EDITOR'S CHOICE

Azithromycin in the treatment of infection with *Neisseria gonorrhoeae*

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ABSTRACT

The efficacy of azithromycin as sole antimicrobial treatment for infection with *Neisseria gonorrhoeae* is reviewed. Aggregate cure rates for urethral and endocervical infection were 520/539 (96.5%; 95% CI 94.3% to 97.6%) for a 1 g dose from nine studies and 392/396 (99%; 95% CI 97.5% to 99.6%) for a 2 g dose from two studies. Azithromycin cured 46/47 (97.9%) cases of oropharyngeal infection and 34/35 (97.1%) cases of rectal infection evaluated within the clinical trials. Reports of in vitro resistance to azithromycin reveal a wide geographical spread of clinical isolates, with raised minimal inhibitory concentration to azithromycin and the emergence of high-level resistance in 2001. Concerns about resistance preclude azithromycin from general recommendation as sole antimicrobial therapy for gonorrhoea. However, azithromycin may have a valuable role in specific clinical situations and in combination with extended spectrum cephalosporins in the treatment of gonorrhoea.

INTRODUCTION

Azithromycin is an azalide derived from the macrolide class of antibiotics. It offers better oral absorption, better tissue penetration, unique pharmacokinetics and a wider spectrum of antimicrobial activity than erythromycin. The mode of action of azithromycin is inhibition of RNA-dependent peptide synthesis by binding to the 50 s ribosomal subunit. Azithromycin levels in tissues are up to 50 times higher than in plasma and tissue depletion half-life is 2–4 days.[1] In animal studies high concentrations of azithromycin have been found in phagocytes, resulting in high concentrations of the drug being delivered to sites of infection.

Azithromycin has activity against the major bacterial sexually transmitted pathogens—notably, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Ureaplasma urealyticum*, *Mycoplasma genitalium*, *Treponema pallidum* and *Haemophilis ducreyii*. It is the recommended treatment for uncomplicated genital infection with *C trachomatis*[2 3] and seems a particularly attractive option as an oral, single-dose treatment in syndromic and epidemiological management of bacterial STIs. This paper reviews published data on the use of azithromycin as sole treatment for infection with *N gonorrhoeae* and the growing resistance to this antimicrobial agent.

AZITHROMYCIN AS TREATMENT FOR GONORRHOEA

A Medline search was conducted using PubMed under the major headings of 'gonorrhoea and azithromycin', '*N gonorrhoeae* and azithromycin' and 'macrolide' and 'antimicrobial resistance.' The search was not confined to randomised controlled trials but was confined to the English language. Thirteen studies on treatment outcome were identified and reviewed.[4–16] Microbiological outcome for azithromycin in the treatment of urethral and endocervical infection with *N gonorrhoeae* is summarised in table 1. The treatment outcome for 35 rectal and 46 pharyngeal infections is presented in table 2. Studies show considerable variation in report detail, design, size, recruitment and the proportion and definition of evaluable patients. Aggregate microbiological cure rates for urethral or endocervical infection with *N gonorrhoeae* in the clinical trials were 392/396 (99%; 95% CI 97.5% to 99.6%) for patients receiving a single 2 g oral dose of azithromycin and 520/539 (96.5%; 95% CI 94.3% to 97.6%) for patients receiving 1 g of azithromycin. This would suggest that the clinical efficacy of a 1 g dose of azithromycin fails to meet the stringent criterion for consideration in US Centers for Disease Control and Prevention (CDC) treatment guidelines, defined by Moran and Levine as a 95% cure rate with the lower level of the 95% CI exceeding 95% in summed clinical trials.[18] The addition of retrospective data by Habib and Fernando[15] on clinical outcome of 1 g azithromycin in the treatment of gonorrhoea increases the proportion cured by this dose to 688/709 (97.0%; 95% CI 95.2% to 97.9%). Treatment efficacy was not diminished against *N gonorrhoeae* showing in vitro resistance to penicillin, tetracycline or quinolones. Treatment failures in the reviewed studies were not generally attributable to resistance, although post-treatment sensitivities were rarely performed or cited. Where described, pretreatment isolates did not show in vitro decreased susceptibility to azithromycin. Of historical note, a failure rate exceeding 20% was observed with erythromycin in the treatment of gonococcal urethritis and failure was associated with higher minimal inhibitory concentrations (MICs).[19]

Most reported side effects of azithromycin are gastrointestinal. Handsfield *et al*[4] reported a rate of 35.3% for gastrointestinal symptoms with a 2 g oral dose and this study is widely cited as rendering azithromycin untenable as a treatment for gonorrhoea. Studies using 2 g as a single oral dose in the treatment of syphilis report much lower rates of gastrointestinal side effects (11.4%) and these were rated only mild to moderate and not sufficient to deter patients repeating the treatment.[20 21] Side effects are either low or not reported in the other studies reviewed. Azithromycin tablets taken with food have bioequivalence to capsules taken on an empty stomach. There appears to be no data on

Table 1 Studies reporting outcome of azithromycin treatment of *Neisseria gonorrhoeae* infection of the urethra or endocervix

Author and year of publication	Participants	Study design	Azithromycin dose	Sensitivity testing to azithromycin	Bacterial cure rate of evaluable participants	Comments
Handsfield 1994[4]	Male and female STD clinics, USA	RCT versus ceftriaxone	2 g	No	370/374 (98.9%)	Side effects reported by 35.3% (moderate 10.1%; severe 2.9%)
Khaki 2007[5]	Males STD clinic, New Delhi	RCT versus ceftriaxone	2 g	Yes	22/22 (100%)	Side effects <10%—all mild
Lassus 1990[6]	Male and female Helsinki University Central Hospital	RCT versus doxycycline	1 g 500/250/250 mg	Yes	20/20 (100%) 22/22 (100%)	No side effects reported by patients
Steingrimsson 1990[7]	Males + 1 female. STD clinic Reykjavik	RCT versus doxycycline	1 g 500 mg×2 500/250/250 mg	Yes	11/12 (91.7%) 7/8 (87.5%) 7/7 (100%)	Failure MIC 0.125 mg/l Failure MIC 0.5 mg/l Mild sideeffects 8.5%
Odugbemi 1993[8]	Male and female STD clinics Nigeria	Non-comparative	1 g	No	114/120 (95%) Inconsistency of figures in paper	Cure = clinical + bacteriological Gastrointestinal side effects 2.7%—all mild/moderate
Waugh 1993[9]	Male and female, STD clinic Leeds, UK	Non-comparative	1 g	Yes	85/89 (95.5%)	MIC of failures 0.25 mg/l
Steingrimsson 1994[10]	Males only. STD clinic Reykjavik	RCT versus doxycycline	1 g	Yes	27/28 (96.4%)	Failure MIC 0.125 mg/l Side effects 'negligible'
Gruber 1995[11]	Men; STD centre Rijeka, Croatia	RCT versus doxycycline	1 g	No	24/25 (96.0%)	No details on failure. Gastrointestinal side effects 4/66 (6%)
Gruber 1997[12]	Males and females, Rijeka, Croatia	RCT versus ciprofloxacin	1 g	No	48/50 (96.0%)	Gastrointestinal side effects 4/50 (8%)—all mild
Swanston 2001[13]	Male and female STD clinic Trinidad	Non-comparative	1 g	Yes	125/127 (98.4%)	Failures MIC 0.064 mg/l and 0.094 mg/l No side effects
Rustomjee 2002[14]	Symptomatic women. STD clinic Durban, S. Africa	RCT versus ciprofloxacin + doxycycline	1 g	No	30/31 (96.8%)	One failure in dual infected patient. Side effects were 'few and minor'
Habib 2004[15]	Male and female STD clinic Wolverhampton, UK	Retrospective review	1 g	Not stated	168/170 (98.8%)	Failures: 1 'due to azithromycin-resistant strain'; 1 attributed to vomiting soon after 1 g dose

MIC, minimal inhibitory concentration; RCT, randomised control trial.

whether the frequency of side effects differs between capsules and tablets. Studies rarely cite the form of azithromycin used, but a capsule preparation appears to have been used in the Handsfield study. The frequency and generally mild nature of gastrointestinal side effects should not discount the use of a 2 g single dose of azithromycin as treatment for gonorrhoea.

RESISTANCE TO AZITHROMYCIN

There are three main mechanisms by which bacteria acquire resistance to antibiotics: by alteration of the target site, by alteration in antibiotic transport and by modification of the antibiotic. Selection pressures on gonococci are both antibiotic and host driven with changes occurring from spontaneous mutation and from acquisition of genes from other bacteria (horizontal gene transfer).[22] Azithromycin resistance to *N gonorrhoeae* is attributable to modification of the ribosomal attachment site and to changes in permeability and antibiotic transport. Alterations of the 23S rRNA ribosomal target by genetic mutation and by methylase-associated modification have been described.[23–25] Mutations affecting the peptidyl-transferase loop of domain V of 23S rRNA have been described in association with high levels of azithromycin resistance.[23 25] *Erm* genes (erythromycin ribosome methylation) encode for 23S rRNA methylases and these genes can be transferred between *N gonorrhoeae* and oral commensal *Neisseria* species by conjugation.[24]

Efflux pumps actively export toxic compounds including antibacterial peptides and several antibiotics from the bacterial cell. In *N gonorrhoeae*, the *mtr*(CDE)-encoded efflux pump is one system that exports macrolides and, while not the major mechanism, this efflux pump also contributes to chromosomal resistance to penicillin, tetracyclines and quinolones.[26–30] This pump system is regulated by proteins coded by the repressor *MtR* gene and activator *MtA* gene. Different mutations in these controlling genes confer decreased susceptibility and low-level resistance to azithromycin.[26–29]

Table 2 Outcome of azithromycin treatment of rectal and pharyngeal infection with *Neisseria gonorrhoeae*

Author and year of publication	Azithromycin dose	Bacterial cure rate of evaluable participants	Comments
Rectal infection			
Handsfield 1994[4]	2 g	26/27	
Lassus 1990[6]	1 g 500/250/250 mg	1/1 3/3	
Waugh 1993[9]	1 g	4/4	
Total rectal		34/35 (97.1%)	
Pharyngeal infection			
Handsfield 1994[4]	2 g	19/19	
Dan 2006[16]	2 g	20/21	Pre- and post-treatment MIC of failure 0.5 mg/l
Lassus 1990[6]	1 g 500/250/250 mg	1/1 2/2	
Waugh 1993[9]	1 g	2/2	
Steingrimsson 1994[10]	1 g	1/1	
Manavi 2005[17]	1 g	1/1	
Total pharyngeal		46/47 (97.9%)	

EPIDEMIOLOGY OF RESISTANCE IN *N GONORRHOEAE* TO AZITHROMYCIN

Monitoring trends in the antimicrobial susceptibilities of *N gonorrhoeae* has proved crucial in ensuring the appropriate recommendation of gonococcal treatment. In vitro susceptibility testing of *N gonorrhoeae* in surveillance programmes is the principal source of data on azithromycin resistance. Resistance of *N*

gonorrhoeae to azithromycin is generally defined as an MIC ≥1 mg/l.[31] One isolate with an MIC of 2 mg/l and Mtr phenotype was identified among 300 strains collected in 1984 and 1985.[32] The Gonococcal Isolate Surveillance Project in the USA was established in 1986, with azithromycin susceptibility testing introduced in 1992. An isolate with resistance to azithromycin was first identified in 1993 in New Mexico.[33] The number of isolates with resistance has remained low in the Gonococcal Isolate Surveillance Project with 27 of 6009 (0.4%) having an MIC ≥2.0 mg/l in 2007.[34]

Cases have been geographically scattered, with the exception of a cluster in Kansas City in 1999/2000.[35] Five isolates with an MIC of 4 mg/l were identified among 91 isolates collected in Cuba between 1995 and 1998.[36] Reduced susceptibility was also reported in isolates from Brazil and Caribbean.[37 38] The Australian Gonococcal Surveillance Programme has been reporting since 1996 and is linked to the WHO Western Pacific Region Gonococcal Antimicrobial Surveillance Programme. These programmes report a 'low proportion of resistance to azithromycin' with no high-level resistance.[39] In Europe, two isolates with an MIC of 4 mg/l were collected in Spain in 2000 to 2001.[40] The Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) was established in England and Wales in 2000. Susceptibility testing for azithromycin was added in 2001, when six of 2350 isolates (0.3%) were found to have an MIC ≥1 mg/l. The prevalence of resistant isolates in GRASP increased annually until 2007 when 4.1% showed resistance to azithromycin, including six isolates with MIC ≥256 mg/l.[41] Resistance fell in 2008 to 0.8% with no high-level resistance identified. The European Surveillance of Sexually Transmitted Infections programme reported an overall prevalence of resistance to azithromycin of 8.2% (79/965) in isolates collected in 2004, with considerable variation between participating countries.[42] Azithromycin resistance exceeded 9% in five of seven federal districts in Russia in 2007, with lower levels reported in 2008.[43] Data on resistance in Africa are limited but no azithromycin resistance was identified in Lilongwe, Malawi in 2007.[44]

A strain of *N gonorrhoeae* highly resistant to azithromycin (MIC > 2048 mg/l) was isolated in Argentina in 2001 and has recently been shown to be associated with a mutation in the 23S rRNA gene.[25 45] More recently, high-level azithromycin resistance (MIC ≥256 mg/l) has been identified in Scotland,[46] England and Wales[47] and Italy.[48] High-level azithromycin resistance was first detected in Scotland in 2004 and was present in 33/845 (3.9%) isolates tested in 2007.[46] *N gonorrhoeae* multiantigen sequence typing (NG-MAST) revealed that these highly resistant strains belong to a small number of sequence types. High-level azithromycin resistance emerged in England and Wales in 2007 with six isolates of the same sequence type identified.[47] This outbreak is linked to high-level resistance in Scotland. No high-level resistance was detected in 2008 in GRASP. The multiclonal and geographically disparate emergence of low-level and high-level azithromycin resistance in surveillance programmes strongly argues for caution in the use of azithromycin as the sole treatment for gonorrhoea.

RESISTANCE AND CLINICAL OUTCOME

Azithromycin is not a recommended treatment for gonorrhoea and does not appear to be widely used as sole antimicrobial therapy. MICs provide an indicator as to whether resistant mechanisms are present in an isolate of *N gonorrhoeae*. The correlation between MIC and treatment failure with azithromycin has not been well studied and relies on observations from clinical trials and case reports of treatment failures. In 1997 Young *et al* reported a case of azithromycin treatment failure with characterisation of the pre- and post-treatment isolate. The azithromycin MIC pretreatment was 0.125 mg/l and post-treatment 3.0 mg/l.[49] Treatment failures in clinical trials and in a series of case reports have not shown pretreatment resistance.[50] This indicates that treatment failure cannot be reliably predicted on the basis of in vitro MICs and test of cure may be advisable if azithromycin is used as the sole antimicrobial agent to treat gonorrhoea. Cases with high-level resistance identified in surveillance programmes do not appear to have received treatment with azithromycin.

If azithromycin is not sufficiently robust as a single agent in the treatment of gonorrhoea, it might potentially have a role in combination with other antimicrobial agents. Furuya *et al* investigated in vitro synergy between azithromycin and cefixime in 25 isolates of *N gonorrhoeae* from male patients with urethritis in Japan.[51] Significant decreases in the median MICs of both cefixime (0.25 mg/l to 0.008 mg/l) and azithromycin (0.125 mg/l to 0.03 mg/l) were observed when cefixime was combined with azithromycin. Dual treatment has been advocated for oropharyngeal gonococcal infection.[52] Azithromycin may have a valuable role in combination with extended-spectrum cephalosporins to maintain treatment efficacy in the presence of the progressive increase in MICs to oral cephalosporins.

SUMMARY

The ability of *N gonorrhoeae* to acquire resistance to antimicrobial agents is a major concern and challenge in maintaining effective treatment and control of this infection. Clinical trials of the efficacy and acceptability of azithromycin as a treatment for gonorrhoea were conducted more than a decade ago in an era when azithromycin resistance was rare. Surveillance programmes of antimicrobial resistance have clearly documented a shift in the susceptibility of *N gonorrhoeae* to azithromycin and the emergence of high-level resistance. It has been suggested that an antimicrobial agent should not be used for the treatment of gonorrhoea when >5% of strains demonstrate resistance.[53 54] In response to an increasing prevalence of penicillinase-producing *N gonorrhoeae* in 1987, the CDC proposed a lower threshold of >3% for switching treatment recommendations.[55] These thresholds may not be appropriate for an antimicrobial agent such as azithromycin for which treatment failure does not seem

Key messages

- A single 2 g dose of azithromycin has shown good efficacy in clinical trials in the treatment of infection with *N gonorrhoeae*.
- Subsequent to clinical trials, in vitro resistance of clinical isolates has been widely described, including high-level resistance.
- Azithromycin cannot be generally recommended as a sole antimicrobial treatment for gonorrhoea but may have a role in specific circumstances or in combination therapy with third-generation cephalosporins.
- Pretreatment MIC may not predict treatment outcome and test of cure should be considered when azithromycin is used as the sole antimicrobial agent for treatment of gonorrhoea.

closely predicted by pretreatment MIC. Surveillance programmes remain crucial for updating recommendations of effective antimicrobial treatment. The history of acquisition of antimicrobial resistance to multiple classes of antimicrobial agents and the resistance data we now have on azithromycin argue against the routine use of azithromycin as single antimicrobial treatment for gonorrhoea.

Competing interests None.

Contributors CB conceived the review. CB and JG contributed to the literature review, drafted sections of the paper and edited the final manuscript.

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