Retrospective Study of the Effectiveness of Azithromycin Single Dose Versus One-week Doxycycline for Anorectal Chlamydia in Men Who Have Sex with Men

Premnaath TORAYRAJU[1], Kiran KALIDINDI[2], Usha HARTGILL[1,3] and Harald MOI[1,3]*
[1]Olafiaklinikken, Trondheimsveien 2, Bygg N, NO-0560 Oslo, [2]Surestat Ltd, London, UK and [3]Faculty of Medicine, University of Oslo, Oslo, Norway. *E-mail: harald.moi@medisin.uio.no
Accepted Jan 21, 2021; Epub ahead of print Jan 21, 2021

Chlamydia trachomatis (Ct) is the most common curable sexually transmitted infection (STI) in men (1), infecting all body orifices; urethra, anus and throat. After Iceland and Denmark, Norway has the third highest reported rate of Ct infection in Europe, with 450–500 cases per 100,000 population during the last 11 years. Repeat anorectal infections, including persistence after treatment among men who have sex with men (MSM) is a cause for concern.

Unfortunately, there are currently no published prospective randomized studies comparing azithromycin and doxycycline for treatment of anorectal Ct in MSM. Meta-analysis of 8 observational studies, of which 7 were in males, have shown cure rates of doxycycline of 99.6% and of azithromycin of 82.9% (2).

Despite these observational studies showing superior efficacy of doxycycline, current recommendations for treatment of anorectal Ct in the USA is still 1 g single-dose azithromycin as first line and 100 mg doxycycline twice daily for 7 days as second line (3). In Europe 7 days doxycycline is recommended as first-line treatment (4). No treatment study of anorectal Ct has been published from the Nordic countries.

The aim of this retrospective study is to supplement existing observational studies comparing azithromycin and doxycycline treatment of anorectal Ct in an MSM population with high test of cure (TOC) compliance.

METHODS (see Appendix S1[1])

RESULTS

Mean and median age of 1,491 patients included in 2004 to 2005 was 33.6 and 32 years, respectively, and for 2,466 patients in 2010 to 2011 34.6 and 32 years, respectively. Age distribution of patients with positive anal tests, see STable I, Appendix S1[1].

Out of 1,491 tests for Ct in 2004 to 2005, 170 were positive (11.4%), including 135 anorectal positive. Out of 2,466 tests in 2010 to 2011, 185 (7.5%) were Ct positive, including 146 anorectal positive (see flow chart, SFig. 1, Appendix S1[1]). The prevalence of Ct in the tested groups was significantly different across the years (χ^2=16.829, n=3,787, df=1, p=4×10^{-5}); however, the prevalence of anorectal Ct among those with Ct was not significantly different across the years (see statistical analysis).

In 2010 to 2011 all positive anorectal Ct tests were analysed for *lymphogranuloma venereum* (*LGV*) genotype, with 13 shown to be LGV. In 2004 to 2005, testing for LGV was not performed.

TOC is defined as the outcome of positive or negative nucleic acid amplification test (NAAT) for Ct from anal swab at the first visit after treatment initiation. All patients had an appointment for TOC 5 weeks after the first day of treatment.

A total of 130 patients were treated with azithromycin 1 g single dose, 123 in 2004 to 2005 and 7 in 2010 to 2011. Of these, 104 (80%) returned for TOC, of whom 84 (80.8%) had a negative TOC. Sixteen patients with a positive TOC after azithromycin were administered doxycycline 100 mg ×2 for a week as second-line treatment. Eight of them returned for TOC and all tested negative.

A total of 135 patients were treated with doxycycline for one week, 131 in 2010 to 2011 and 4 in 2004 to 2005. Of these, 118 (87.4%) returned for TOC, of whom all (100%) had a negative test (see statistical analysis section for test of significance in treatment efficacies).

A total of 29 patients with anorectal Ct were excluded from the treatment study, 13 because of LGV and 16 because of treatment not recorded or other treatment, including 3 treated with doxycycline who received azithromycin or moxifloxacin because of double infection with *M. genitalium*.

Statistical analysis

Since this was a retrospective study in which some patients had multiple treatments, the authors have selected a subset of the data to best compare the efficacy of the azithromycin vs doxycycline. This is where patients mutually exclusively had either treatment and returned for TOC; that is, 104 patients received single-dose azithromycin and 118 patients received doxycycline 100 mg ×2 for 7 days as first-line therapy.

The patients in the different treatment groups are, in general, separated by 6 years (2004 to 2005 vs 2010 to 2011). The authors consider that, as these groups do not differ significantly in terms of age distribution and prevalence of anorectal Ct among those with positive Ct, the data for patients from the 2 time-periods of collection can be combined for analysis. Two χ^2 tests were performed: 1 on the age distributions (split into 7 age ranges, see Appendix S1[1]) of the 2004 to 2005 vs 2010 to 2011 patient groups (χ^2=4.8, n=281, df=6, p=0.5694); another on the ratio of anorectal Ct within the Ct-positive patients across the time-periods, which was (135/170) 7.94% vs (146/185) 7.89% (χ^2=0, n=355, df=1, p-value=1). Power analysis was performed for both tests and N was sufficient to detect a medium-size effect. There does appear to have been a significant reduction in the prevalence of Ct and anorectal Ct in the tested populations in the intervening years (anorectal Ct, χ^2=13.4, n=3,957, df=1, p=0.0003).

A χ^2 test comparing the 2 treatments (without collection date as a factor) indicates that the difference in cure rate of 80.8% vs 100% is highly significant, χ^2=22.6, n=222, d.f.=1., p=2e–6.

DISCUSSION

The current study, with a high compliance of TOC of over 80%, with cure rate of 100% for doxycycline and 81% for azithromycin, is consistent with data from previous observational studies (4). A recently published small study from Reunion Island found a 100% cure rate of

[1]https://www.medicaljournals.se/acta/content/abstract/10.2340/00015555-3750

doi: 10.2340/00015555-3750
Acta Derm Venereol 2021; 101: adv00396

azithromycin (6), and 2 positive TOC were regarded as re-infections. However, less than half of the 50 included patients returned for TOC.

Two planned randomized multicentre studies of azithromycin compared with doxycycline for treating anorectal Ct infection have been registered; the results of these studies are pending (7, 8).

A meta-analysis of 12 randomized clinical trials of azithromycin vs doxycycline for the treatment of urogenital Ct infection demonstrated that the treatments were equally efficacious, with microbial cure rates of 97% and 98%, respectively (9).

What could be the reasons for the high cure rate of azithromycin in urethral Ct compared with anorectal Ct? In Ct infection, high microorganism loads are reported at the anorectal site compared with genital sites (10). Whilst doxycycline is lipid soluble and therefore easily accessible to cells, azithromycin is transported to the site of infection via phagocytic cells released during host immune response to infection (11). Furthermore, the bioavailability of azithromycin could be disrupted due to loss of epithelial tissue due to factors such as pre-sex douching; water-based anal lubricants, or diarrhoea within 72 h of azithromycin (12).

The limitations of the study are that it is a retrospective observational study and not a randomized trial study. The overall prevalence differences among those tested with anorectal Ct across the time-periods could be a confounding issue. In addition, there may be a placebo effect with the 2 treatments, and doxycycline requires more pills. Finally, another possible limitation is whether the reasons for not attending for TOC have changed over the intervening years. However, it is reasonable to assume those not attending TOC are similar across the 2 time-periods.

In 2010 to 2011, all Ct-positive anorectal tests were screened for LGV genotype, and 13 were found to be positive and treated with a course of 3 weeks' doxycycline. Such screening was not available in 2004 to 2005. LGV has been endemic among European MSM since 2003. However, the first case of LGV in MSM in Norway was reported from our clinic in 2006 (13). Treatment failures after single-dose azithromycin in 2004 to 2005 were cured with one week of doxycycline. Despite being an observational, non-randomized study, the current study has several strengths. Almost all patients during the respective periods received the recommended treatment, azithromycin or doxycycline. Compliance is a concern for 1-week doxycycline treatment compared with single-dose azithromycin, with potentially better adherence in a prospective, controlled study than in "real life". However, the current study found a 100% cure rate of doxycycline in "real life", and the rate of TOC was higher after doxycycline.

In conclusion, doxycycline is significantly more effective than azithromycin for the treatment of anorectal Ct. The findings are consistent with other available observational studies. While the results of randomized, controlled studies are not yet available, the evidence from observational studies are strongly in favour of doxycycline, as recommended in the International Union against Sexually Transmitted Infections (IUSTI) European Guidelines (4).

The authors have no conflicts of interest to declare.

REFERENCES

1. Rowley J, Vander Hoorn S, Korenromp E, Low N, Unemo M, Abu-Raddad LJ, et al. Chlamydia, gonorrhoea, trichomoniasis and syphilis:global prevalence and incidence estimates, 2016. Bull World Health Organ 2019; 97: 548–562.
2. Kong FYS, Tabrizi SN, Fairley CK, Vodstrcil A, Huston WM, Chen M, et al. The efficacy of azithromycin and doxycycline for the treatment of rectal chlamydia infection: a systematic review and meta-analysis. J Antimicrob Chemother 2015; 70: 1290–1297.
3. Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep 2015; 64: 1–137.
4. Lanjouw E, Ouburg S, de Vries HJ, Stary A, Radcliffe K, Unemo M. 2015 European guideline on the management of Chlamydia trachomatis infections. Int J STD AIDS 2016; 27: 333–348.
5. Reinton N, Moi H, Olsen AO, Zarabyan N, Bjerner J, Tønseth TM, et al. Anatomic distribution of Neisseria gonorrhoeae, Chlamydia trachomatis and Mycoplasma genitalium infections in men who have sex with men. Sexual Health 2013; 10: 199–203.
6. Macaux L, Zemali N, Jaubert J, Koumar Y, Manaquin R1, Poubeau P, et al. Single dose of azithromycin for treatment of patients with asymptomatic rectal chlamydia trachomatis. Acta Derm Venereol 2020; 100: adv00313
7. Peuchant O, Lhomme E, Krêt M, Ghezzoul B, Roussillon C, Bébéar C et al. Randomized, open-label, multicenter study of azithromycin compared with doxycycline for treating anorectal Chlamydia trachomatis infection concomitant to a vaginal infection (CHLAZIDOXY study). Medicine 2019; 98: e14572.
8. Lau A, Kong F, Fairley CK, Donovan B, Chen M, Bradshaw C, et al. Treatment efficacy of azithromycin 1 g single dose versus doxycycline 100 mg twice daily for 7 days for the treatment of rectal chlamydia among men who have sex with men – a double-blind randomised controlled trial protocol. BMC Infect Dis 2017; 17: 35.
9. Lau CY, Qureshi AK. Azithromycin versus doxycycline for genital chlamydial infections: a meta-analysis of randomized clinical trials. Sex Transm Dis 2002; 29: 497–502.
10. Kong FY, Tabrizi SN, Fairley CK, Phillips S, Fehler G, Law M, et al. Higher organism load associated with failure of azithromycin to treat rectal chlamydia. Epidemiol Infect 2016; 144: 2587–2596.
11. Gladue RP, Bright GM, Isaacson RE, Newborg MF. In vitro and in vivo uptake of azithromycin (CP-62,993) by phagocytic cells: possible mechanism of delivery and release at sites of infection. Antimicrob Agents Chemother 1989; 33: 277–282.
12. Fuchs EJ, Lee LA, Torbenson MS, Parsons TL, Bakshi RP, Guidos AM, et al. Hyperosmolar sexual lubricant causes epithelial damage in the distal colon: potential implication for HIV transmission. J Infect Dis 2007; 195: 703–710.
13. Haugstvedt A, Thorvaldsen J, Halsos AM. [Lymphogranuloma venerum as ulcerous proctitis in men who have sex with men]. Tidsskr Nor Laegeforen 2007; 127: 2094–2095 (in Norwegian).