Azithromycin in Acute Bacterial Upper Respiratory Tract Infections: An Indian Non-Interventional Study

Shaantanu Donde · Anupam Mishra ·
Puja Kochhar

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Abstract To assess the effectiveness, safety and tolerability of azithromycin in acute bacterial upper respiratory tract infections (URTIs). In this open-label, prospective, multi-center, non-interventional study in bacterial URTI, the decision to prescribe azithromycin was independent of enrolment. Follow up was 1 week after treatment and if possible, at Week 2. Investigators' assessment of clinical outcome (Success/Failure) at the end of study was the primary endpoint for efficacy analysis. Clinical outcome of 'Success' was defined as the global response of Cure or Improvement. A pharmacoeconomic analysis of management of URTIs was also attempted. Of the 410 patients recruited, all were evaluated for safety and 278 for efficacy. The median treatment duration was 3 days. Following treatment with azithromycin, overall success rate was 98.92% (95% CI 96.88–99.78%; Clopper–Pearson method). The success rate was similar across the subgroups of acute otitis media—100%, bacterial sinusitis—95.83%, and pharyngotonsillitis—99.38%. The success rate was 100% among children and adolescents (age ≤ 18 years) and 98.6% among adults (age > 18 years). Most of the common signs and symptoms of URTI reported during baseline, significantly improved at the end of the study. Sixteen (3.90%) patients reported treatment emergent adverse events, the most common being diarrhea—5 (1.2%) and flatulence—2 (0.5%). The average cost of treating bacterial URTI was INR 716 per patient. Azithromycin is effective and well tolerated in Indian patients with bacterial URTIs.

Keywords Upper respiratory tract infections (URTI) · Antibiotics · Macrolides · Azithromycin · Non-interventional study

Introduction

In India, upper respiratory tract infections (URTIs) are one of the commonest diagnoses at primary health centers [1]. Acute respiratory infections accounted for 20–40% of outpatient and 12–35% of inpatient attendance in a general hospital and URTIs including nasopharyngitis, pharyngitis, tonsillitis and otitis media constituted 87.5% of the total episodes of respiratory infections [2].

Though most upper respiratory infections are self-limiting viral infections and do not warrant anti-infective therapy, antibacterial therapy is appropriate for patients with group A Streptococcal pharyngitis, bacterial sinusitis, epiglottitis, and otitis media [3]. Penicillin remains the Infectious Diseases Society of America (IDSA) drug of choice for acute Streptococcal pharyngitis, but the guidelines have also recommended macrolides as first line regimen [4].

Azithromycin is an azalide macrolide antibiotic that has been approved in more than 100 countries world-wide for the treatment of a variety of community-acquired infections, including those of the respiratory tract, the genitourinary tract and skin and skin structures [4]. Azithromycin is not only effective against most common upper respiratory bacterial pathogens such as group A *streptococci*, *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* but also has a good safety profile [1]. The recommended duration of therapy ranges from 1–5 days, depending on the infection being treated. Amongst the macrolides, major advantages of azithromycin are its comparable efficacy, safety and dosing schedule [3].

S. Donde (✉) · A. Mishra · P. Kochhar
Pfizer Limited, Pfizer Centre, Patel Estate, S.V.Road,
Jogeshwari (W), Mumbai 400 102, India
e-mail: Shaantanu.Donde@pfizer.com

It is well known that increased length of antibiotic treatment affects patient compliance and increases overall cost. The duration of therapy for antibiotics such as amoxicillin is 7–10 days. It is preferable to prescribe an antibiotic like azithromycin, for 3 days, to ensure better patient compliance and reduce the chances of development of bacterial resistance [1]. There is accumulating evidence that short term courses may be appropriate treatment for acute bacterial sinusitis and acute otitis media. Short-term courses have been advocated even for acute pharyngitis [5, 6]. In an observational study of drug utilization at Indian primary health centres, azithromycin was also found to be less expensive than amoxicillin. Overall cost comparison showed a difference of INR 19–64 (46–62%) between various brands of amoxicillin and azithromycin [1].

There has been an increase in morbidity and mortality due to infectious disease in the last two decades. Therefore, drug research and surveillance after authorization becomes more and more important for several reasons. Post marketing studies give useful information on drug utilization patterns, safety and tolerability that can be extrapolated to a more generalized population. Non-interventional studies (NIS) investigate various aspects of drug use including efficacy and safety under real life conditions. Their objective is the presentation of an unaffected picture of real world medical practice [7].

There is limited data on the use of azithromycin in URTI in the Indian population. This study was conducted to assess the effectiveness, safety and tolerability of azithromycin in acute bacterial URTIs. A pharmacoeconomic analysis of management of URTIs was also attempted [8].

Methods

This was an open-label, prospective, multi-center, non-interventional study conducted between February and July 2009 at 11 sites in India, across the cities—New Delhi, Mumbai, Chennai, Pune, Lucknow, Nagpur, Guwahati, and Visakhapatnam. The primary objective of this study was to assess the effectiveness of azithromycin in acute bacterial URTIs. The secondary objective was to determine the safety and tolerability of azithromycin treatment in patients suffering from URTIs. A sample size of 400 patients was chosen so that the estimated treatment response rate had a 95% confidence interval (CI) of <10% in width.

The study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with IEC, informed consent regulations, and generally accepted research practices such as Pharmaceutical Research and Manufacturers Association (PhRMA) guidelines and similar.

Patients were eligible for enrollment if they were diagnosed with acute bacterial URTI (e.g. acute bacterial sinusitis, acute

pharyngotonsillitis or acute otitis media) and the investigator had decided to prescribe azithromycin. The decision to prescribe azithromycin was independent of enrolment into the study. At baseline (Week 0), the completed parent/guardian consent form and the demographic details were collected. Data on the differential diagnosis, vital signs, medical history, physical examination, laboratory investigations and concomitant medications were noted. The investigations included complete blood count (CBC), erythrocyte sedimentation rate (ESR), X-ray, throat/pharyngeal swab for culture/sensitivity, Serology-Rapid Antigen Detection Test (RADT) for group A β -hemolytic *Streptococci* (GABHS) and others. Laboratory investigations were not mandatory and were recorded only as a part of the routine clinical practice.

Azithromycin was prescribed on the basis of the approved local product document (LPD) and dosage was adjusted solely according to medical and therapeutic necessity [9]. In general, a total dose of 30 mg/kg was given over a period of 3–5 days, as a single daily dose. Children with Streptococcal pharyngitis were given a single dose of 10 mg/kg for 3 days or 10 mg/kg on day 1 and 5 mg/kg on days 2–5 with daily dose not exceeding 500 mg. The maximum recommended total dose of azithromycin in children for any treatment was 1,500 mg.

Patients were followed up (via a clinic visit or telephone) after Week 1 of treatment and if possible, at Week 2 depending on the routine practice at the study site. Patients were also followed up at Week 2 if they were given an alternative antibiotic at Week 1 or if their signs/symptoms had not recovered at Week 1 (Fig. 1). Adverse event information was collected at Weeks 1 and 2.

The primary efficacy was evaluated on the basis of the investigator's assessment of clinical outcome at the end of the study (EOS). Clinical outcomes were based on global response to treatment in bacterial URTIs as assessed by the investigator. Global response was rated on a 4 point categorical scale as defined below:

- Cure: Disappearance of all pre-treatment signs and symptoms of infection

Fig. 1 Study flow

- Improvement: Improvement in, or partial disappearance of signs and symptoms without requirement for further antibacterial therapy. Patients in whom study drug was discontinued for reasons other than lack of clinical response to study drug, i.e., despite clinical improvement, were included in this category
- Failure: No change in, or worsening of baseline signs and symptoms requiring modification of treatment, i.e., addition of or switch to another systemic antibacterial therapy
- Unknown

Clinical Outcome

The clinical outcome of ‘Success’ was defined as the global response of Cure or Improvement. The clinical outcome of ‘Failure’ was defined as the global response of Failure. Treatment success rate was calculated at the end of the study based on investigator’s assessment of clinical outcome (Success/Failure) and was presented with 95%, 2-sided confidence intervals using the Clopper–Pearson method. Descriptive statistics appropriate for the data type (continuous, categorical or binary) was used. Subgroup analysis (defined by primary diagnosis and by baseline age) was performed to supplement the main results on the efficacy endpoints alone. Statistical analysis system (SAS) (version 9.2) was used as the analysis software.

The full analysis set (FAS) was the primary analysis population for this study and included patients who received at least one dose of study medication. The efficacy evaluable (EVAL) population included the subset of patients in the FAS having at least 1 definitive follow up global response assessment to the treatment. Patients with global response graded as “complete response (cure)”, “partial response (improvement)” or “Failure”; were included in the EVAL population and patients with global response graded “missing” or “Unknown” were not included. The safety analysis set was the same as the FAS.

Data on cost of consultation, cost of investigations (if done) and cost of medications (the study drug, analgesics, antipyretics, anti-inflammatory drugs, vitamins and others) was also collected. The number of days of sick leave since the onset of the current disease episode was captured. Cost analysis was done separately after the study and summarized by descriptive statistics. The analysis population was the FAS.

Results

A total of 410 patients were recruited in the study of which 245 were male (mean age = 33.2, mean weight = 63.2) and 155 were female (mean age = 31.4, mean weight = 54.4).

Global response: EVAL population (N=278)

Fig. 2 Global response: EVAL population

Four hundred (97.56%) patients completed the study, and 10 (2.44%) discontinued from the study. Five of the discontinued patients withdrew from the study willingly, 4 patients were lost to follow up and 1 discontinued due to an AE.

Most patients were treated with azithromycin for 2–7 days [378/410 (92.19%)]. The median duration of treatment was 3.0 days (Range 1–35).

Of the 278 patients included in the EVAL population, a global response of cure was seen in 249 (89.57%) patients, improvement in 26 (9.35%) patients and failure in 3 (1.08%) patients (Fig. 2). The 3 patients with failure, discontinued at the end of Week 1, with 1 patient lost to follow up and 2 withdrawing from the study.

Thus, in the EVAL population, an overall Success rate for Clinical Outcome was 98.92% (95% confidence interval 96.88–99.78%; the Clopper–Pearson method) and Failure rate was 1.08% in patients suffering from URTI at the end of study (Table 1).

The success rate was similar across the sub-groups defined by primary diagnosis. All 53 (100%) patients with acute otitis media showed a clinical outcome of success. Forty six out of 48 (95.83%) with bacterial sinusitis and 160 out of 161 (99.38%) with pharyngotonsillitis had a clinical outcome of success (Fig. 3).

There were no severe or serious adverse events (SAEs) reported during the study. In total, 16 (3.90%) patients reported 17 treatment emergent adverse events (TEAEs). Majority (13) were classified as gastrointestinal disorders including-diarrhea 5 (1.2%) and flatulence 2 (0.5%). One patient developed drug intolerance a day after taking 500 mg of the study drug.

Pharmacoeconomics

When the antibiotic used was azithromycin, the average cost of treating bacterial URTI was INR 716 per patient (Table 2). Very few (0.9–3.6%) patients underwent investigations in the routine practice in this study. The average number of sick leave days was 0.4 days ($n = 242$).

Table 1 Summary of clinical outcome at the end of the study-EVAL

Number [n (%)] of patients	End of study, N ^a	Success	Failure	95% Confidence interval ^b
EVAL	278	275 (98.92)	3 (1.08)	96.88–99.78
Primary diagnosis ^a				
Bacterial sinusitis	48	46 (95.83)	2 (4.17)	85.75–99.49
Pharyngotonsillitis	161	160 (99.38)	1 (0.62)	96.59–99.98
Acute otitis media	53	53 (100.00)	0	93.28–100.00
Other	5	5 (100.00)	0	47.82–100.00
Baseline Age				
≤18 Years	56 ^c	56 (100.00)	0	93.62–100.00
>18 Years	215	212 (98.60)	3 (1.40)	95.98–99.71
Unspecified	7	7 (100.00)	0	59.04–100.00

^a There were 11 patients who had more than 1 primary diagnosis marked on the case report form; they are not included in subgroup analysis by diagnosis

^b 95% confidence interval calculated using Clopper–Pearson method

^c The FAS population included paediatric patients <18 years whereas the EVAL population included paediatric subjects ≤18 years

Fig. 3 Success rate in upper respiratory tract infections**Table 2** Pharmacoeconomic analysis for azithromycin

Category ^a	No. of patients	Average cost (INR)
Cost of general consultations	346	557
Cost of azithromycin	390	177
Overall cost ^b	396	716

^a At Baseline, Weeks 1 and 2

^b The overall cost may not equal the sum of the cost of the individual components because the number of patients was different

Discussion and Conclusion

Macrolides such as azithromycin, have enhanced in vitro activity against Gram-negative respiratory tract pathogens, most notably, *H. influenzae*. They also offer better pharmacokinetic/pharmacodynamic properties with less frequent daily dosing and reduced gastrointestinal side effects [10]. Several trials of azithromycin in the treatment of URTIs, have studied a 5-day once daily (OD) course and

found it to be as effective as a 7–14-day course of commonly used oral antimicrobials, administered 2–4 times a day [5, 11]. In children, although both azithromycin and clarithromycin are well tolerated, azithromycin has the advantage of shorter treatment regimens and improved tolerance, potentially improving compliance in the treatment of respiratory tract and skin or soft tissue infections [12].

In a clinical study comparing the 3-day azithromycin course with other agents, patients who were treated with azithromycin exhibited a significantly higher degree of compliance. They showed a higher degree of perception of effectiveness and were overall more satisfied with the treatment regimen than patients who were treated with other anti-infectives [13]. Short course antibiotic therapy decreases health care costs and resistance selection. Recent antibiotics were shown effective for short course (5 days) treatment of Streptococcal pharyngitis, acute otitis media, and sinusitis [14].

Azithromycin has shown clinical efficacy in bacterial sinusitis, acute otitis media and tonsillopharyngitis. Macrolides increase mucociliary clearance, improve sinusitis symptoms, and decrease nasal secretions and polyp size in patients with sinusitis. They also have been shown to modify the inflammatory response associated with chronic sinusitis [15]. Azithromycin has shown comparable efficacy with existing therapy in previous clinical studies. A single daily dose of 10 mg/kg azithromycin for 3 days showed the same efficacy as 45 mg/kg amoxicillin–clavulanate given 3 times/day for 10 days in a prospective study of bacterial sinusitis in children aged 5–15 years [16]. In a clinical study of cephalosporin refractory sinusitis in children, clinical efficacy with azithromycin treatment was 68.3% [17].

The American Academy of Pediatrics and American Academy of Family Physicians recommend amoxicillin as drug of choice for treatment of acute otitis media. These clinical practice guidelines recommend azithromycin as alternative agent in event of hypersensitivity to amoxicillin [18]. In an open randomized study of children with acute otitis media, clinical efficacy of single-dose intramuscular ceftriaxone (85.3%) and 5-day azithromycin treatments (87.1%) was found to be comparable with the traditional 10-day high-dose amoxicillin/clavulanate therapy (87.2%) [19].

In a systematic review of 21 randomized controlled trials, 3–6 days of oral antibiotics had comparable efficacy with the standard 10 day duration of oral penicillin in treating children with acute GABHS pharyngitis [20]. Clinical efficacy of 3 day azithromycin therapy (95–100%) was similar to 10 day penicillin therapy (95–97%) in a review of management of acute Streptococcal tonsillopharyngitis. Bacteriological eradication was less in azithromycin 10 mg/kg/day groups (38–58%) compared to penicillins (81–84%) whereas azithromycin 20 mg/kg/day therapy achieved bacteriological eradication in 95% cases. Authors suggested that a higher dose of azithromycin was more appropriate for management of acute Streptococcal tonsillopharyngitis [21]. Bacteriological eradication is more important from point of view of preventing progression of pharyngitis to acute rheumatic fever. Indian Academy of Pediatrics reviewed management of rheumatic fever and recommend Streptococcal eradication with appropriate antibiotics (benzathine penicillin single dose or penicillin V oral or azithromycin) as primary prevention for rheumatic heart disease [22].

This observational study also demonstrated good clinical outcome with azithromycin in patients of URTI, most of whom received short course therapy (median duration 3 days). The study showed high success rate and good tolerability with azithromycin in the treatment of bacterial URTI in Indian patients. Success rate did not vary much across various diagnostic subgroups and was similar across age groups as well.

The study limitations include its non-interventional, non-comparative design. Since treatment visits and investigations were not mandated, outcomes of only 278 (67.8%) patients were known. This study was performed in the absence of a comparator or control group. For the study results to be applied to a larger population, a comparative study with a commonly prescribed antibiotic would be needed. Since URTIs are more common among children, studies in the pediatric population specifically would be of value. The pharmaco-economic benefit of a 3-day treatment with azithromycin in bacterial URTIs can also be assessed from such studies.

This post marketing study with azithromycin in the treatment of URTIs gave useful information on effectiveness,

safety and tolerability that will benefit physicians in clinical practice. In conclusion, azithromycin was found to be effective and well tolerated in pediatric as well as adult patients with acute bacterial upper respiratory tract infections.

The overall Success rate for Clinical Outcome in the Evaluable (278 of 410) population was 98.92% (95% confidence interval 96.88–99.78%; the Clopper–Pearson method) in patients of bacterial URTI treated with azithromycin. There were no severe or serious adverse events (SAEs) reported during the study.

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