of DOXY treatment, are presented in Table 2. Overall, 100% MC

was found among MSM with rectal LGV treated with 7- and 21-days of DOXY [7 days: 100% MC (95%CI=85%-100%) vs 21 days: 100%MC (95%CI=90%-100%), equivalence in MC proportions]. Moreover, among either symptomatic or asymptomatic people with rectal LGV, treated with 7- or 21-days of DOXY, equivalence in MC rates was found.

Conclusions

Among MSM with rectal LGV Ct genotypes, comparable clinical and microbiologic cure proportions were found after 7- or 21-days of DOXY, also among symptomatic people. LGV detection was frequent, in line with previous findings among key population members.[7-9] As international guidelines recommend treatment of LGV with 21-days of DOXY and that cases can be asymptomatic or clinically similar to non-LGV genotypes, LGV genotypes need to be actively detected.[1] Indeed, LGV detection requires specialized laboratories and, given the high incidence of Ct among key-populations, results in substantial economic costs.[9-10] Providing a unified treatment for all Ct cases, regardless of Ct serovar, could reduce diagnostic costs by rendering genotype determination unnecessary, except from surveillance.[11]

Several study limitations should be acknowledged. The retrospective nature of this study and the limited number of included individuals is prone to bias. However, the number of details recorded in our electronic health records from people receiving continuum care at our center may mitigate this. Next available Ct tests after infection were collected heterogeneously according to referring physician choice, given the lack of specific guidelines in the Italian setting, and often long after Ct. However, self-clearance of Ct at the rectal site among men has been reported to be low with long infection duration in the absence of treatment when compared to women, which corroborates the interpretation of study results.[12-14] Anoscopy

examination was not performed limiting the details on the clinical status of infection, as compared to other studies.[2] Possibility of selection bias should also be acknowledged, although we believe that the choice of treatment based on the timing of available sequencing results may mitigate this. Lastly, this study focuses on MSM with rectal asymptomatic or relatively mild LGV genotypes, limiting the applicability to other clinical scenarios. We also note that international discussion on the very definition of LGV, whether microbiological or clinical, is ongoing.[11]

Overall, we believe that, although various retrospective studies support that 7 days of doxycycline could be considered as a treatment option, especially for clinically mild or asymptomatic LGV genotypes, these data reinforce the need for randomized controlled clinical trials on shorter LGV treatment regimens.

Conflict of Interest

None to disclose.

Funding

None to disclose.

Statements

Written informed consent was obtained by included individuals. Data were extracted from the electronic health records of the Infectious Diseases Unit of San Raffaele Hospital [Centro San Luigi (CSLHIV) Cohort]. The CSLHIV Cohort was approved by the Ethics Committee of San Raffaele Hospital (4th December 2017, protocol n.34); on their first visit to our center, individuals provided written informed consent on the use of their anonymized data in scientific analyses. The planning conduct and reporting of this study was in line with the declaration of Helsinki. Recorded data were anonymized and managed according to the Good Clinical Practice.

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Legends

Table 1. Characteristics of included individuals diagnosed with LGV genotypes proctitis according to presence of symptoms and length of doxycycline treatment.

Table 2. Proportions of microbiologic cure (MC) among men who have sex with men with LGV genotypes proctitis, who received 7- or 21-days of doxycycline treatment.

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Table 1. Characteristics of included individuals diagnosed with LGV according to presence of symptoms and length of doxycycline treatment.

	Overall	Asymptomatic 7 DOXY days	Asymptomatic 21 DOXY days	p- value	Overall	Symptomatic 7 DOXY days	Symptomatic 21 DOXY days	p- value
	N=14	N=10	N=4		N=44	N=12	N=32	
Living with HIV	10 (71.4%)	8 (80%)	2 (50%)	0.520	42 (95.5%)	12 (100%)	30 (93.8%)	1.000
Age (years)	42.0 [36.3;46.7]	41.6 [36.3;44.5]	44.7 [39.7;48.7]	0.572	38.3 [33.6;46.6]	37.1 [34.6;43.8]	39.5 [33.1;46.6]	0.693
Nadir CD4+ (cells/microL)	425 [319;526]	442 [391;581]	334 [319;350]	0.295	438 [258;604]	470 [261;661]	438 [249;570]	0.469
CD4+ (cells/microL)	861 [743;1027]	861 [755;934]	902 [754;1050]	0.794	730 [622;927]	741 [617;973]	730 [644;909]	0.845
HIVRNA (<50 copies/mL)	14 (100%)	10 (100%)	4 (100%)	-	36 (85.7%)	10 (83.3%)	26 (86.7%)	1.000
LGV genotype				0.329				0.928
L1	2 (14.3%)	2 (20%)	0 (0%)		1 (2.27%)	0 (0%)	1 (3.1%)	
L2	2 (14.3%)	2 (20%)	0 (0%)		21 (47.7%)	7 (58.3%)	14 (43.8%)	
L2b	2 (14.3%)	2 (20%)	0 (0%)		8 (18.2%)	2 (16.7%)	6 (18.8%)	
L2c	8 (57.1%)	4 (40%)	4 (100%)		14 (31.8%)	3 (25%)	11 (34.4%)	

Table 2. Proportions of microbiologic cure (MC) among men who have sex with men with LGV genotypes proctitis, who received 7- or 21-days of doxycycline treatment.

	Treated with 7 DOXY days	MC with 7 DOXY days	MC proportion (95% CI)	Treated with 21 DOXY days	MC with 21 DOXY days	MC proportion (95% CI)	MC proportions difference
<i>Overall LGV</i>	n=22	n=22	100 (85%-100%)	n=35*	n=35	100 (90%-100%)	0%
<i>Symptomatic LGV</i>	n=12	n=12	100% (74%-100%)	n=31*	n=31	100% (89%-100%)	0%
<i>Asymptomatic LGV</i>	n=10	n=10	100% (69%-100%)	n=4	n=4	100% (40%-100%)	0%

Note. * One person with positive non-amplifiable next chlamydia test after LGV treatment with 21 days of DOXY excluded.

Abbreviations. LGV: lymphogranuloma venereum. MC: microbiologic cure.