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ADR Assessment on Azithromycin Drugs

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ABSTRACT: Azithromycin is an acid-stable orally administered macrolide antimicrobial drug, structurally related to erythromycin. AZM is a macrolide antibiotic with a 15-membered lactone ring. It is broad-spectrum antibiotics with long serum half-life near about 68 h and large volume of distribution.Azithromycin is indicated for respiratory, urogenital, dermal and other bacterial infections, and exerts immunomodulatory effects in chronic inflammatory disorders, including diffuse panbronchiolitis, post-transplant bronchiolitis and rosacea. Azithromycin should not be used routinely to treat COVID-19 in the community in older adults, in the absence of additional indications.

Keywords: Azithromycin, Covid-19, hospitalization, clinical trial

I. INTRODUCTION

Azithromycin:-

AZM is a macrolide antibiotic with a 15-membered lactone ring. It is broad-spectrum antibiotics with long serum half-life near about 68 h and large volume of distribution. [1]

AZM has excellent tissue penetration. In infected tissues, AZM concentrations are about 300- fold higher than in plasma, due to recruitment of leukocytes at the site of infection. [2]

It also has anti-inflammatory activity, decreases pro-inflammatory cytokine and hastening of the macrophages phagocytosis ability. [3]

Due to its antibacterial and anti-inflammatory effects, it is used for many chronic lung diseases including chronic obstructive pulmonary disease, asthma, interstitial lung diseases, bronchiectasis, and cystic fibrosis. [4]

Azithromycin is an acid-stable orally administered macrolide antimicrobial drug, structurally related to erythromycin. [5]

Due to its broad antibacterial spectrum against Streptococcus pneumonia, Moraxella catarrhalis, and atypical pathogens, azithromycin has been used extensively for the treatment of paediatric infectious diseases and became one of the most commonly prescribed antibiotics in children [6–10].

During the last 20 years, azithromycin mass drug administration (MDA) has been used to control trachoma with over 700 million doses of azithromycin being prescribed to children in areas of active trachoma programs [11].

Recent large trials have suggested that periodical azithromycin MDA may reduce post-neonatal infant and child mortality [12].

However, the long-term rationale for mass antibiotic distribution for trachoma is still the subject of debate with concerns of potential toxicity with azithromycin in paediatrics [13,14].

A systematic review that evaluated the tolerance or toxicity of azithromycin in children with asthma found that gastrointestinal adverse reactions such as nausea, diarrhoea, and abdominal pain were the main adverse events [15].

Another systematic review of azithromycin use in neonates highlighted the risk of infantile hypertrophic pyloric stenosis (IHPS) [16].

This systematic review aims to evaluate the toxicity of azithromycin both as MDA or non-MDA in neonates, infants, and children from birth to 18 years old. This systematic review was proposed by the World Health Organization (WHO), as one of the systematic reviews in support of developing a guideline of azithromycin use in paediatrics to help national and international policymakers in determining the role of prophylactic azithromycin in reducing child mortality [14].

Mode of action of Azithromycin:-

Azithromycin is a macrolide antibiotic which inhibits bacterial protein synthesis, quorum-sensing and reduces the formation of biofilm. Accumulating effectively in cells, particularly phagocytes, it is delivered in high concentrations to sites of infection, as reflected in rapid plasma clearance and extensive tissue distribution. Azithromycin is indicated for respiratory, urogenital, dermal and other bacterial infections, and exerts immunomodulatory effects in chronic

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inflammatory disorders, including diffuse panbronchiolitis, post-transplant bronchiolitis and rosacea. Modulation of host responses facilitates its long-term therapeutic benefit in cystic fibrosis, non-cystic fibrosis bronchiectasis, exacerbations of chronic obstructive pulmonary disease (COPD) and non-eosinophilic asthma.

Initial, stimulatory effects of azithromycin on immune and epithelial cells, involving interactions with phospholipids and Erk1/2, are followed by later modulation of transcription factors AP-1, NFκB, inflammatory cytokine and mucin release. Delayed inhibitory effects on cell function and high lysosomal accumulation accompany disruption of protein and intracellular lipid transport, regulation of surface receptor expression, of macrophage phenotype and autophagy. These later changes underlie many immunomodulatory effects of azithromycin, contributing to resolution of acute infections and reduction of exacerbations in chronic airway diseases. A sub-group of post-transplant bronchiolitis patients appears to be sensitive to azithromycin, as may be patients with severe sepsis. Other promising indications include chronic prostatitis and periodontitis, but weak activity in malaria is unlikely to prove crucial. Long-term administration of azithromycin must be balanced against the potential for increased bacterial resistance. Azithromycin has a very good record of safety, but recent reports indicate rare cases of cardiac torsades des pointes in patients at risk.[17]

Indication of Azithromycin:-

Azithromycin is a broad-spectrum macrolide antimicrobial and is among the most prescribed antimicrobial drugs in the United States. It is a derivative of erythromycin with greatly enhanced activity against gram-negative bacteria (including Enterobacteriaceae) and provides coverage of many gram- positive organisms.[18]

As an inhibitor of bacterial protein synthesis (rather than a peptidoglycan cell-wall inhibitor like beta-lactam agents), azithromycin is effective against many “atypical” bacteria such as chlamydiae (e.g., Chlamydia trachomatis and Chlamydophila psittaci), legionella (i.e., Legionella pneumophila), mycoplasma (e.g., Mycoplasma pneumoniae), and mycobacteria (e.g., Mycobacterium avium).[19]

Together with its activity against Streptococcus pneumoniae, Hemophilus influenzae,
and Moraxella catarrhalis, azithromycin is indicated—and FDA approved—for the treatment of community-acquired pneumonia (CAP). [20]

Azithromycin also has approval for use in other upper respiratory infectious processes, including acute otitis media and acute exacerbation of chronic obstructive pulmonary disease (COPD).[21]
Additionally, azithromycin has approval for the treatment of pharyngitis caused
by Streptococcus pyogenes, as an alternative to a beta-lactam agent; skin or skin structure infection due to S. pyogenes, Streptococcus agalactiae, or Staphylococcus aureus; M.

avium complex (MAC) infection treatment and prophylaxis for patients with advanced acquired immunodeficiency syndrome (AIDS); and sexually transmitted infections including chlamydia, gonococcal disease, chancroid (caused by Hemophilus ducreyi), and Mycoplasma genitalium.[22,23,24,25,26]
Azithromycin also has efficacy against some protozoal organisms such as Babesia sp. (e.g., B. microti), Plasmodium sp. (i.e., malaria), and Toxoplasma gondii and is sometimes used off-label for the treatment of these parasitic diseases in combination with antiprotozoal drugs (e.g., atovaquone).[27,28,29]

Administration:-

Azithromycin is available for both oral and parenteral (intravenous) administration. The extended- release formulation of azithromycin has been discontinued. The usual dose is 250 mg or 500 mg given once daily for 3 to 5 days, and in severe infections, a higher dose is used.

- Oral formulations include tablets (250 mg, 500 mg), packets (1 gram dissolved in ¼ cup or 60 ml of water), and suspension for reconstitution (100 mg/5 ml, 200 mg/5 ml). Dosing can be administered with or without food.
- Intravenous (IV) azithromycin is available in a 500 mg preservative-free solution for reconstitution. It should be infused over at least 60 minutes, and azithromycin administration should not be via intramuscular injection or IV bolus.
- The ophthalmic solution (1%) is available in a 2.5 ml bottle which is used in bacterial conjunctivitis.

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Azithromycin demonstrates excellent tissue penetration and intracellular accumulation. Metabolism is hepatic, and excretion is mainly biliary.[30] Its long half-life and extensive tissue and intracellular distribution permit once-daily dosing and a shorter course of treatment than other antimicrobials (e.g., treatment of chlamydia infection with a single administration of 1 g of azithromycin versus 100 mg of doxycycline twice daily for seven days).

Azithromycin may be administered to patients with renal disease or failure without regard for creatinine clearance. No dose adjustment is usually necessary.[31]

Contraindication:-

- Azithromycin is contraindicated in patients with a history of severe hypersensitivity (e.g., anaphylaxis or SJS) to azithromycin or another macrolide antimicrobial. In addition, clinicians should be cautious regarding the concomitant use of azithromycin and other medications that prolong the QTc interval (e.g., antipsychotics).
- Azithromycin is contraindicated for patients taking the first-generation antipsychotic pimozide. Macrolide antimicrobials inhibit CYP3A4, the same cytochrome that metabolizes pimozide; concomitant use of azithromycin with pimozide can cause dangerous plasma concentrations of pimozide, leading to QTc prolongation and, potentially, lethal arrhythmias. While azithromycin is a poor inhibitor of CYP3A4 relative to other macrolides, avoidance of this interaction is still advisable.[32,33]
- Additionally, azithromycin is an inhibitor of p-glycoprotein/ABCB1, a cell membrane glycoprotein transporter. Drugs that are substrates of P-glycoprotein, particularly those that are also substrates of CYP3A4, may represent a relative contraindication to azithromycin. Examples include colchicine and small-molecule calcitonin gene-related peptide (CGRP) antagonists.[34,35]

- Azithromycin effectively preserves FEV and ameliorates bronchiolitis obliterans (BO) with no effect on overall survival in lung transplant patients; however, a study comparing azithromycin with placebo for the prevention of BO in hematopoietic stem cell transplant (HSCT) recipients demonstrated decreased BO-free and overall survival with azithromycin.[36] Hence, long-term azithromycin prophylaxis in HSCT recipients is inadvisable.

Azithromycin acts on COVID-19

II. INTRODUCTION:-

Identifying treatments that can be used to speed recovery and reduce hospitalisations due to COVID-19 in the community is critically important, particularly among older adults and people with comorbidities, who are at a high risk of adverse outcomes. [37]

Azithromycin, a licensed, widely available, cheap, and generally safe drug has been proposed as a treatment for COVID-19, with in-vitro studies suggesting activity against some viruses, including SARS-CoV-2. [38, 39]

Azithromycin might increase the pH of the Golgi network and recycling endosome, [40] which could in turn interfere with intracellular SARS-CoV-2 activity and replication. The drug might also reduce levels of the enzyme furin; [40] this could interfere with the ability of SARS-CoV- 2 to enter cells, as the virus is believed to have a furin-like cleavage site in the spike protein. [41]

The ability of azithromycin to reduce the levels of pro-inflammatory cytokines, such as IL-6,

[42] could reduce the ability of SARS-CoV-2 infection to trigger a cytokine storm, along with associated tissue damage. Furthermore, some patients with viral respiratory illness might develop a secondary bacterial infection or present with a bacterial co-infection, which azithromycin could effectively treat. Azithromycin use in primary care has increased during the COVID-19 pandemic, [43] which could contribute to antimicrobial resistance. [44]

Randomised trials have found that azithromycin is not an effective treatment for patients who are admitted to hospital with COVID-19, either alone or in combination with hydroxychloroquine. [45, 46, 47]

However, there is a paucity of evidence regarding the effectiveness of azithromycin for treatment of suspected COVID-19 in the community, where earlier treatment might speed recovery and prevent hospital admissions. We aimed to assess the effectiveness of azithromycin to treat COVID-19 in the platform randomised trial of interventions against COVID-19 in older people (PRINCIPLE) study.

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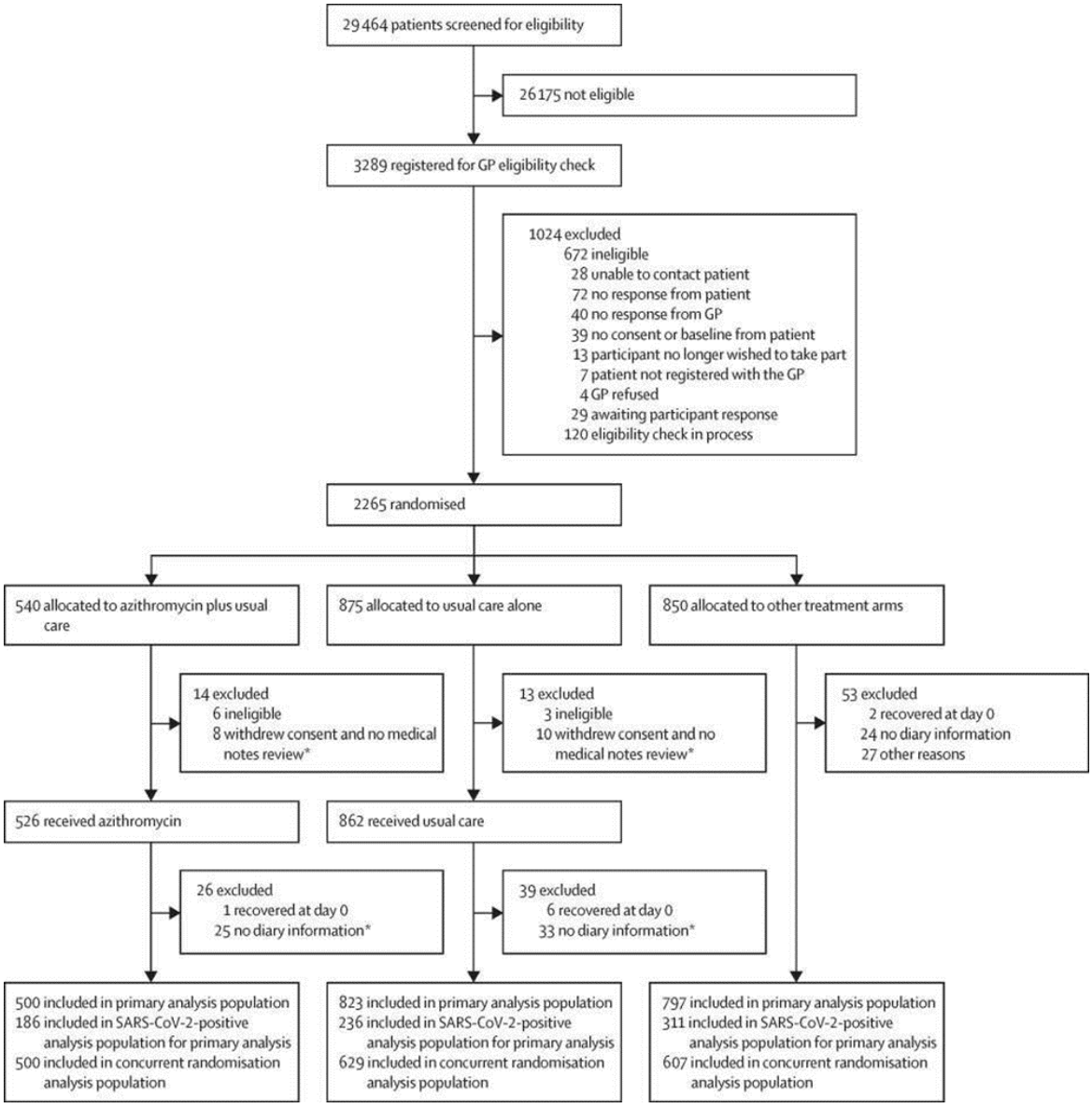

Figure 1: Trial profile
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III. RESULTS

On Nov 30, 2020, after review of planned interim analyses by the Data Monitoring and Safety Committee, the PRINCIPLE Trial Steering Committee advised the Trial Management Group to stop random assignment of patients to the azithromycin group of the trial because the pre-specified futility criterion was met. By this date, 2265 participants from 1460 GP practices were enrolled into PRINCIPLE across the UK (appendix p 210). 679 (30%) of 2265 participants were enrolled directly through 231 GP practices and 1586 (70%) participants via online or telephone contact with the study team. 540 participants were randomly allocated to azithromycin plus usual care, 875 to usual care alone, and 850 to other interventions. After exclusion of those who were ineligible, those who withdrew consent, and those without medical notes review and with no diary information available, 526 eligible participants were randomly assigned to receive azithromycin plus usual care, 862 to usual care alone, and 823 to

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other interventions (figure 1). 2120 (94%) of 2265 participants provided follow-up data and were included in the Bayesian primary analysis, 500 participants in the azithromycin plus usual care group, 823 in the usual care alone group, and 797 in other intervention groups. The concurrent randomisation analysis population included data from all participants randomly assigned to azithromycin plus usual care (n=500), and those concurrently assigned to usual care alone (n=629) for analysis of secondary outcomes, plus participants assigned to other interventions (n=607) for sensitivity analyses of co-primary outcomes (figure 1).

Characteristics of participants randomly assigned to azithromycin and concurrent controls were similar (table 1). The mean participant age was 60·7 years (SD 7·8), 1233 (88%) of 1388 participants had comorbidities, and the median duration of illness before randomisation was 6 days (IQR 4–10). 1148 (83%) of 1388 participants had a SARS-CoV-2 PCR result available, and 434 (31%) of 1388 participants had a positive result. 455 (87%) of 526 participants allocated to azithromycin plus usual care reported taking at least one dose of azithromycin and 374 (71%) took all three doses. 402 (80%) of 500 participants in the azithromycin plus usual care group and 631 (77%) of 823 participants in the usual care alone group reported feeling recovered within 28 days (table 2). Median time to first reported recovery for patients in the azithromycin plus usual care group was 7 days (IQR 3 to 17) and for patients in the usual care group was 8 days (2 to 23; figure 2; table 2).

Based on the Bayesian primary analysis model, we found no evidence of a meaningful benefit in the azithromycin plus usual care group in time to first reported recovery versus usual care alone (HR 1·08, 95% Bayesian credibility interval [BCI] 0·95 to 1·23), equating to an estimated benefit in median time to first recovery of 0·94 days (95% BCI –0·56 to 2·43; figure 2). The probability that median time to recovery was shorter in the azithromycin plus usual care group compared with the usual care alone group (ie, probability of superiority) was 0·89 and did not meet the 0·99 threshold to declare superiority. The probability that there was a clinically meaningful benefit of at least 1·5 days in time to recovery was 0·23.

16 (3%) of 500 participants in the azithromycin plus usual care group and 28 (3%) of 823 participants in the usual care alone group were hospitalised (absolute benefit in percentage 0·3%, 95% BCI –1·7 to 2·2; table 2). There were no deaths in either study group. The probability that hospitalisations or deaths were lower in the azithromycin plus usual care groupcompared with the usual care alone group (probability of superiority) was 0·64, and was not formally analysed for significance due to the gate-keeping hypothesis structure. The probability that there was a reduction in hospitalisations or deaths of at least 2% (the predefined threshold of a clinically meaningful benefit) was 0·042. Results of both primary outcomes were consistent in participants with SARS-CoV-2 and the concurrent randomisation analysis population.

Analysis of the secondary outcomes using the concurrent randomisation analysis population showed that there was no evidence of any difference between the two study groups in the daily score (1–10) of how well participants felt over 28 days (appendix p 217), nor the WHO wellbeing score at any of the follow-up time points, nor any of the hospitalisation secondary outcomes (table 3). Similarly, we found no evidence of treatment benefit in the azithromycin plus usual care group in time to first alleviation of symptoms, time to sustained alleviation of symptoms, and time to initial reduction of severity of symptoms (appendix p 218).

More GP healthcare service use was reported in the azithromycin plus usual care group compared with the usual care alone group (table 3). We found some evidence that sustained recovery from nausea and vomiting and diarrhoea was more rapid in the azithromycin plus usual care group compared with the usual care alone group (appendix p 218). In subgroup analyses, we found no impact of the duration of illness before random assignment nor of the baseline illness severity score on the time to first feeling recovered (figure 3). Estimates of treatment benefit were similar for those younger than 65 years and aged 65 years and older, as well as between those with and without comorbidities (figure 3). In patients who tested SARS- CoV-2 positive and received azithromycin, we observed an estimated median benefit of 1·4 days (HR 1·12, 95% BCI 0·91–1·38; table 2) and a probability of benefit of 0·86, which was below the threshold for superiority of 0·99. Additional sensitivity analyses of interactions of swab results with time to first reported recovery in the concurrent randomisation analysis population supported these findings (appendix p 219).

Results for the concurrent randomisation analysis population in SARS-CoV-2-positive participants for the secondary outcomes were similar to the concurrent randomisation analysis

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population results for all participants (appendix p 215). One participant had side-effects from azithromycin and subsequently withdrew from the study. Two (1%) of 455 participants in the azithromycin plus usual care group and four (1%) of 668 participants in the usual care alone group reported admission to hospital, unrelated to COVID-19, during the trial (p>0·99).

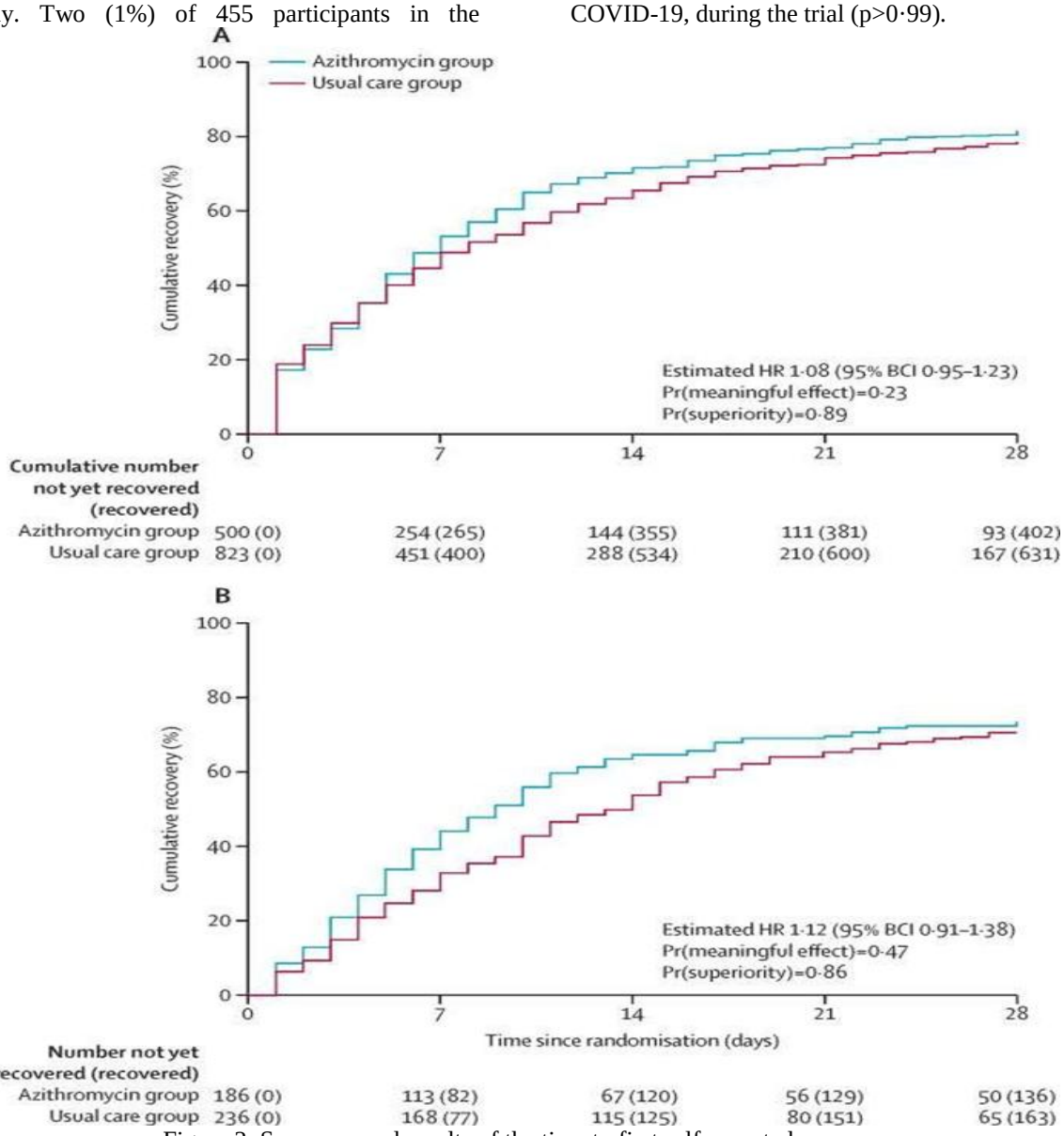

Figure 2: Summary and results of the time to first self-reported recovery

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IV. DISCUSSION

Discussion In this trial of interventions for people with suspected COVID-19 within 14 days of symptom onset, and at increased risk of complications, azithromycin plus usual care did not substantially shorten the time to first self-reported recovery or decrease the risk of hospitalisation. There are over 80 clinical trials of azithromycin for COVID-19 planned or underway, but few have reported results and none, to our knowledge, are in a community setting. Similar to our findings, several randomised trials among patients admitted to hospital have found that azithromycin was not effective as a treatment for COVID-19. Azithromycin has been evaluated as part of a hospital-based, platform, open-label

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randomisedclinical trial of different COVID-19 treatments in the UK.9 2582 patients were randomly assigned to azithromycin (500 mg once a day for 10 days, or until discharge if this occurred sooner) plus usual care and 5181 received usual care alone. Azithromycin did not improve the primary outcome of mortality at 28 days (22% in both groups; rate ratio 0·97, 95% CI 0·87–1·07; p=0·50). Similarly, the authors reported no difference in 28-day mortality between groups when the analyses were limited to patients with confirmed SARS-CoV-2 infection (rate ratio 0·95, 95% CI 0·86–1·06; p=0·38). There was no difference in the occurrence of new cardiac arrhythmias between groups. One serious adverse event attributed to azithromycin was reported (pseudomembranous colitis). A Brazilian randomised clinical trial of hospitalised adults with known or suspected mild to moderate COVID-19 randomly assigned 667 patients to usual care alone (n=227), usual care plus hydroxychloroquine (n=221), or usual care plus hydroxychloroquine and azithromycin (500 mg once a day for 7 days; n=227).10 The primary outcome was clinical status at day 15, recorded on a 7-point ordinal scale from 1 (no longer in hospital and no limitation of activities) through to 7 (deceased). Among patients with confirmed COVID-19, the authors found that there was no difference in the odds of having poorer clinical status at day 15 between the groups (hydroxychloroquine plus azithromycin vs control odds ratio [OR] 0·99, 95% CI 0·57–1·73; p>0·99; hydroxychloroquine plus azithromycin vs hydroxychloroquine OR 0·82, 95% CI 0·47–1·43; p>0·99). More participants who received hydroxychloroquine plus azithromycin and hydroxychloroquine alone had adverse events compared with the usual care alone group (39·3%, 33·7%, and 22·6%, respectively). Prolongation of the corrected QT interval was most common in the hydroxychloroquine plus azithromycin group; however, the authors noted that participants in the usual care alone group were less likely to have electrocardiogram monitoring. The same Brazilian study group conducted a trial of azithromycin 500 mg once daily for 10 days plus usual care versus usual care alone in 447 adult, hospitalised patients with severe COVID-19 (COALITION II).11 at the time of the trial, usual care for patients with severe COVID-19 was hydroxychloroquine 400 mg twice daily for 10 days. Thus, patients in the azithromycin group additionally received hydroxychloroquine. The authors reported no difference between the groups in the primary outcome of the odds of poorer clinical status at day 15, according to a 6- point ordinal scale of clinical status, among patients with confirmed COVID-19 (OR 1·36, 95% CI 0·94–1·97; p=0·11). The proportion of serious adverse events between the intervention and control groups were similar (42% vs 38%; p=0·35), and there was no difference in patients with a prolonged corrected QT interval between the intervention and control groups (20% vs 21%; p=0·66). These studies provide good evidence that azithromycin is not an effective treatment in hospitalised COVID-19 patients. Furthermore, there is no evidence of synergy between azithromycin and hydroxychloroquine in the context of COVID-19, as has previously been suggested.

V. CONCLUSION

In conclusion, our findings show that azithromycin should not be used routinely to treat COVID-19 in the community in older adults, in the absence of additional indications. These findings have important antibiotic stewardship implications during this pandemic, as inappropriate use of antibiotics leads to increased antibiotic resistance, and there is evidence that azithromycin use increased during the pandemic in the UK.7 Using antibiotics to treat COVID-19 might also encourage patients to believe that antibiotics are an appropriate treatment for other viral respiratory infections, and our findings guide clinicians to avoid prescribing antibiotics to patients seeking treatment for COVID-19 in the absence of an additional indication. Finally, our findings highlight the importance of randomised controlled trials to assess medications during the COVID-19 pandemic and prevent the use of ineffective medications which, in the case of azithromycin, might contribute to other public health problems such as antimicrobial resistance.

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