Treatment of *Mycoplasma genitalium* with azithromycin 1 g is less efficacious and associated with induction of macrolide resistance compared to a 5 day regimen

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Background: *Mycoplasma genitalium* (MG) is an emerging important STI and is often treated with azithromycin 1g. However, failure rates with azithromycin 1g are increasing.[1] This may be due to the emergence of macrolide antimicrobial resistance as a consequence of extensive use of azithromycin 1g.[1,2] An extended regimen of azithromycin 500 mgs on day one then 250mgs daily for 4 days (5 day regimen) was introduced in the 1990s for treatment of MG and has high efficacy rates (if no pre-existing macrolide resistance) and is less associated with induction of macrolide resistance. There are no comparative trials of the two regimens. We undertook a meta-analysis of MG treatment studies using the two azithromycin regimens to determine which is more effective.

Methods: Medline was used to identify published articles including the search terms '*Mycoplasma genitalium*' , 'macrolide', 'azithromyicin' and 'resistance' up to August 2015. Treatment studies using azithromycin 1g or 5 days were identified in which patients were initially assessed for macrolide resistance genetic mutations, and those who failed were again resistance genotyped. Sensitivity analyses included only patients without prior treatment.

Study	Setting	Sample size for analysis*	Treated with 5 day regimen			Number treated with 1g regimen			Diff in failure rate (95% CI) (1g compared to 5 day)	Diff in resistance rate (95% CI) (1g compared to 5 day)
			Total	Failure	Resistance	Total	Failure	Resistance		
Anagrius[3]	Swedish STD clinic. Men and women.	191	77	0 (0%)	0	114*	7* (6.1%)	7* (6.1%)		
Twin[4]	Melbourne Sexual Health Centre. Men and women.	66	0			66	14 (21.2%)	14 (21.2%)		
Couldwell[5]	Western Sydney Sexual Health Centre. Men and women.	12	0			12	4 (33.3%)	3 (25%)		
Walker[6]	Australian primary care clinics. Women only.	28	0			28	3 (10.7%)	3 (10.7%)		
Bissessor[7]	Melbourne Sexual Health Centre. Men and women.	99	0			99	11 (11.1%)	11 (11.1%)		
Falk[8]	Swedish STD clinics. Men and Women	56	46	3 (6.5%)	3 (6.5%)	10	1 (10.0%)	1 (10.0%)		
Ito[9]	Urologic clinic in Sendai, Japan	24	0			24	7 (29.2%)	4 (16.7%)		
Total		476	123	3 (2.4%)	3 (2.4%)	353	47 (13.3%)	43 (12.2%)	10.9% (6.4%,15.3%)	9.7% (5.4%,14.1%)

Table detailing studies included in meta-analysis

* 3 additional men of 117 excluded as no information on antimicrobial resistance prior to treatment in 2 and no information prior to and after treatment in one man i.e. failure rate 8.5% (10/117).

Results

Seven studies were identified totaling 476 patients of whom 123 (25.8%) had received the 5 day regimen. Only 3 people failed the 5 day regimen and resistance was detected in 3 people also. Compared to the 5 day regimen, azithromycin 1g had a higher risk of failure (difference: 10.9%, 95% CI: 6.4%, 15.3%) and more developed macrolide resistance (risk difference: 9.7% (5.4%, 14.1%) %, which are significantly greater p<0.001 and p=0.001 respectively.

Sensitivity analysis: The 5 day regimen included 52 patients with prior doxycycline treatment when these were excluded sensitivity analysis showed a failure risk difference of 9.1% (3.2%, 15.0%). Resistance risk difference was 8.0% (2.2%, 13.7%).

Comment

This meta-analysis provides good evidence that an azithromycin 1g regimen is associated with rates of failure of 13.3%, and of macrolide resistance of 12.2% in uro-genital tract *M. genitalium* infection in which no pre-existing macrolide resistance mutations are present.

While heteroresistance[10] because of pre-existing macrolide resistant micro-organisms, due to random mutations, is the most likely cause of development of macrolide resistance it would not explain the difference in efficacy between the 1g and 5 day regimen suggesting other mechanism(s) may play a role. Azithromycin has unusual pharmacokinetics and it is unknown whether a different extended regimen would be more efficacious.[2]

Conclusions:

- 13.3% wild type *M. genitalium* infection failed treatment with azithromycin 1g and 12.2% developed macrolide antimicrobial resistance.
- 2.4% wild type *M. genitalium* infection failed treatment with azithromycin 500mgs then 250mgs od 4 days and 2.4% developed macrolide antimicrobial resistance, although this is based on small numbers.
- This equates to a difference in failure rate of 10.9% and difference in development of antimicrobial resistance rate of 9.7%, which are significantly greater p<0.001 and p=0.001 respectively.
- **Azithromycin 500mgs then 250mgs od 4 days appears to be more efficacious than the azithromycin 1g, if no pre-existing macrolide resistance is present .**

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