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Nonquinolone Options for the Treatment of *Mycoplasma genitalium* in the Era of Increased Resistance

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In the era of increasing macrolide- and quinolone-resistant *Mycoplasma genitalium* (MG), we report the efficacy of 2 nonquinolone antimicrobials in patients with limited treatment options. Pristinamycin + doxycycline cured 75% (95% CI, 64%–85%), and minocycline cured 71% (95% CI, 54%–85%) of cases. These data provide useful estimates to inform clinical practice.

Keywords. multidrug failure; *Mycoplasma genitalium*; sexually transmitted infections; treatment.

Mycoplasma genitalium (MG) is becoming increasingly difficult to treat with recommended antimicrobials. Macrolide resistance exceeds 50% in many regions [1], and quinolone resistance is as high as 20% in the Asia-Pacific [2, 3]. Although resistance-guided therapy with macrolides and quinolones has increased cure to >90% [4, 5], nonquinolone alternatives are increasingly being sought to treat patients with macrolide-resistant MG infections who have failed quinolones, for whom these drugs are contraindicated, or for whom there is concern regarding the safety profile of fluoroquinolones. A number of new antimicrobials, including gepotidacin, zoliflodacin, and lefamulin, hold promise, but these agents have not been evaluated for MG [2, 6, 7]. Due to the intrinsically restricted susceptibility of MG to many of the available classes, options within existing licensed drugs are limited. Two older oral agents displayed favorable minimum inhibitory concentrations (MICs) against MG: pristinamycin and minocycline [2, 8, 9]. However, published data on their efficacy and tolerability are limited.

We previously reported early data from 2012–2014 on pristinamycin for MG infections [9]. This series (n = 114) reported 75% cure in predominantly macrolide-resistant

MG infections, whether pristinamycin was used as monotherapy or in combination with doxycycline [9]. However, there were limited data available on adherence to and tolerability of pristinamycin. There are only 2 prior case reports, published in 2017–2019, of minocycline use in 4 MG-infected individuals who had failed a fluoroquinolone; all were cured following 14 days of minocycline (100 mg twice daily) [8, 10].

We report the efficacy and tolerability of 2 series, doxycycline + pristinamycin and minocycline, to provide more precision around proportion cured and adverse effects in order to assist clinicians making management decisions with complex cases.

METHODS

This was a prospective evaluation of patients with macrolide-resistant MG who were treated with (i) pristinamycin 1 g 3 times daily (TDS) in combination with doxycycline 100 mg twice daily (BD) for 10 days (pristinamycin + doxycycline) between September 2018 and December 2019 OR (ii) minocycline 100 mg BD for 14 days between May 2018 and February 2020 at Melbourne Sexual Health Centre (MSHC).

During the study period, the Resistance Plus MG assay (SpeeDx Pty Ltd., Melbourne, Victoria, Australia) was used for all MG tests, and treatment was individualized according to our resistance-guided therapy pathway; the efficacy of this has been reported elsewhere [4]. Macrolide-resistant patients were treated with doxycycline 100 mg BD for 7 days, followed by moxifloxacin 400 mg daily for 7 days.

From September 2018, treatment for clients with macrolide-resistant MG in whom moxifloxacin failed or was contraindicated was pristinamycin + doxycycline for 10 days. Due to a global pristinamycin shortage in December 2019, minocycline was used instead of pristinamycin+doxycycline; before this, minocycline had only been used at MSHC in 7 patients who had exhausted other available treatment options.

Patients were asked to return for a test of cure (TOC) 14–28 days after completing treatment. Two attempts were made to contact patients who had failed to attend. At the TOC visit, clinicians used a standardized electronic form to capture symptom persistence, adherence, adverse events, sexual activity, and partner treatment.

Cases were included if (i) they were diagnosed with macrolide-resistant MG between May 2018 and February 2020; (ii) they were treated with pristinamycin + doxycycline for 10 days OR minocycline 100 mg BD for 14 days; (iii) the TOC was obtained 14–90 days after finishing antibiotics. Patients who did not fulfill all criteria were excluded, regardless of their TOC result, to prevent bias. Cases reporting condomless sex

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with an untreated, ongoing sexual partner were also excluded due to high risk of reinfection.

Microbial cure was defined as a negative TOC 14–90 days after completing treatment. Proportion with microbial cure and 95% confidence intervals were calculated by exact methods. Univariate logistic regression was used to explore characteristics associated with treatment failure. Ethics approval was obtained from the Alfred Health ethics committee (approval No. 232/16).

RESULTS

Characteristics of Study Population

Over the study period, 95 cases were treated with pristinamycin + doxycycline for 10 days; 19 were excluded because they failed to attend for a TOC within 14–90 days of completing treatment, and 3 were excluded due to high risk of reinfection (condomless sex with an untreated partner). Seventy-three patients were included in the final pristinamycin + doxycycline analysis; the majority ($n = 60$) received pristinamycin + doxycycline after failing moxifloxacin, 12 because moxifloxacin was contraindicated and 1 because their partner received it. Twenty-six (35%) patients received 4–7 days of doxycycline 100 mg BD before pristinamycin + doxycycline.

Forty-one cases were treated with minocycline 100 mg BD for 14 days, and 6 were excluded as they did not provide a TOC. Thirty-five patients were included in the final minocycline analysis. Twenty-eight (68%) had previous antibiotics: 17 failed moxifloxacin, 4 failed pristinamycin, 4 failed moxifloxacin and pristinamycin, and 3 failed moxifloxacin, pristinamycin, and sitafloxacin. Five clients received minocycline first-line as other antimicrobials were contraindicated, and 1 because their sexual partner was prescribed it.

Of the 108 patients included in the analysis, 35 (32%) were men who have sex with men (MSM), 38 (35%) were women, and 35 (32%) were heterosexual men (Table 1). The median ages for the minocycline and pristinamycin + doxycycline cases (interquartile range [IQR]) were 30 (26–34) and 27 (23–33), respectively, and median time to TOC (IQR) was 28 days (27–35) and did not differ between groups. The majority of cases (77%) were symptomatic, and the most common indication for testing was nongonococcal urethritis in men ($n = 54$) and vaginal discharge, dysuria, or abnormal bleeding in women ($n = 22$). Most infections were urethral (62%), 33 (30%) were cervicovaginal, and 10 (9%) were rectal (Table 1). Two patients had multisite MG infections (rectal and urethral), and 19 (18%) were diagnosed with concurrent genital infections; 6 (6%) had bacterial vaginosis (BV), 6 (6%) had chlamydia, 4 (4%) had gonorrhea, 2 (2%) herpes, and 1 patient had both trichomoniasis and BV.

Microbiological Cure, Adherence, and Adverse Effects

Of the 73 patients treated with pristinamycin + doxycycline, 55 were cured (75%; 95% CI, 64%–85%). Of the 35 patients treated

with minocycline, 25 were cured (71%; 95% CI, 54%–85%). Of the 11 patients in the minocycline series who had previously failed treatment with pristinamycin, 7 (64%) were cured.

Being symptomatic at TOC was significantly associated with both pristinamycin + doxycycline failure (odds ratio [OR], 3.76; 95% CI, 1.10–12.82; $P = .034$) and minocycline failure (OR, 7.33; 95% CI, 1.30–41.35; $P = .024$). Participant age and having an overseas sexual partner were both associated with minocycline failure (OR, 1.15; 95% CI, 1.02–1.29; and OR, 5.25; 95% CI, 1.02–26.98; respectively) but not with doxycycline + pristinamycin failure (Supplementary Table 1). Adjusted analyses were not performed due to small numbers.

Adherence data were available for 61 (84%) pristinamycin + doxycycline cases and 33 (94%) minocycline cases. Adherence was high, with 90% of patients reporting 100% adherence to either agent. There was no difference in cure between those who missed doses and those who did not.

Tolerability data were available for 63 (86%) pristinamycin + doxycycline cases; 38 (59%) reported side effects. The most common were diarrhea ($n = 21$), nausea ($n = 10$), headache ($n = 4$), lethargy ($n = 5$), and dizziness ($n = 3$). One patient reported severe nausea resulting in occasional missed doses.

Tolerability data were available for 33 (94%) minocycline cases: 15 (46%) reported mild side effects including dizziness or light headedness ($n = 7$), headache ($n = 5$), diarrhea ($n = 2$), nausea ($n = 2$), fatigue ($n = 2$), and reflux ($n = 2$).

DISCUSSION

Macrolide and fluoroquinolone failure and contraindications and/or concerns about fluoroquinolones are becoming increasingly common, and alternative licensed agents with known safety profiles are needed for MG. In urban STI services in Australia, macrolide resistance exceeds 50% and fluoroquinolone mutations are present in 20% of patients [3]. Data on minocycline efficacy are limited, with only 2 case reports of its use in 4 patients [8, 10]. Our data provide the first published estimates for minocycline cure in a series of 35 patients and indicate that 71% of individuals with macrolide-resistant MG will be cured with 14 days. Our pristinamycin + doxycycline series indicates that 75% of macrolide-resistant MG infections will be cured with this regimen. Importantly, when we compare these data with our previously reported 2012–2014 data (74%; 95% CI, 60%–85%) [9], there has been no change in proportion cured over the past 8 years. Both of these regimens appear to have relatively similar efficacy, and while adverse effects were common with both regimens, they were mild and tolerable.

This study has limitations. First, data are from case series with the inherent biases common to observational data. Adherence, reinfection risk, and side effect data were all self-reported and subject to reporting and recall bias. Cure estimates for

Table 1. Characteristics, Adherence, and Side Effect Data of Patients With Macrolide-Resistant *M. genitalium* by Antibiotic Regimen

	Pristinamycin + Doxycycline (n = 73)	Minocycline (n = 35)
Median age (IQR), y	30 (26–34)	27 (23–33)
Time to test of cure, median (IQR), d	28 (27–32)	28 (27–35)
Gender/orientation		
Female	24 (33)	14 (40)
Heterosexual men	21 (29)	14 (40)
Men who have sex with men	28 (38)	7 (20)
Site of infection		
Cervix/vagina	21 (28)	12 (34)
Urine/urethral	44 (59) ^a	23 (66)
Rectum	10 (14) ^a	0
HIV serostatus		
Negative	58 (80)	34 (97)
Untested	12 (16)	1 (3)
Positive	3 (4)	0
Previous <i>M. genitalium</i> infection		
Yes	20 (27)	9 (26)
No	53 (73)	26 (74)
Symptoms at diagnosis		
No (asymptomatic)	19 (26)	5 (14)
Yes (symptomatic)	54 (74)	30 (86)
Clinical diagnosis/indication for test		
Nongonococcal urethritis	34 (47)	20 (57)
Contact of <i>M. genitalium</i>	8 (11)	5 (14) ^b
PID	1 (1)	1 (3)
Vaginal discharge/abnormal bleeding/dysuria	13 (18)	9 (26)
Proctitis	2 (3)	0
Other	13 (18)	0
NGU contact	2 (3)	0
PrEP		
Yes	13 (18)	2 (6)
No	60 (82)	33 (94)
	Pristinamycin (n = 61–63) ^c	Minocycline (n = 33) ^d
Adherence		
Took all doses	55 (90)	30 (91)
Missed 1–5 doses	6 (10)	3 (9)
Side effects to medication	38 (60)	15 (46)
Headache	4 (6)	5 (14)
Diarrhea	21 (33)	2 (6)
Rash	1 (2)	0
Vomiting	1 (2)	0
Nausea	10 (16)	2 (6)
Insomnia	2 (3)	N/A
Fatigue/lethargy	5 (8)	2 (6)
Reflux/indigestion	N/A	2 (6)
Dizziness/light headedness	3 (5)	7 (20)
Other	N/A	1

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: IQR, interquartile range; NGU, nongonococcal urethritis; PID, pelvic inflammatory disease; PrEP, pre-exposure prophylaxis.

^aTwo patients in the pristinamycin + doxycycline group had both urine and rectal MG infections.

^bOne patient with NGU was also a contact of MG.

^cAdherence and side effect data were available for 61 and 63 of the 73 patients prescribed pristinamycin + doxycycline, respectively.

^dAdherence and side effect data were available for 33 of the 35 patients prescribed minocycline.

pristinamycin + doxycycline may have been influenced by a lead-in with doxycycline of 4–7 days reducing the bacterial load; however, we found no difference in proportion cured in

those who were pretreated with doxycycline and those who were not ([Supplementary Table 1](#)). Our past published estimates for cure did not show a difference between monotherapy and

combination therapy for pristinamycin [9]; however, the latter was used due to concerns that monotherapy with pristinamycin may more readily lead to development of resistance. MSHC is the only free sexual health clinic in Melbourne, and the results may not be generalizable to the community. Loss to follow-up occurred in 20% of patients, which is consistent with our past studies [4, 5]. This may have resulted in a higher proportion of failures, as patients with resolved symptoms may have been less likely to return for a TOC. Lastly, data on fluoroquinolone resistance-associated mutations were not available for this study.

Overall, these data provide useful efficacy estimates and tolerability data for clinicians when considering nonquinolone treatment regimens for macrolide-resistant MG infections.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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