Phase 3 trial of treating gonorrhoea with solithromycin

Marcus Y Chen and colleagues[1] describe the results of a 262-patient phase 3 trial in which oral solithromycin monotherapy was tested for non-inferiority against intramuscular ceftriaxone plus oral azithromycin in patients with uncomplicated gonorrhoea. The results require thoughtful consideration of some unusual features of this trial.

The study was a comparison of single-dose monotherapy with a new macrolide, solithromycin, with a single-dose combination of two drugs, of which one was also a macrolide. In a regulatory trial, the preference is for the experimental drug to be used alone against the standard of care, which for this infection is two drugs: ceftriaxone and azithromycin.

Another feature is the nature of the study population. In this trial, 94% of patients were men, and most were men who have sex with men. There were no treatment failures in the few women treated with solithromycin. How could the authors be sure that some of the treatment failures (only a 4% difference in failures between groups) were not re-infections? Having the same strain at the end of 7–14 days in an outpatient trial could simply mean re-introduction from the same partner. In addition, 11 (8%) of 131 patients in the solithromycin group had HIV infection. These patients should have been grouped separately as their inclusion might explain the lower proportion of patients in the solithromycin group than in the ceftriaxone plus azithromycin group who responded to therapy. Solithromycin is metabolised by CYP3A4, an enzyme induced by HIV protease inhibitors, such as ritonavir, that are commonly used in patients with HIV. In the comparator group, although azithromycin would also be metabolised by CYP3A inducers, the patients would be protected by ceftriaxone.

The question of increased liver enzymes was raised even though no increases of alanine transaminase were noted in this trial. In two large phase 3 trials in which multiple doses of solithromycin were tested, increases of alanine transaminase were uncommon, and those that occurred were transient.[2–4] To place the increase in alanine transaminase into perspective, only 3·4% of 426 patients[2] treated orally for 5 days with solithromycin showed increases that were three times the upper limit of normal, which is not unusual for a macrolide antibiotics such as clarithromycin. Oral bioavailability and pharmacokinetics were not a concern in any of these trials. In addition, solithromycin has shown no adverse events in patients with hepatic impairment.[5] Let us not cloud the results of this trial with the US Food and Drug Administration's lingering concerns of hepatic adverse events from telithromycin, which were not observed in clinical trials of solithromycin.

A Comment[6] describes the hope for a potential new drug, zoliflodacin, which is currently being pursued to treat gonorrhoea. The phase 2 trial of zoliflodacin[7] had only 97% success in urogenital sites, whereas several pharyngeal infections were not cleared. By contrast, in its phase 2 trial, solithromycin achieved 100% eradication of culture-proven uncomplicated gonorrhoea detected at urogenital sites, the oropharynx, and the rectum.[8] Pharyngeal gonococcal infections are not to be dismissed since in Chen and colleagues' trial,[1] 83 (32%) of 262 patients had pharyngeal gonococcal infection.

Solithromycin has been shown to be bactericidal against drug-resistant *Neisseria gonorrhoeae*, including intracellular organisms.[9] Although the phase 3 trial could provide more accurate results than the previously published phase 2 trial,[8] the differences between the phase 2 and phase 3 outcomes are striking, since the size of the solithromycin group in the phase 3 trial was roughly only twice that of the phase 2 trial (59 patients in the phase 2 *vs* 131 in the phase 3).

There is an enormous need to find an alternative antibiotic for treating drug-resistant gonorrhoea, so let us not dismiss solithromycin without properly testing its potential.

PF has a patent on the uses of solithromycin. She was the founder and chief executive officer of Cempra. JCC was a scientific advisory board member at Cempra.

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