

Continued use of azithromycin for mild COVID-19 in India: Evidence and implications?

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ABSTRACT

Azithromycin is an antibiotic commonly used for treating respiratory, gastrointestinal infections besides enteric fever, otitis media etc. It's convenient short duration oral dosing regimens and good tolerability make it a popular drug in routine outpatient settings in primary to tertiary care. Pre-clinical studies have shown immunomodulatory and in vitro activity of azithromycin against SARS CoV-2, which has led to its widespread usage in COVID-19. However, subsequent reviews of observational studies assessing its efficacy in different grades of COVID-19, as well as data from well conducted randomised clinical trials (RCTs) in mild - moderate COVID-19 have shown no or very low quality evidence of benefit of the drug on various clinical outcome parameters. Still, the drug continues to be used indiscriminately in many parts of India for treatment of home isolated patients of mild COVID-19. Such injudicious use in the community should be stopped, otherwise there will be serious adverse consequences of development of resistance to this very useful antibiotic during this pandemic.

Keywords: Azithromycin, antimicrobial resistance, COVID-19

Azithromycin is a macrolide antibiotic with bactericidal and bacteriostatic actions. It inhibits bacterial protein synthesis by reversibly binding to the 50S ribosomal subunit of the sensitive microorganisms, thereby inhibiting the translocation step, leading to cell growth inhibition and cell death.^[1] The common approved and recommended indications in India are community-acquired pneumonia (CAP), mild-to-moderate upper respiratory tract infections (RTIs), uncomplicated enteric fever, uncomplicated skin and skin structure infections, pelvic inflammatory disease (non-gonococcal urethritis, cervicitis), acute otitis media in adults and pediatric patients, cholera, bacterial dysentery, rickettsial and scrub typhus infections and for antibiotic coverage during caesarian delivery and abortion. The convenient dosing regimens of 500–1000 mg once daily orally for 3-5 days for most indications and good tolerability

profile makes it a very popular choice of antibacterial in outpatient settings.^[2,3]

Beyond its antibacterial activity, this macrolide has shown antiviral and immunomodulatory activities that have been of interest in viral infections, including COVID-19. Preclinical studies have found that it can exert antiviral effects against Zika, Rhino and Ebola viruses. According to in-silico and other studies,^[4-6] potential mechanisms of action of azithromycin in the treatment of COVID-19 are based on predominantly on its immunomodulatory activity along with the antiviral effect. It interferes with SARS-CoV-2 binding with host cells by increasing pH of Trans-Golgi network which alters the glycosylation of the human ACE2 (hACE2) receptor and affects binding of the spike protein to target cells. It can also interfere with ligand CD147 receptor interactions, alter membrane fusion and endocytosis. It causes suppression of CD4+ T-cell activation and reduction of pro-inflammatory cytokines and chemokines like Interleukin (IL)-1 β , IL-6, IL-8, IL-12, Interferon (IFN)- γ , IP-10, Tumor Necrosis Factor (TNF)- α , and GM-CSF. It has also been

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known to cause increased apoptosis, antifibrotic activity through inhibition of fibroblast proliferation, reduction of collagen production, decreased transforming growth factor (TGF- β) production, inhibition of TGF- β induced pro-fibrotic gene stimulation.^[7-9]

Although scientific bodies have proposed that azithromycin's antibacterial properties may continue to be useful in the empirical treatment of CAP in COVID-19 patients and has also been useful in influenza associate pneumonia, the proofs of its direct activity in COVID-19 have been largely inconclusive.^[10,11] In India, although this drug is not advised in the national (ICMR or AIIMS New Delhi) COVID treatment guidelines, it is recommended for treating mild COVID-19 patients under home isolation in treatment guidelines of some major states like Uttar Pradesh, Madhya Pradesh where a large burden of cases presently lie in the country. In clinical practice, the drug is known to being prescribed commonly on OPD basis in some parts of the country.^[12-14] Running a search on the US government's clinical trial registry portal (clinicaltrials.gov) shows 28 clinical trials on azithromycin in treatment for COVID-19 have been completed out of total 125 trials registered at the time of writing.^[15] In India, presently there is only one multicentric randomized controlled trial registered on the Clinical Trial Registry of India (CTRI) to compare the efficacy of hydroxychloroquine versus azithromycin in the treatment of COVID-19, whereas another registered study is a single center observational study.^[16]

In an exhaustive review by Gyselinck *et al.*^[8] to critically appraise the rationale and evidences of using azithromycin in COVID-19, a wide effect range was reported from studies assessing azithromycin monotherapy versus standard of care mainly in hospitalized patients. There was a great deal of variations in these studies (heterogeneity), and most studies were retrospective providing low-quality inconsistent, contrasting evidence. Although no studies reported a significantly increased risk of adverse outcomes with azithromycin monotherapy, one of the published^[17] meta-analyses pooling azithromycin-containing regimens (mostly in combination) confirmed the increased mortality risk in patients treated with hydroxychloroquine plus azithromycin. There have been genuine concerns raised regarding QTc prolongation, increased transaminases, and even cardiac arrest in the hydroxychloroquine-containing regimens in a few studies, but not with azithromycin alone. An interpretation could be that short-term mortality may be increased by these drug interactions. Furthermore, the confounder-adjustment approaches differences in outcomes assessed, target populations studied (mild – severe COVID-19) and varying follow-up periods make it difficult to make certain interpretations from such studies. Overall, the authors concluded that widespread use of azithromycin in treatment of COVID-19 cannot be endorsed based on the limited and low-quality evidence.^[8] Similar low-quality evidence, mainly from retrospective observational studies was reported by another review written by Esnal *et al.*^[7] azithromycin was shown to provide no benefit in treating SARS-CoV-2 pneumonia), whereas the drug maintains its well-known safety profile.

Higher quality evidence has now been generated through publication of results of a few large well-designed adequately powered randomized clinical trials (RCT's) conducted to assess the effect of azithromycin monotherapy, specifically in the treatment of mild-moderate COVID-19, primarily in the UK and Brazil. Perhaps the prominent trial evaluating azithromycin use in non-hospitalized COVID-19 patients is the ongoing PRINCIPLE trial, a UK-based, primary care (community based), open-label, multi-arm, randomized trial of interventions. In this trial, 2265 participants with confirmed or suspected symptomatic COVID-19, aged 50 years or older with at least one comorbidity like known immunosuppressed state, heart disease, hypertension, asthma or lung disease; diabetes; hepatic impairment, stroke or neurological problems (and all patients above 65 years of age), were randomly assigned to usual care plus azithromycin 500 mg daily for three days ($n = 540$), usual care plus other interventions (like HCQ, doxycycline; $n = 850$), or usual care alone ($n = 875$). Very little evidence of a meaningful benefit in the azithromycin group in the key clinical outcomes of time to first reported recovery (hazard ratio 1.08, 95% CI 0.95 to 1.23 versus standard care alone), need for hospitalization and death at 28 days was noted. The researchers concluded that these results in conjunction with previous evidence do not justify the routine use of azithromycin in community or hospital settings for COVID-19.^[18] This has also led the UK Medicines and Healthcare products Regulatory Agency (MHRA) to issue a COVID-19 Therapeutic Alert in January 2021 that azithromycin (and also doxycycline) 'should not be used within primary care for the treatment of COVID-19'.^[19]

Prior to this, the RECOVERY trial,^[20] which took place in 176 hospitals of UK, was conducted on hospitalized patients ($n = 7763$) with COVID-19, of whom 2582 patients were randomly allocated to receive azithromycin (500 mg once per day orally or intravenously for 10 days or until discharge) and 5181 patients were randomly allocated to receive usual care alone. These patients included those who did not or did require oxygen support at baseline as well those requiring ventilatory support (i.e., mild/moderate/severe COVID). There was no difference in the 28-day mortality (rate ratio 0.97, 95% CI 0.87–1.07; $P = 0.50$), or duration of hospitalization (median 10 days [IQR 5 to >28] vs. 11 days [5 to >28]) or the composite outcome of invasive mechanical ventilation or death. In fact, outcomes were found to be poorer in the azithromycin group at 15 days.

Other than these major trials, a couple of RCTs have been conducted in Brazil. The COALITION I study compared standard of care, hydroxychloroquine plus azithromycin, and hydroxychloroquine monotherapy for the treatment of mild–moderate COVID-19 in 675 hospitalized patients at multiple centers.^[21] The study found no significant differences in clinical outcome, measured on an ordinal score scale, at day 15. COALITION II was a multicenter study on 447 patients admitted to the hospital with severe COVID-19 who were randomly allocated to either standard of care plus

azithromycin (500 mg orally or intravenously once daily for 10 days) or standard of care alone. In this study, all patients were given hydroxychloroquine (400 mg twice daily for 10 days) as a part of standard of care. The results were non-significant, and adding azithromycin to standard treatment did not improve or worsen clinical outcomes. There was no significant difference found in clinical status, as assessed by an ordinal scale at day 15 (OR 1.36, 95% CI 0.94–1.97, $P = 0.11$).^[22]

All major international guidelines (WHO, NIH, IDSA) strongly recommend against using azithromycin in conjunction with hydroxychloroquine owing to a lack of high-quality evidence in favor and concerns about possible side effects,^[23–25] and similar nature of recommendation, although with lesser certainty, is there for azithromycin alone as well. Azithromycin is a relatively cheap antibiotic; cost of generic azithromycin 500 mg one tablet (Jan Aushadhi Portal) is Rs 13.5 per tablet and for entire treatment of 3–5 day azithromycin is Rs 40.5–67.5 (<US \$1). This is a safe and often well-tolerated drug (with mild gastrointestinal adverse effects like stomach upset, diarrhea/loose stools, nausea, vomiting, or abdominal pain), inexpensive, and readily available. That is why physicians perhaps are continuing to prescribe it and patients are using it even as an over the counter remedy for asymptomatic or mild COVID.^[14,26,27] It also begs the question as to why are state guidelines still recommending it in their treatment protocols for mild COVID-19 – is it just to offer a ‘placebo’ effect to the public that they are being given ‘some treatment for corona’?

During this COVID-19 pandemic, there are enough evidences and reports that azithromycin use has increased around the world, including in India.^[14,28,29] Antimicrobial resistance is a global problem that is of significant immediate concern already. There are possible risks to the antimicrobial stewardship activities and increase in antimicrobial resistance during the ongoing COVID-19 pandemic due to the indiscriminate use of this antibiotic widely prescribed for common respiratory, gastrointestinal and genitourinary infections, and categorized as a “highest-priority critically important antimicrobial” (HPCIA) by the WHO.^[30,31] A feature article in BMJ addresses this threat of acceleration of antimicrobial resistance during COVID-19 due to inappropriate use or rather misuse of antibiotics worldwide.^[32] One of the possible serious implications is that we may lose the clinical utility of this conveniently dosed, well-tolerated, safe antibiotic altogether in our communities, particularly in primary care in this country.

Conclusion: The available evidence does not support the use of azithromycin for improving any useful clinical parameter such as time to recovery or need for hospitalization in COVID-19 including that in patients of mild–moderate disease. Its injudicious use in the community by primary care physicians and patients alike should be stopped, and it should be withdrawn from any government recommendations in the country. Otherwise, the indiscriminate use of this popular and an useful antibiotic will lead to resistance and will pose a serious problem in the

management of infections for which azithromycin is currently recommended and effective

New message: Evidence does not support the use of azithromycin for improving any clinical parameter in mild-to-moderate COVID-19 infections and indiscriminate use of this very useful antibiotic will lead to serious problem of antibiotic resistance.

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Conflicts of interest

There are no conflicts of interest.

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