of risk, but vaccinated children might need to receive additional support during the period of enhanced risk through education, improved access to treatment, and regular distribution of insecticide-treated bed nets.

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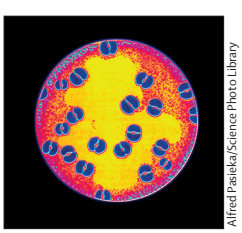
Solithromycin for the treatment of drug-resistant gonorrhoea

In *The Lancet Infectious Diseases*, Marcus Chen and colleagues[1] report on the efficacy of solithromycin, a novel fourth generation macrolide, as a treatment option for urogenital gonorrhoea. In the SOLITAIRE-U trial, solithromycin was compared with a combination of ceftriaxone plus azithromycin, which is the standard therapy in many countries. To date, *Neisseria gonorrhoeae*, the pathogen that causes gonorrhoea, has acquired antimicrobial resistance against all available first-line antibiotic treatment options, including penicillin, tetracycline, ciprofloxacin, and spectinomycin, leading to treatment failure.[2] WHO recommends a minimum cure rate of 95% for an antibiotic to be used as first-line treatment.[3] Therefore, the current first-line option, ceftriaxone (given as monotherapy or in combination with azithromycin), is considered a safe option since the ceftriaxone cure rate remains above 95%. However, the number of strains with decreased susceptibility for ceftriaxone is increasing[4] and treatment failure with both monotherapy and dual therapy has been reported.[5,6] Since all previous treatment options for gonorrhoea have been abandoned, and resistance to ceftriaxone might soon become a problem, alternative antibiotics are urgently needed.

The SOLITAIRE-U trial assessed solithromycin as an alternative treatment option for gonorrhoea. In the microbiological intention-to-treat population, solithromycin was not non-inferior to standard first-line treatment: genital gonorrhoea was eradicated in 99 (80%) of 123 patients in the solithromycin group compared with 109 (84%) of patients in the ceftriaxone plus azithromycin group (difference −4·0%, 95% CI −13·6 to 5·5). In this analysis, patients lost to follow-up or those who did not return for assessment at test-of-cure (on day 7 or 21) were considered to have treatment failure. In a secondary analysis restricted to patients from whom a test of cure sample was obtained (microbiologically evaluable population), the eradication rate with solithromycin was 92% compared with 100% for ceftriaxone plus azithromycin. In all analyses, less than 95% of patients had eradication with solithromycin, which is below the minimum cure rate recommended by WHO, and was not found to be non-inferior to the first-line treatment.

Treatment failures were not associated with resistance to solithromycin. Moreover, whole genome sequencing was used to type strains cultured before and after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treatment, and the authors found no indication that persisting infections were due to reinfection rather than treatment failure. So, what did cause the failure of solithromycin? Chen and colleagues used a single dose regimen since this is preferred in the treatment of sexually transmitted infections to ensure compliance.[7] However, a single dose of solithromycin seems insufficient and m ultiday courses or multiple doses might be needed. The authors did not assess the pharmacokinetic or pharmacodynamic properties of solithromycin, which could have provided important data for an optimal regimen. In a related trial (NCT02348424), the investigators hope to further explore the pharmacodynamics of solithromycin. 44% of patients given solithromycin had significant gastrointestinal side-effects compared with 24% of patients given ceftriaxone plus azithromycin, which suggests that higher single doses of solithromycin might not be feasible.

The use of solithromycin might also be threatened by emerging azithromycin-resistant gonorrhoea strains. The switch from ceftriaxone monotherapy to dual therapy with azithromycin was adapted in many countries without a strong evidence base and has since been associated with the emergence of strains highly resistant to azithromycin.[8] The emergence of resistance has led to the abandonment of dual therapy in the 2019 UK gonorrhoea guidelines; intramuscular ceftriaxone 1 g given as a single dose is now the advised first-line option in the UK.[9] In the SOLITAIRE-U trial, one patient treated with ceftriaxone and azithromycin was infected with an azithromycin-resistant strain. As suggested by the authors, future trials that include azithromycin-resistant isolates would be needed to determine the efficacy of solithromycin against azithromycin-resistant gonorrhoea.

Alternatives treatments are being explored. Zoliflodacin, a novel class antibiotic that targets type 2 topoisomerases (like fluoroquinolones), showed promising results in a phase 2 trial.[10] A phase 3 trial done in association with the Global Antibiotic Research and Development Partnership (a joint initiative of WHO and the Drugs for Neglected Diseases initiative) is planned for 2019. The NABOGO trial (NCT03294395) is exploring the older antibiotics gentamicin, fosfomycin, and ertapenem for the treatment of gonorrhoea. Once ceftriaxone becomes ineffective, no empirically proven successful treatment options exist for gonorrhoea. The SOLITAIRE-U trial contributes important information in the further search for options to ensure gonorrhoea remains a treatable disease.

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HJCdV and MFS-vdL will collaborate in a phase 3 randomised controlled trial on the efficacy of zoliflodacin for the treatment of urogenital gonorrhoea funded by the Global Antibiotic Research and Development Partnership, a subsidiary of Drugs for Neglected Diseases initiative starting later this year.

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