Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

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Summary

Background Azithromycin has been proposed as a treatment for COVID-19 on the basis of its immunomodulatory actions. We aimed to evaluate the safety and efficacy of azithromycin in patients admitted to hospital with COVID-19.

Methods In this randomised, controlled, open-label, adaptive platform trial (Randomised Evaluation of COVID-19 Therapy [RECOVERY]), several possible treatments were compared with usual care in patients admitted to hospital with COVID-19 in the UK. The trial is underway at 176 hospitals in the UK. Eligible and consenting patients were randomly allocated to either usual standard of care alone or usual standard of care plus azithromycin 500 mg once per day by mouth or intravenously for 10 days or until discharge (or allocation to one of the other RECOVERY treatment groups). Patients were assigned via web-based simple (unstratified) randomisation with allocation concealment and were twice as likely to be randomly assigned to usual care than to any of the active treatment groups. Participants and local study staff were not masked to the allocated treatment, but all others involved in the trial were masked to the outcome data during the trial. The primary outcome was 28-day all-cause mortality, assessed in the intention-to-treat population. The trial is registered with ISRCTN, 50189673, and ClinicalTrials.gov, NCT04381936.

Findings Between April 7 and Nov 27, 2020, of 16 442 patients enrolled in the RECOVERY trial, 9433 (57%) were eligible and 7763 were included in the assessment of azithromycin. The mean age of these study participants was 65·3 years (SD 15·7) and approximately a third were women (2944 [38%] of 7763). 2582 patients were randomly allocated to receive azithromycin and 5181 patients were randomly allocated to usual care alone. Overall, 561 (22%) patients allocated to azithromycin and 1162 (22%) patients allocated to usual care died within 28 days (rate ratio 0·97, 95% CI 0·87–1·07; p=0·50). No significant difference was seen in duration of hospital stay (median 10 days [IQR 5 to >28] *vs* 11 days [5 to >28]) or the proportion of patients discharged from hospital alive within 28 days (rate ratio 1·04, 95% CI 0·98–1·10; p=0·19). Among those not on invasive mechanical ventilation at baseline, no significant difference was seen in the proportion meeting the composite endpoint of invasive mechanical ventilation or death (risk ratio 0·95, 95% CI 0·87–1·03; p=0·24).

Interpretation In patients admitted to hospital with COVID-19, azithromycin did not improve survival or other prespecified clinical outcomes. Azithromycin use in patients admitted to hospital with COVID-19 should be restricted to patients in whom there is a clear antimicrobial indication.

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See Online for appendix

Introduction

A substantial proportion of individuals infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) develop a respiratory illness requiring hospital care, which can progress to critical illness with hypoxic respiratory failure requiring prolonged ventilatory support. Among patients with COVID-19 admitted to UK hospitals in the first wave of the epidemic, the case fatality rate was greater than 26%, and in excess of 37% in patients requiring invasive mechanical ventilation.[1]

In patients with severe COVID-19, the host immune response is thought to play a key role in driving an acute pneumonic process with diffuse alveolar damage, inflammatory infiltrates, and microvascular thrombosis.[2] The beneficial effects of dexamethasone and other corticosteroids in patients with hypoxic lung damage suggest that other drugs that suppress or modulate the immune system might provide additional improvements in clinical outcomes.[3,4]

Macrolide antibiotics, such as azithromycin, clarithromycin, and erythromycin, are widely available and their safety is well established. In addition to antibacterial properties, they are known to have immunomodulatory activity, decreasing production of pro-inflammatory cytokines and inhibiting neutrophil activation.[5–7] They are widely used both in bacterial pneumonia due to their antimicrobial activity and in chronic inflammatory lung disease due to their immunomodulatory effects.[8–10] In

Research in context

Evidence before this study

Azithromycin is commonly used in patients with COVID-19 for either its antimicrobial, anti-inflammatory, or purported antiviral activity. We searched MEDLINE, Embase, bioRxiv, medRxiv, and the WHO International Clinical Trials Registry Platform, from Sept 1, 2019, up to Nov 12, 2020, for completed clinical trials published in any language evaluating the effect of azithromycin or other macrolide antibiotics in patients with COVID-19. We used the search terms ("COVID.mp." OR "COVID-19.mp." OR "SARS-CoV-2.mp." OR "2019-nCoV.mp." OR "coronavirus/" or "CORONAVIRUS.mp.") AND ("azithromycin.mp." OR "macrolide.mp."), filtered by randomised controlled trials according to validated filters. We identified three published randomised clinical trials (two at low risk of bias and one with some concerns due to limited information on the randomisation process) that compared the effect of azithromycin (500 mg once a day) to usual care in patients admitted to hospital with COVID-19. In all three studies, all patients also received hydroxychloroquine. None of the three studies, which in combination included 1223 patients, found differences in mortality or odds of clinical improvement; however, all were underpowered to exclude moderate but clinically relevant treatment effects.

Added value of this study

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is a large, randomised trial evaluating the effect of azithromycin monotherapy on mortality in patients admitted to hospital with COVID-19. We found no significant difference between the azithromycin group and the usual care group in 28-day all-cause mortality, the probability of discharge alive within 28 days, or, among the patients who were not receiving invasive mechanical ventilation at randomisation, the probability of progressing to the composite outcome of invasive mechanical ventilation or death. We saw no evidence of clinical benefit of azithromycin in any patient subgroup.

Implications of all the available evidence

Azithromycin should not be used to treat patients admitted to hospital with COVID-19 unless there is a clear antimicrobial indication.

addition, azithromycin has in-vitro antiviral activity against a range of viruses and has been reported to inhibit SARS-CoV-2 replication in Vero cells and human epithelial cells at concentrations (50% effective concentration 2·12 μM) that are achieved in lung tissue with a dose of 500 mg once per day.[11–13]

For the **protocol, statistical analysis plan, and additional information** see https://www.recoverytrial.net

The use of macrolides in influenza-associated pneumonia has been associated with a faster reduction in inflammatory cytokines and, in combination with naproxen, decreased mortality.[14–16] However, randomised trials have so far not shown convincing clinical benefit of macrolides in COVID-19.[17–19] Here, we report the results of a randomised controlled trial of azithromycin in which we aimed to assess whether azithromycin improves clinical outcomes in patients admitted to hospital with COVID-19.

Methods

Study design and participants

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is an investigator-initiated, individually randomised, controlled, open-label, adaptive platform trial to evaluate the effects of potential treatments in patients admitted to hospital with COVID-19. Details of the trial design and results for other possible treatments (dexamethasone, hydroxychloroquine, and lopinavir–ritonavir) have been published previously.[3,20,21] The trial is underway at 176 hospitals in the UK (appendix pp 2–22), supported by the National Institute for Health Research (NIHR) Clinical Research Network. The trial is coordinated by the Nuffield Department of Population Health at the University of Oxford (Oxford, UK), the trial sponsor. The trial is done in accordance with the principles of the International Conference on Harmonisation–Good Clinical Practice guidelines and approved by the UK Medicines and Healthcare products Regulatory Agency and the Cambridge East Research Ethics Committee (20/EE/0101). The protocol, statistical analysis plan, and additional information are available on the study website. Although the azithromycin, dexamethasone, hydroxychloroquine, lopinavir–ritonavir, convalescent plasma, and tocilizumab groups have now been stopped, the trial continues to study the effects of REGN-COV2 (a combination of two monoclonal antibodies directed against SARS-CoV-2 spike glycoprotein), aspirin, and colchicine. Other treatments might be studied in future.

Patients admitted to hospital were eligible for the study if they had clinically suspected or laboratory confirmed SARS-CoV-2 infection and no medical history that might, in the opinion of the attending clinician, put the patient at substantial risk if they were to participate in the trial. Initially, recruitment was limited to patients aged at least 18 years, but from May 9, 2020, the age limit was removed. Patients with known prolonged QTc interval or hypersensitivity to a macrolide antibiotic and those already receiving chloroquine or hydroxychloroquine were excluded from random assignment between azithromycin and usual care.

Written informed consent was obtained from all patients, or a legal representative if they were too unwell or unable to provide consent.

Randomisation and masking

Baseline data were collected using a web-based case report form that included demographics, amount of respiratory support, major comorbidities, suitability of the study treatment for a particular patient, and treatment availability at the study site (appendix pp 23–25). Eligible and consenting patients were assigned to either usual standard of care or usual standard of care plus azithromycin or one of the other available RECOVERY treatment groups using web-based simple (unstratified) randomisation with allocation concealed until after randomisation (appendix pp 23–25). Randomisation to usual care was twice that of any of the active treatment groups the patient was eligible for (eg, 2:1 in favour of usual care if the patient was eligible for only one active group, 2:1:1 if the patient was eligible for two active groups). For some patients, azithromycin was unavailable at the hospital at the time of enrolment or a macrolide antibiotic was considered by the managing physician to be either definitely indicated or definitely contraindicated. These patients were excluded from the randomised comparison between azithromycin and usual care. Patients allocated to azithromycin were to receive azithromycin 500 mg by mouth, nasogastric tube, or intravenous injection once a day for 10 days or until discharge, if sooner. Allocated treatment was prescribed by the managing doctor. Azithromycin was supplied from routine National Health Service (NHS) stocks.

For eligible participants, factorial randomisations were introduced such that participants could simultaneously be randomly assigned to convalescent plasma versus REGN-COV2 versus usual care and to aspirin versus usual care (appendix pp 23–25). Within 21 days of initial random assignment, participants with evidence of hypoxia and inflammation could be additionally randomly assigned to tocilizumab versus usual care alone. Participants and local study staff were not masked to the allocated treatment. The steering committee, investigators, and all others involved in the trial were masked to the outcome data during the trial.

Procedures

A single online follow-up form was completed when participants were discharged from hospital, died, or at 28 days after randomisation, whichever occurred earliest (appendix pp 29–35). Information was recorded on adherence to allocated study treatment, receipt of other COVID-19 treatments, duration of admission, receipt of respiratory or renal support, and vital status (including cause of death). In addition, routine health-care and registry data were obtained, including information on vital status (with date and cause of death), discharge from hospital, receipt of respiratory support, or renal replacement therapy. Details of how this information was used to derive baseline characteristics and clinical outcomes are provided in the appendix (pp 112–31).

Outcomes

Outcomes were assessed at 28 days after randomisation, with further analyses specified at 6 months. The primary outcome was 28-day all-cause mortality. Secondary outcomes were time to discharge from hospital and, among patients not on invasive mechanical ventilation at randomisation, invasive mechanical ventilation (including extracorporeal membrane oxygenation) or death. Prespecified subsidiary clinical outcomes were cause-specific mortality, use of haemodialysis or haemofiltration, major cardiac arrhythmia (recorded in a subset), and receipt and duration of ventilation. Among those on invasive mechanical ventilation at randomisation, a subsidiary clinical outcome of successful cessation of invasive mechanical ventilation was defined as cessation within (and survival to) 28 days. Information on suspected serious adverse reactions was collected in an expedited manner to comply with regulatory requirements.

Statistical analysis

An intention-to-treat comparison was made between patients randomly assigned to azithromycin and those

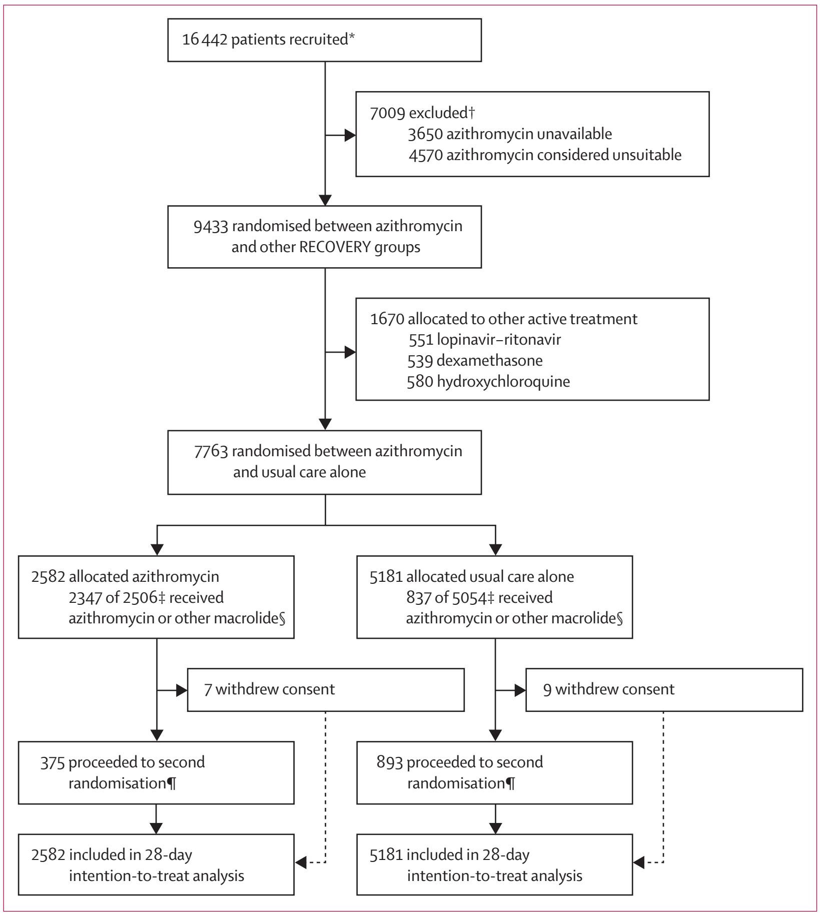

Figure 1: **Trial profile**

*Number recruited overall during the period that participants could be recruited into the azithromycin comparison. †Some patients were included in both of the below groups. ‡2506 (97%) of those allocated to azithromycin and 5054 (98%) of those allocated to usual care had a complete follow-up at time of analysis. §3993 patients were additionally randomly assigned to convalescent plasma versus REGN-COV2 versus control (1320 [51·1%] patients allocated to azithromycin versus 2673 [51·6%] patients allocated usual care) and 975 patients were additionally randomly assigned to aspirin versus usual care (323 [12·5%] patients allocated to azithromycin versus 652 [12·6%] patients allocated usual care). ¶Includes 198 (7·7%) of 2582 patients in the azithromycin group and 450 (8·7%) of 5181 patients in the usual care group allocated to tocilizumab.

randomly assigned to usual care but for whom azithromycin was both available and suitable as a treatment. For the primary outcome of 28-day mortality, the log-rank observed minus expected statistic and its variance were used to both test the null hypothesis of equal survival curves (ie, the log-rank test) and to calculate the one-step estimate of the mortality rate ratio. We constructed Kaplan-Meier survival curves to display cumulative mortality over the 28-day period. We used similar methods to analyse time to hospital discharge and successful cessation of invasive mechanical ventilation, with patients who died in hospital right-censored on day 29. Median time to discharge was derived from Kaplan-Meier estimates. For the prespecified composite secondary outcome of invasive mechanical ventilation or death within 28 days (among those not receiving invasive mechanical ventilation at randomisation) and the subsidiary clinical outcomes of receipt of ventilation and use of haemodialysis or haemofiltration, the precise dates were not available and so the risk ratio was estimated instead.

Prespecified analyses of the primary outcome were done separately in six subgroups defined by characteristics at the time of random assignment: age, sex, ethnicity, days since symptom onset, level of respiratory support, and use of corticosteroids (appendix p 105). Observed effects within subgroup categories were compared using a χ^2 test for heterogeneity or trend, in accordance with the prespecified analysis plan.

Estimates of rate and risk ratios are shown with 95% CIs. All p values are two-sided and are shown without adjustment for multiple testing. The full database is held by the study team who collected the data from study sites and did the analyses at the Nuffield Department of Population Health (University of Oxford, Oxford, UK).

As stated in the protocol, appropriate sample sizes could not be estimated when the trial was being planned at the start of the COVID-19 pandemic as it was unknown how large the epidemic would become (appendix p 26). As the trial progressed, the trial steering committee, whose members were unaware of the results of the trial comparisons, determined that sufficient patients should be enrolled to provide at least 90% power at a two-sided p value of 0·01 to detect a clinically relevant proportional reduction in the primary outcome of 20% between the two groups. Consequently, on Nov 27, 2020, the steering committee, masked to the results, closed recruitment to

	Azithromycin (n=2582)	Usual care (n=5181)
Age, years	65·4 (15·6)	65·2 (15·7)
<70*	1508 (58%)	3014 (58%)
≥70 to <80	615 (24%)	1167 (23%)
≥80	459 (18%)	1000 (19%)
Sex		
Men	1604 (62%)	3215 (62%)
Women†	978 (38%)	1966 (38%)
Ethnicity		
White	1961 (76%)	3978 (77%)
Black, Asian, and minority ethnic	372 (14%)	737 (14%)
Unknown	249 (10%)	466 (9%)
Number of days since symptom onset	8 (5–11)	8 (5–11)
Number of days since admission to hospital	2 (1–4)	2 (1–4)
Respiratory support received		
No oxygen received	490 (19%)	918 (18%)
Oxygen only‡	1940 (75%)	3963 (76%)
Invasive mechanical ventilation	152 (6%)	300 (6%)
Previous diseases		
Diabetes	700 (27%)	1433 (28%)
Heart disease	693 (27%)	1350 (26%)
Chronic lung disease	621 (24%)	1313 (25%)
Tuberculosis	3 (<1%)	16 (<1%)
HIV	7 (<1%)	22 (<1%)
Severe liver disease§	45 (2%)	65 (1%)
Severe kidney impairment¶	155 (6%)	334 (6%)
Any of the above	1507 (58%)	3013 (58%)
Use of corticosteroids		
Yes	1567 (61%)	3171 (61%)
No	182 (7%)	397 (8%)
Not asked or missing‖	833 (32%)	1613 (31%)
SARS-CoV-2 test result		
Positive	2350 (91%)	4743 (92%)
Negative	202 (8%)	386 (7%)
Unknown	30 (1%)	52 (1%)

Data are mean (SD), n (%), or median (IQR). SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. *Includes 26 children (<18 years). †Includes 25 pregnant women. ‡Includes non-invasive ventilation. §Defined as requiring ongoing specialist care. ¶Defined as estimated glomerular filtration rate <30 mL/min per 1·73 m². ‖Information on use of corticosteroids was collected from June 18, 2020, onwards, following announcement of the results of the dexamethasone comparison from the RECOVERY trial.

Table 1: **Baseline characteristics**

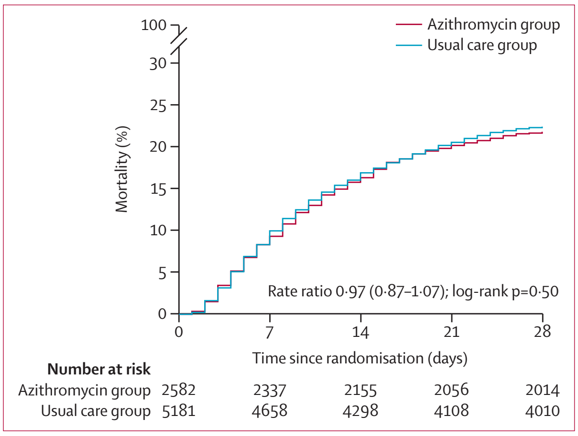

Figure 2: **Effect of allocation to azithromycin on 28-day mortality**

the azithromycin comparison as sufficient patients had been enrolled.

Analyses were done using SAS, version 9.4, and R, version 3.4.0. This trial is registered with ISRCTN, 50189673, and ClinicalTrials.gov, NCT04381936.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between April 7 and Nov 27, 2020, 9433 (57%) of 16 442 patients enrolled in the RECOVERY trial were eligible to be randomly allocated to azithromycin (ie, azithromycin was available in the hospital at the time and the attending clinician was of the opinion that the patient had no known indication for or contraindication to azithromycin, figure 1, appendix p 38). 2582 patients were randomly allocated to azithromycin and 5181 were randomly allocated to usual care, with the remainder being randomly allocated to one of the other treatment groups. The mean age of study participants in this comparison was 65·3 years (SD 15·7) and the median time since symptom onset was 8 days (IQR 5–11; table 1; appendix p 38).

The follow-up form was completed for 2506 (97%) patients in the azithromycin group and 5054 (98%) patients in the usual care group. Among patients with a completed follow-up form, 2269 (91%) allocated to azithromycin versus 68 (1%) allocated to usual care received at least one dose, and 2347 (94%) versus 837 (17%) received any macrolide antibiotic (appendix p 39). The median duration of treatment with azithromycin was 6 days (IQR 3–10). Use of other treatments for COVID-19 was similar among patients allocated azithromycin and among those allocated usual care, with more than half receiving a corticosteroid, about a quarter receiving remdesivir, about a fifth receiving convalescent plasma, and about a twelfth receiving tocilizumab or sarilumab (appendix p 39).

We observed no significant difference in the proportion of patients who met the primary outcome of 28-day mortality between the two randomised groups (561 [22%] of 2582 patients in the azithromycin group *vs* 1162 [22%] of 5181 patients in the usual care group; rate ratio 0·97, 95% CI 0·87–1·07; p=0·50; figure 2). We observed similar results across all prespecified subgroups (figure 3). In an exploratory analysis restricted to the 7093 (91%) of 7763 patients with a positive SARS-CoV-2 test result, the result was similar (rate ratio 0·95, 95% CI 0·86–1·06; p=0·38).

	Azithromycin group	Usual care group	Rate ratio (95% CI)
Age, years (χ^2_1=0·9; p=0·34)			
<70	173/1508 (11%)	341/3014 (11%)	1·02 (0·85–1·23)
≥70 to <80	206/615 (33%)	399/1167 (34%)	0·98 (0·83–1·16)
≥80	182/459 (40%)	422/1000 (42%)	0·91 (0·76–1·08)
Sex (χ^2_1=1·0; p=0·32)			
Men	391/1604 (24%)	782/3215 (24%)	1·00 (0·89–1·13)
Women	170/978 (17%)	380/1966 (19%)	0·90 (0·75–1·07)
Ethnicity (χ^2_1=0·4; p=0·54)			
White	458/1961 (23%)	936/3978 (24%)	0·99 (0·89–1·11)
Black, Asian, and minority ethnic	66/372 (18%)	145/737 (20%)	0·90 (0·68–1·20)
Days since symptom onset (χ^2_1=0·0; p=0·91)			
≤7	289/1163 (25%)	599/2354 (25%)	0·98 (0·85–1·12)
>7	272/1418 (19%)	558/2812 (20%)	0·96 (0·83–1·11)
Respiratory support at randomisation (χ^2_1=0·1; p=0·70)			
No oxygen received	66/490 (13%)	120/918 (13%)	1·02 (0·76–1·39)
Oxygen only*	430/1940 (22%)	908/3963 (23%)	0·97 (0·86–1·09)
Invasive mechanical ventilation	65/152 (43%)	134/300 (45%)	0·94 (0·70–1·27)
Use of corticosteroids (χ^2_1=1·1; p=0·30)			
Yes	332/1567 (21%)	682/3171 (22%)	0·99 (0·87–1·13)
No	26/182 (14%)	72/397 (18%)	0·78 (0·51–1·20)
Not recorded	202/828 (24%)	404/1600 (25%)	0·95 (0·80–1·13)
All participants	**561/2582 (22%)**	**1162/5181 (22%)**	**0·97 (0·87–1·07)**
			p=0·50

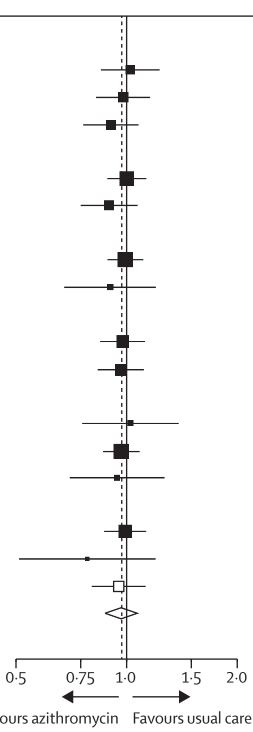

Figure 3: **Effect of allocation to azithromycin on 28-day mortality by baseline characteristics**
Subgroup-specific rate ratio estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to 95% CIs. The ethnicity, days since onset, and use of corticosteroids subgroups exclude those with missing data, but these patients are included in the overall summary diamond. Information on use of corticosteroids was collected from June 18, 2020, onwards following announcement of the results of the dexamethasone comparison from the RECOVERY trial. *Includes patients receiving non-invasive ventilation.

	Azithromycin (n=2582)	Usual care (n=5181)	RR (95% CI)	p value
Primary outcome				
28-day mortality	561 (22%)	1162 (22%)	0·97 (0·87–1·07)	0·50
Secondary outcomes				
Time to being discharged alive, days	10 (5 to >28)	11 (5 to >28)	NA	NA
Discharged from hospital within 28 days	1788 (69%)	3525 (68%)	1·04 (0·98–1·10)	0·19
Receipt of invasive mechanical ventilation or death*	603/2430 (25%)	1273/4881 (26%)	0·95 (0·87–1·03)	0·24
Invasive mechanical ventilation	211/2430 (9%)	461/4881 (9%)	0·92 (0·79–1·07)	0·29
Death	496/2430 (20%)	1028/4881 (21%)	0·97 (0·88–1·07)	0·52
Subsidiary clinical outcomes				
Receipt of ventilation†	226/1368 (17%)	491/2705 (18%)	0·91 (0·79–1·05)	0·20
Non-invasive ventilation	214/1368 (16%)	467/2705 (17%)	0·91 (0·78–1·05)	0·19
Invasive mechanical ventilation	57/1368 (4%)	115/2705 (4%)	0·98 (0·72–1·34)	0·90
Successful cessation of invasive mechanical ventilation‡	54/152 (36%)	96/300 (32%)	1·15 (0·82–1·62)	0·42
Use of haemodialysis or haemofiltration§	105/2539 (4%)	224/5102 (4%)	0·94 (0·75–1·18)	0·61

Data are n (%), median (IQR), or n/N (%), unless otherwise indicated. RR=rate ratio for the outcomes of 28-day mortality, hospital discharge, and successful cessation of invasive mechanical ventilation, and risk ratio for other outcomes. NA=not applicable. *Analyses exclude those on invasive mechanical ventilation at randomisation. †Analyses exclude those on any form of ventilation at randomisation. ‡Analyses restricted to those on invasive mechanical ventilation at randomisation. §Analyses exclude those on haemodialysis or haemofiltration at randomisation.

Table 2: **Effect of allocation to azithromycin on key study outcomes**

Allocation to azithromycin was associated with a similar time until discharge from hospital alive as usual care (median 10 days [IQR 5 to >28] *vs* 11 days [5 to >28]) and a similar probability of discharge alive within 28 days (69% *vs* 68%, rate ratio 1·04, 95% CI 0·98–1·10; p=0·19; table 2). Among those not on invasive mechanical ventilation at baseline, the number of patients progressing to the prespecified composite secondary outcome of invasive mechanical ventilation or death among those allocated to azithromycin was similar to that among those allocated to usual care (25% *vs* 26%, risk ratio 0·95, 95% CI 0·87–1·03; p=0·24; table 2). Allowing for multiple testing in interpretation of the results, there was no evidence that the effect of allocation to azithromycin versus usual care on time until discharge from hospital alive or on invasive mechanical ventilation or death differed between prespecified subgroups of patients (appendix pp 43–44).

We found no significant differences in the prespecified subsidiary clinical outcomes of cause-specific mortality (appendix p 40), use of ventilation, successful cessation of invasive mechanical ventilation, or need for renal dialysis or haemofiltration (table 2). We observed no significant differences in the frequency of new cardiac arrhythmias (appendix p 41). There was one report of a serious adverse reaction believed to be related to azithromycin: a case of pseudomembranous colitis from which the patient recovered with standard treatment.

Discussion

The results of this large, randomised trial show that azithromycin is not an effective treatment for patients admitted to hospital with COVID-19. Allocation to azithromycin was not associated with reductions in mortality, duration of hospital stay, or the risk of being ventilated or dying for those not on ventilation at baseline. These results were consistent across the prespecified subgroups of age, sex, ethnicity, duration of symptoms before randomisation, level of respiratory support at randomisation, or use of corticosteroids at randomisation.

Azithromycin was proposed as a treatment for COVID-19 on the basis of its immunomodulatory activity.[7] Although no major organisation or professional society has recommended the routine use of azithromycin in COVID-19 unless there is evidence of bacterial superinfection, it has nevertheless been used widely in patients with COVID-19, particularly in combination with hydroxychloroquine.[22–24] Macrolides have long been suggested as potential therapies for inflammatory viral pneumonias but this hypothesis has been based on in-vitro, animal, and observational data, with very little evidence of benefit in clinical trials.[13–15] The benefit of dexamethasone in patients with COVID-19 requiring respiratory support suggests that inflammation has a causal role in mortality.[3] Noting that the absence of meaningful effect of azithromycin was consistent regardless of whether patients were also being given a corticosteroid or not, we conclude that the immunomodulatory properties of azithromycin are either insufficient in COVID-19.

Macrolides are commonly used to treat bacterial infections of the lower respiratory tract because of their activity against Gram-positive bacteria and atypical pathogens such as *Mycoplasma pneumoniae* and *Legionella* spp, as well as their excellent tissue penetration. More than 75% of patients with COVID-19 who were admitted to hospital in the UK during 2020 were prescribed antibiotics and the widespread clinical use of macrolides in COVID-19 is likely to be driven largely by concerns of bacterial superinfection rather than purported immunomodulatory activity.[25] It is therefore important to highlight that in patients with moderate or severe COVID-19, who might be expected to have some burden of secondary bacterial lung infection, there was no observed clinical benefit of azithromycin use. This absence of meaningful effect could either reflect the relatively low rate of secondary bacterial infection in COVID-19 or the widespread use of β-lactam or other antibiotics, which might have abrogated any antibacterial benefit of allocation to azithromycin in this trial.[26,27] Our results showed that the addition of azithromycin to routine clinical care of patients admitted to hospital with COVID-19 confers no clinical benefit, whether that be anti-inflammatory or antimicrobial. Although we detected no harm to individual patients given azithromycin, there is a risk of harm at a societal level from widespread use of antimicrobial agents. Azithromycin is classified within the WHO Watch Group of Antibiotics (ie, antibiotics that have higher resistance potential and should be prioritised as key targets of antimicrobial stewardship programmes).[28] In light of the new evidence from the RECOVERY trial, the widespread use of macrolides in particular and antibiotics in general in patients with COVID-19 should be questioned.[29]

Strengths of this trial included that it was randomised, had a large sample size, broad eligibility criteria, and more than 98% of patients were followed up for the primary outcome. The trial also had some limitations. Detailed information on laboratory markers of viral load, inflammatory status, immune response, coexistent bacterial infection, or use of non-macrolide antibiotics was not collected, nor was information on radiological or physiological outcomes. Following random assignment, 17% of patients in the usual care group were given azithromycin or another macrolide antibiotic. Although this randomised trial is open label (ie, participants and local hospital staff are aware of the assigned treatment), the outcomes are unambiguous and were ascertained through linkage to routine health data systems (regardless of treatment allocation).

Three other randomised controlled trials have assessed the efficacy of azithromycin for the treatment of COVID-19 in patients admitted to hospital, all of which additionally treated patients with hydroxychloroquine.[17–19] The COALITION I and COALITION II trials found that for patients with COVID-19 who had been admitted to hospital, treatment with azithromycin and hydroxychloroquine was not associated with any improvement in mortality, duration of hospital stay, or clinical status as assessed using an ordinal outcome scale.[17,18] A small trial in Iran that randomly assigned patients to hydroxychloroquine and lopinavir–ritonavir with or without azithromycin also found no significant difference in mortality or intensive care unit admission, but suggested a reduction in duration of hospital stay.[19] The total number of patients in all three previous trials combined was 1223, with 130 deaths. The RECOVERY trial, with 7763 participants and 1723 deaths in this assessment of azithromycin, is well powered to detect modest treatment benefits; however, none were observed.

At the time of writing, 24 trials evaluating the use of macrolides in patients with COVID-19 were registered in the WHO International Clinical Trials Registry Platform, of which three (COALITION I and COALITION II, and Q-PROTECT, a study in patients who had not been admitted to hospital) have published results.[17,18,30] Of the remaining 21, 16 are studying macrolides in inpatients either alone or in combination with other putative treatments, while five are studying macrolides in patients who had not been admitted to hospital with suspected or confirmed COVID-19.

Although our findings do not address the use of macrolides for the treatment of patients with COVID-19 who had not been admitted to hospital with early, mild disease, the results do show that azithromycin is not an effective treatment for patients admitted to hospital with COVID-19.

Contributors

This manuscript was initially drafted by PWH and MJL, further developed by the writing committee, and approved by all members of the trial steering committee. PWH and MJL vouch for the data and analyses, and for the fidelity of this report to the study protocol and data analysis plan. PWH, MM, JKB, LCC, SNF, TJ, KJ, WSL, AMo, KR, EJ, RH, and MJL designed the trial and study protocol. MM, AR, GP-A, CB, BP, DC, AU, AA, ST, BY, RB, SS, DM, RH, the data linkage team at the RECOVERY coordinating centre, and the health records and local clinical centre staff listed in the appendix collected the data. ES, NS, and JRE verified the data and did the statistical analysis. All authors contributed to data interpretation and critical review and revision of the manuscript. PWH and MJL had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Declaration of interests

We declare no competing interests.

Data sharing

The protocol, consent form, statistical analysis plan, definition and derivation of clinical characteristics and outcomes, training materials, regulatory documents, and other relevant study materials are available online. As described in the protocol, the trial steering committee will facilitate the use of the study data and approval will not be unreasonably withheld. De-identified participant data will be made available to bona fide researchers registered with an appropriate institution within 3 months of publication. However, the steering committee will need to be satisfied that any proposed publication is of high quality, honours the commitments made to the study participants in the consent documentation and ethical approvals, and is compliant with relevant legal and regulatory requirements (eg, relating to data protection and privacy). The steering committee will have the right to review and comment on any draft manuscripts before publication. Data will be made available in line with the policy and procedures described on the Nuffield Department of Population Health website Those wishing to request access should complete the online form and e-mail data.access@ndph.ox.ac.uk.

For **trial details** see https://www.recoverytrial.net

For **data access details** see https://www.ndph.ox.ac.uk/data-access

For **online form** see https://www.ndph.ox.ac.uk/files/about/data_access_enquiry_form_13_6_2019.docx

For the **WHO International Clinical Trials Registry Platform** see https://www.who.int/clinical-trials-registry-platform

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