Use of azithromycin as treatment against *Chlamydia trachomatis*?

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Abstract

Azithromycin and doxycycline effectiveness has been demonstrated in the treatment of urogenital chlamydiasis, which has remained unchanged for a long time. Autoinoculation has been proposed as a method of reinfection and persistence of the disease in women and probably also owing to azithromycin pharmacokinetics in this tissue. With the new diagnostic methods and tests of cure, a difference has been demonstrated in favor of doxycycline in the treatment of rectal chlamydiasis. Antimicrobial resistance has not played a relevant role since no treatment-resistant strains have been found in vivo. Nevertheless, azithromycin remains a first-choice drug, since it can be administered as a single dose, which favors therapeutic adherence.

KEY WORDS: *Chlamydia trachomatis*. Azithromycin. Test of cure.

Introduction

Chlamydia infection caused by *Chlamydia trachomatis* (genotypes A-K) constitutes the most reported disease and is among the most prevalent sexually transmitted infections in the United States; the age group of 15 to 24 years is the most affected.^{1,2} According to the World Health Organization, there is an annual estimate of 131 million new infections caused by *Chlamydia trachomatis*.³

The disease is asymptomatic in 70 % of women and 50 % of men.⁴ When it produces symptoms, women often show changes in vaginal discharge, intermenstrual bleeding or dyspareunia (data suggestive of cervicitis); on physical examination, cervical erythema, friable cervix and endocervical discharge are identified. In addition, symptoms can mimic urinary tract infection. In men, it occurs more commonly as urethritis (dysuria, discomfort and urethral discharge) and on physical examination, irritation or erythema of the urinary meatus and sometimes urethral discharge (which tends to be mucoid and not purulent) are observed; it can also occur in the form of orchitis or epididymitis. In women, it can cause serious sequelae

such as pelvic inflammatory disease, ectopic pregnancy, miscarriage and infertility.^{5,6}

To establish the diagnosis of urogenital chlamydia, there are different methods such as cell culture, rapid diagnostic test, serum antibodies against chlamydia and nucleic acid amplification test (NAAT), which is the method of choice, since it reaches the highest sensitivity and a specificity that is comparable to that of cell culture and, in addition, the World Health Organization recommends it. The ideal sample to perform the NAAT in men is the first jet of the first urine of the day, while in women it is that obtained by vaginal smear.^{4,6}

The World Health Organization and the Centers for Disease Control and Prevention (CDC) suggest 1 g of oral azithromycin in a single dose or 100 mg of oral doxycycline twice daily for 7 days for the treatment of chlamydia.^{4,7}

Azithromycin

Azithromycin is an antibiotic from the family of macrolides, a semisynthetic derivative of erythromycin.⁸ It expresses its antibiotic activity by binding to the 50S ribosomal subunit (rRNA 23S) and inhibits protein

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synthesis by preventing the formation of the peptide bond between the amino acids of the nascent protein.⁹ Its pharmacokinetic profile is characterized by a rapid and extensive uptake from circulation to intracellular compartments (including the so-called inflammatory cells); subsequently, it is released little by little where it is needed, which allows a single-dose regimen or one dose for a single day.⁹⁻¹¹

Azithromycin or doxycycline?

As previously mentioned, for uncomplicated urogenital chlamydia, the World Health Organization and the CDCs recommend 1 g of oral azithromycin as a single dose or 100 mg oral doxycycline twice daily for seven days. This recommendation is based on a meta-analysis of 12 clinical trials on azithromycin versus doxycycline for the treatment of urogenital chlamydia carried out in 2002,¹¹ which demonstrated that both are equally efficacious, with rates of microbial cure of 97 and 98% for azithromycin and doxycycline, respectively. However, in 11 of those clinical trials, less sensitive diagnostic and follow-up methods were used to monitor cure (culture and immunoassays) than those that are currently recommended (NAAT), which may have caused underestimation of the ranges of treatment failure.^{7,12,13} In a new meta-analysis carried out in 2014, it was concluded that there is an efficacy greater than 3 % in favor of doxycycline for the treatment of urogenital chlamydia and of approximately 7 % for the treatment of symptomatic urethral infection in men.¹³

Rectal chlamydia

The difference in efficacy between azithromycin in comparison with doxycycline for the treatment of rectal chlamydia may be greater than that reported in urogenital chlamydia.^{14,15} In 2015 an efficacy of 83 % was recorded for azithromycin and higher than 99 % for doxycycline in the treatment of rectal infection by chlamydia, although the quality of evidence was acknowledged to be low.¹⁶ Nevertheless, an approximate effectiveness of 83 % for azithromycin is much lower than 97.4 % indicated in the treatment of urogenital chlamydia infection.¹⁴

This might be due to the bioavailability of azithromycin in rectal tissue, and it is unknown if it is similar to that of urethral and cervical mucosa. Some experimental studies in animals, which investigate chlamydia in the large intestine, show a lack of local immune response, as well as an absence of polymorphonuclear cells,¹⁷ and given that azithromycin uses these cells to reach the site

of infection, the lack of these and a decreased immune reaction in the rectum might decrease azithromycin effectiveness. In 2013, the inflammatory response to chlamydia rectal infection was examined, with suppressed inflammatory cytokines being reported in HIV-negative subjects infected with chlamydia, which provides further data and supports the aforementioned.¹⁸

In addition to all this, chlamydia autoinoculation from the gastrointestinal to the urogenital tract in women has been proposed, and it has acquired relevance recently. Thus, the gastrointestinal tract has been mentioned as a persistent infection niche.¹⁷ In 2015, using a mathematical model, the probability was estimated for a woman with chlamydia genital infection treated either with azithromycin or doxycycline to remain chlamydia-free when the possibility of autoinoculation was taken into account; it was demonstrated that when the probability of autoinoculation was assumed to be 100 %, the likelihood for the patient to remain free of genital infection after treatment with doxycycline was 96.8 and 81.9 % with azithromycin; that is, 3.2 and 18.1 % of probability, respectively, not to eliminate the infection, 5.7 times more chance for not eliminating the infection with azithromycin in comparison with doxycycline. Furthermore, if the patient had rectal infection, the probability of remaining free of genital infection after the treatment with azithromycin was 78.2 to 94.3 %, and after treatment with doxycycline from 96.7 to 97.1%, which corresponds to 2 to 6.6 times higher probability not to eliminate the chlamydia infection with azithromycin in comparison with doxycycline.¹⁵

Currently, the CDCs recommend as treatment for rectal chlamydia the same than that for urogenital chlamydia; however, this is nothing but an extrapolation of the findings on similar efficacy (which is questioned) of both drugs in the treatment of urogenital chlamydia. In an analysis performed in 2015 at a clinic for sexually transmitted diseases in male patients diagnosed with rectal chlamydia between 1993 and 2012, men treated with azithromycin were found to have a significantly higher risk of persistence/recurrence of rectal chlamydia in comparison with subjects treated with doxycycline (similar results were obtained in a retrospective review carried out in 2016¹⁹); in addition, the authors suggest that a 7-day doxycycline regimen may be superior to an azithromycin 1 g single dose for the treatment of rectal chlamydia infection.²⁰ Another study suggests that 100 mg of doxycycline twice daily are highly effective for asymptomatic rectal chlamydia, with bacterial cure (as assessed by NAAT) being achieved in 98.8 % of cases.²¹

Antimicrobial resistance

Bacterial resistance to antibiotics has been proposed as a cause of treatment failure. Given the complexities of *Chlamydia trachomatis* life cycle,^{22,23} it is possible that persistent forms, which are involved in heterotypic resistance, may require several weeks to restore detectable replicative infection after treatment with a single dose of azithromycin.²⁴ However, only heterotypic resistance (which occurs when an infection has a small proportion of resistant organisms among a susceptible population) has been possible to be documented, with mutations in 23S rRNA being associated with in vitro resistance to macrolides. So far, no strains with homotypic resistance (where the entire population of organisms survives after treatment) have been identified.^{25,26}

False-positive test-of-cure

NAAT is the method of choice to perform a “test-of-cure”. Unfortunately this method only provides information about the presence of genetic material, but not on viability of the pathogen or if it’s still infectious; therefore, intermittent positive results could be the result of viable or non-viable genetic material deposition from a sexual partner, release of degraded cells genetic material or elementary bodies containing *Chlamydia trachomatis* genetic material.²⁷ A negative NAAT may indicate an eliminated infection; however, it also can reflect persistent infection.²⁸

Currently, the guidelines recommend a test of cure 3 months after treatment conclusion, instead of performing it 4 weeks after having received it, in order to minimize the risk of false-positive diagnoses.²⁵ False-positive results can occur three weeks after treatment due to DNA persistence, and because persistent disease takes a few weeks to emerge. Tests of cure should be deferred for at least 5 weeks post-treatment.^{22,27} In addition, it has been shown that, in order to prevent reinfection, women should refrain from having intercourse without a condom or, in any case, use a condom in every sexual intercourse for at least one month after having received the treatment.²⁹

Conclusion

Even when efficacy in the treatment of urogenital chlamydia has been shown to be slightly higher favor of doxycycline, azithromycin remains a medication of choice, since it can be administered as a single dose, with higher therapeutic adherence being reached.

However, if gastrointestinal tract autoinoculation is taken into account as a cause of treatment failure, doxycycline should be preferred, since azithromycin pharmacokinetics in rectal tissue is unknown.

In addition, the CDCs recommends the test of cure only if treatment adherence is questionable, if symptoms persist or if reinfection is suspected. Its performance is not recommended if the right treatment was given in the right way; however, given that most urogenital or rectal chlamydia infections are asymptomatic, higher therapeutic efficacy against rectal chlamydia infection has been shown when using doxycycline in comparison with azithromycin, if we take the possibility of autoinoculation into account, we should always suspect reinfection, and every patient should therefore have a test of cure practiced.

This strengthens the reconsideration of urogenital chlamydia treatment and taking rectal infection with chlamydia into account as a source of autoinoculation. In addition, it is advisable to stratify the populations at risk of suffering rectal chlamydia, as well as obtaining genital and rectal samples from patients in whom urogenital chlamydia is suspected.

It is desirable for randomized controlled trials comparing azithromycin efficacy against doxycycline for the treatment of urogenital and rectal chlamydia infection to be conducted.

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