Efficacy and safety of baricitinib or ravulizumab in adult patients with severe COVID-19 (TACTIC-R): a randomised, parallel-arm, open-label, phase 4 trial

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Summary

Background From early in the COVID-19 pandemic, evidence suggested a role for cytokine dysregulation and complement activation in severe disease. In the TACTIC-R trial, we evaluated the efficacy and safety of baricitinib, an inhibitor of Janus kinase 1 (JAK1) and JAK2, and ravulizumab, a monoclonal inhibitor of complement C5 activation, as an adjunct to standard of care for the treatment of adult patients hospitalised with COVID-19.

Methods TACTIC-R was a phase 4, randomised, parallel-arm, open-label platform trial that was undertaken in the UK with urgent public health designation to assess the potential of repurposing immunosuppressants for the treatment of severe COVID-19, stratified by a risk score. Adult participants (aged ≥18 years) were enrolled from 22 hospitals across the UK. Patients with a risk score indicating a 40% risk of admission to an intensive care unit or death were randomly assigned 1:1:1 to standard of care alone, standard of care with baricitinib, or standard of care with ravulizumab. The composite primary outcome was the time from randomisation to incidence (up to and including day 14) of the first event of death, invasive mechanical ventilation, extracorporeal membrane oxygenation, cardiovascular organ support, or renal failure. The primary interim analysis was triggered when 125 patient datasets were available up to day 14 in each study group and we included in the analysis all participants who were randomly assigned. The trial was registered on ClinicalTrials.gov (NCT04390464).

Findings Between May 8, 2020, and May 7, 2021, 417 participants were recruited and randomly assigned to standard of care alone (145 patients), baricitinib (137 patients), or ravulizumab (135 patients). Only 54 (39%) of 137 patients in the baricitinib group received the maximum 14-day course, whereas 132 (98%) of 135 patients in the ravulizumab group received the intended dose. The trial was stopped after the primary interim analysis on grounds of futility. The estimated hazard ratio (HR) for reaching the composite primary endpoint was 1·11 (95% CI 0·62–1·99) for patients on baricitinib compared with standard of care alone, and 1·53 (0·88–2·67) for ravulizumab compared with standard of care alone. 45 serious adverse events (21 deaths) were reported in the standard-of-care group, 57 (24 deaths) in the baricitinib group, and 60 (18 deaths) in the ravulizumab group.

Interpretation Neither baricitinib nor ravulizumab, as administered in this study, was effective in reducing disease severity in patients selected for severe COVID-19. Safety was similar between treatments and standard of care. The short period of dosing with baricitinib might explain the discrepancy between our findings and those of other trials. The therapeutic potential of targeting complement C5 activation product C5a, rather than the cleavage of C5, warrants further evaluation.

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Introduction

SARS-CoV-2 emerged in late 2019 and the outbreak was designated a pandemic in March, 2020. At a time when there were no effective treatments for COVID-19 and no vaccines against SARS-CoV-2, data from China and Italy, and emerging UK data, indicated that COVID-19 manifested as mild-to-moderate respiratory illness in the majority of people, but that approximately 20% of patients with COVID-19 developed severe disease.[1] The progression to severe disease was noted to be contemporaneous with the development of an aggressive adaptive immune response.[1] The TACTIC-R trial was designed in March, 2020, when it was clear that tissue damage in the lungs was associated with spread of the virus through the epithelial barrier and both innate and adaptive effector cascades, including aberrant activation of proinflammatory cytokine networks, the coagulation and complement cascades,

Research in context

Evidence before this study

SARS-CoV-2 emerged in late 2019 and the outbreak was designated a pandemic by WHO on March 11, 2020.
We designed this trial in March, 2020, at which time there were no effective treatments for COVID-19 and no vaccines against SARS-CoV-2. It was imperative to rapidly identify medications with efficacy to reduce mortality and morbidity from COVID-19. Emerging data from China reported that severe COVID-19 developed in susceptible individuals 7–14 days after infection with the virus. Tissue damage appeared to be caused by an aberrant immune response and microangiopathy with thrombosis. Evidence from the SARS-CoV outbreak in 2002–03 and a mouse model of SARS-CoV-2 infection suggested that complement activation contributed significantly to tissue damage. TACTIC-R was designed as an adaptive platform trial that would enable a number of licensed immunosuppressive agents to be evaluated for efficacy in COVID-19. During this period, a number of other clinical trials in COVID-19 were being planned to test immunosuppressives, including dexamethasone and tocilizumab. Two immunosuppressives licensed for use in other diseases were selected for TACTIC-R. The Janus kinase (JAK) inhibitor baricitinib, licensed in the UK for rheumatoid arthritis, atopic dermatitis, and alopecia areata, inhibited signalling from a variety of cytokines, including interleukin-2 (IL-2), IL-6, GM-CSF, IL-12, IL-23, and type I and II inteferons. Baricitinib had also been reported to provide some independent inhibition of receptor-mediated uptake of SARS-CoV-2. The monoclonal complement C5 inhibitor, ravulizumab, licensed in the UK for use in paroxysmal nocturnal haemoglobinuria, atypical haemolytic uremic syndrome, generalised myasthenia gravis, and neuromyelitis optca spectrum disorder, was chosen as a blocker of the amplification of inflammation (C5a) and the cytolytic membrane attack complex (C5b-9). We searched PubMed from database inception to May 20, 2020, for reports published in any language using the search terms ("SARS COV2" AND "baricitinib" AND "randomised clinical trial") OR ("COVID-19" AND "baricitinib" AND "randomised clinical trial") OR ("SARS COV2" AND "ravulizumab" AND "randomised clinical trial") OR ("COVID-19" AND "ravulizumab" AND "randomised clinical trial"). We found no randomised clinical trials for either baricitinib or ravulizumab in COVID-19 at the start of the TACTIC-R trial.

Added value of this study

This is the first clinical trial to have evaluated ravulizumab in patients with moderate COVID-19 (patients who had been admitted to hospital but not given invasive ventilation) and the fourth largest randomised controlled trial to have evaluated baricitinib (RECOVERY had 8156 participants, COV-BARRIER had 1630 participants, and ACTT2 had 1033 participants). TACTIC-R did not show efficacy of baricitinib in COVID-19. However, the relatively small numbers and short dosing period in over 50% of the baricitinib group, might explain the discrepancy between the results of this trial and the results in the RECOVERY trial. TACTIC-R provides no evidence for efficacy of ravulizumab in COVID-19.

Implications of all the available evidence

A randomised controlled trial of zilucoplan, a non-biologic inhibitor of complement C5 activation, also showed no efficacy. However, randomised controlled trials of inhibitors of the complement C5 activation product, C5a, have returned mixed results and require further evaluation. The largest trial evaluating baricitinib in COVID-19 was the RECOVERY trial. Data from this, and a meta-analysis of all the trials evaluating JAK inhibitors (including COV-BARRIER and ACTT2) suggest a modest benefit of treatment with baricitinib in addition to standard of care.

and the development of endothelialitis, sometimes with thrombosis.[2,3]

Cytokine dysregulation is prominent in the pathogenesis of COVID-19 and baricitinib, a selective inhibitor of Janus kinase 1 (JAK1) and JAK2 that is used in the treatment of rheumatoid arthritis, atopic dermatitis, and severe alopecia areata and was considered in the TACTIC-R trial and other studies as a potential treatment option for severe COVID-19 because of its ability to inhibit a broad range of proinflammatory mediators. Unlike other JAK1/2 inhibitors, baricitinib also has a direct antiviral effect by inhibiting endocytic internalisation of SARS-CoV-2.[4] The involvement of complement activation in the pathogenesis of COVID-19 was initially inferred by extrapolation from studies of severe acute respiratory syndrome. A study of SARS-CoV infection in mice demonstrated less severe tissue damage in complement C3-deficient mice than in wild-type mice.[5] SARS-CoV had been shown to activate complement directly via the lectin pathway.[6] In a mouse model of MERS-CoV infection, complement activation was demonstrated by increased levels of circulating C5a and by deposition of components of the membrane attack complex (C5b-9) on bronchiolar epithelial cells, pneumocytes, and infiltrating leucocytes.[7]

The temporal association of the clinical features of COVID-19 with the development of antibodies specific for SARS-CoV-2 spike protein was consistent with complement involvement via the classical pathway of activation. Direct evidence of complement activation at sites of tissue damage in COVID-19 was shown by the deposition of complement components in biopsies of the livedoid rash that is associated with COVID-19, as well as by antemortem and post-mortem lung tissue.[8] Microvascular injury was characterised by endothelial necrosis and thrombosis. Both infectious SARS-CoV-2 virus and pseudovirions colocalised with complement activation products, including C4d, MASP2, and C5b-9, indicating activation of both the early and late complement cascade.[8] A high-throughput proteomic assay showed consistent activation of classical pathway

See Online for appendix 2

components (C1r and C1s), alternative pathway components (factor B and its modulators, factor I and factor H),[9] and C8 alpha chain in the sera of patients with severe COVID-19. These insights contributed to an emerging model of endothelial infection and dysfunction, including complement-induced thrombosis, leading to multiple organ failure.[2,3,10,11]

Eculizumab and ravulizumab are monoclonal IgG2/4 kappa antibodies that share the same antigen-binding site. These antibodies recognise an epitope on complement component C5 and the binding of either antibody inhibits its cleavage into C5a and C5b. This inhibition reduces amplification of the innate inflammatory response through decreased chemoattraction by C5a and inhibits the assembly of the membrane attack complex, thereby reducing complement-mediated cytotoxicity. Ravulizumab is licensed for use in paroxysmal nocturnal haemoglobinuria, a rare acquired anaemia in which red blood cells are destroyed by aberrant activation of complement, and also for atypical haemolytic uraemic syndrome, in which a systemic thrombotic microangiopathy is caused by dysregulated complement activation.[12] Ravulizumab differs from eculizumab in the constant region of the immunoglobulin and has a longer half-life of approximately 50 days.

In the TACTIC-R trial, we addressed the hypothesis that JAK1/2-dependent cytokines and terminal complement activation contribute to disease severity in COVID-19. We investigated whether the addition of either baricitinib (for up to 14 days) or a single ravulizumab infusion to standard-of-care treatment improved outcomes in patients hospitalised with severe COVID-19.

Methods

Study design

TACTIC-R was designed as a randomised, controlled, parallel-arm, open-label, phase 4 platform trial to assess the efficacy of a series of repurposed medications in COVID-19. Interim analyses were integral to the platform. This design enabled the independent data monitoring committee to terminate any arm of the study promptly if efficacy, futility, or a new safety signal was demonstrated. TACTIC-R was conducted at 22 secondary care hospitals in the UK. The protocol was designed by the TACTIC Trial Management Group.[13] The trial documents were granted favourable approval by the Cambridge Central Research Ethics Committee and approved by the UK Medicines and Healthcare Products Regulatory Agency. The trial was registered on ClinicalTrials.gov (NCT04390464).

Participants

We recruited adult patients (aged ≥18 years) admitted to hospital with clinical features that were judged by the clinical team to be strongly suggestive of COVID-19-related disease (with or without a positive PCR test). A full list of inclusion and exclusion criteria is provided in the protocol (appendix 2 pp 26–27). Screened patients were stratified by a severity risk score derived by summing one point for each of the following features on admission:[14] male sex, non-White ethnicity, diabetes, hypertension, neutrophil count of more than $8{\cdot}0\times10^9$ per L, age older than 40 years, C-reactive protein concentration of more than 40 mg/L, and radiographic severity score of more than 3. Patients were eligible for the study if the risk score was 4 or more or if the risk score was 3 with a radiographic score of more than 3, which were taken to indicate approximately a 40% risk of admission to an intensive care unit (ICU) or death.[14] Written, informed consent was obtained from the patient, or from a legally designated representative when patients lacked capacity because of the severity of their condition, with additional consent from the patient at the earliest opportunity.

Randomisation and masking

Participants were randomly assigned by clinical investigators at the participating sites in a 1:1:1 ratio to standard of care alone, standard of care plus baricitinib, or standard of care plus ravulizumab using an independent, online application (www.sealedenvelope.com). We used a block, open-label randomisation, with block sizes that were randomly either six or nine, stratified by site.

Procedures

Baricitinib was administered as a 4 mg oral daily dose (two 2 mg tablets) for 14 days, or until the patient was discharged from hospital or met other cessation criteria. A reduced daily dose of 2 mg was given in patients aged 75 years or older or with an estimated Cockcroft-Gault creatinine clearance of 30–60 mL/min (inclusive) at screening. In the ravulizumab group, the drug was administered as a single intravenous infusion, at a concentration of 5 mg/mL through a 0·2 µm filter. A weight-based regimen was used to deliver 2·4 g ravulizumab for people with a bodyweight of 40–60 kg, 2·7 g for people with a bodyweight of 60–100 kg, and 3·0 g for people with a bodyweight of more than 100 kg.

Patients were evaluated at screening (1 or 2 days before baseline: review of medical history and examination, medication review, full blood count and differential of white cell count, calculated Cockcroft-Gault creatinine clearance, alanine transaminase or aspartate transaminase concentration, C-reactive protein concentration, pregnancy test [blood, for patients in whom pregnancy is possible], chest x-ray, and Eastern Cooperative Oncology Group [ECOG] and Medical Research Council Dyspnoea Scale [MRC] scores), at baseline (day 0 [at first dose]: days since onset of symptoms, demographics, anthropomorphic data, vital signs, position on 7-point ordinal scale, SARS-CoV-2 PCR result [if available], extraction of clinical data from medical records, and ECOG and MRC scores), and then daily until day 14 or discharge, whichever

was sooner (days 1–14: vital signs, position on the 7-point ordinal scale, SARS-CoV-2 PCR result [if available], and review of adverse events). Additional assessments were made on days 2, 6, and 14 (±2 days), which were full blood count and differential of white cell count, calculated Cockcroft-Gault creatinine clearance, alanine transaminase or aspartate transaminase concentations, and retrieval of clinical data. Further evaluations were done on day 28 and day 90 (±2 days), which were discharge status, vaccination status (ravulizumab group only), return to normal function status, mortality status, adverse event reporting, and ECOG and MRC scores. A full description of the procedures is provided in the protocol (appendix 2 pp 33–37).

Outcomes

The primary endpoint was the time from randomisation to incidence (up to and including day 14) of the first event of death, invasive mechanical ventilation (IMV), extracorporeal membrane oxygenation (ECMO), cardiovascular organ support (balloon pump or inotropes), or renal failure (estimated creatinine clearance by Cockcroft-Gault formula <15 mL/min or haemofiltration or dialysis). A competing risk event occurred if the patient was discharged from hospital before a primary endpoint event and a censored observation occurred if the patient reached day 15, or withdrew, before a primary event or discharge. Secondary endpoints for formal statistical inference, in order of importance, were as follows: clinical status, as assessed on a 7-point ordinal scale at day 14; time to discharge from hospital; all-cause mortality at day 28; time to pulse-oximetric oxygen saturation of more than 94% on room air; duration of oxygen therapy in days; time to clinical improvement (defined as >2 point improvement from day 1 on the 7-point ordinal scale); incidence of adverse events of special interest (AESI; venous thromboembolism or new infection requiring antimicrobials); duration of hospitalisation (time to death, discharge, or observing the primary event) from the date of admission; and time to first negative SARS-CoV-2 PCR test. The points on the pulmonary 7-point ordinal scale were as follows: (1) death; (2) IMV or ECMO; (3) non-invasive ventilation or high-flow oxygen; (4) low-flow oxygen; (5) hospitalised, no supplemental oxygen; (6) discharged from hospital, normal activities not resumed; and (7) discharged from hospital, normal activities resumed. In addition, the time to each of the individual components of the composite primary endpoint being met was evaluated. Exploratory endpoints included changes in biochemical predictors and immuno-inflammatory signatures of therapeutic response.

All serious adverse events (SAEs), including serious adverse reactions (SARs) and suspected unexpected serious adverse reactions (SUSARs), were collected. The safety population included all patients who were randomly assigned to a group. The trial was designed not to collect clinical features of progressive COVID-19 and associated complications as adverse events. Data on two AESI, new infection requiring antimicrobial treatment and venous thromboembolism, were collected. We recorded SAEs and AESI at screening, baseline, daily until day 14 (or discharge), and then at day 28 and day 90 (data were collected by a telephone and by retrieval of clinical data from the whole medical record after discharge). The occurrence of venous thromboembolism was determined from imaging results (ultrasound or MRI with contrast) or from autopsy reports.

Statistical analysis

The TACTIC-R trial was designed in March, 2020, at which point there was a dearth of evidence to inform power calculations. We used an adaptive design with an interim analysis planned after 125 patients were recruited to each group. There were provisional plans for second and third interim analyses to be done after recruitment of 229 and 469 patients per group. This decision on the timing of interim analyses was informed by Bayesian posterior distributions for the treatment effects on the primary outcome of each experimental treatment. Specifically, the independent data monitoring committee was provided with estimates of the probabilities for each treatment group relative to control relating to efficacy (hazard ratio [HR] <1·00), moderate or greater efficacy (HR <0·80), similarity (HR >0·80 and <1·25), and harm (HR >1·00). At the first interim analysis, the data monitoring committee reviewed the primary outcome and safety data and determined whether recruitment to each treatment group should cease due to a demonstration

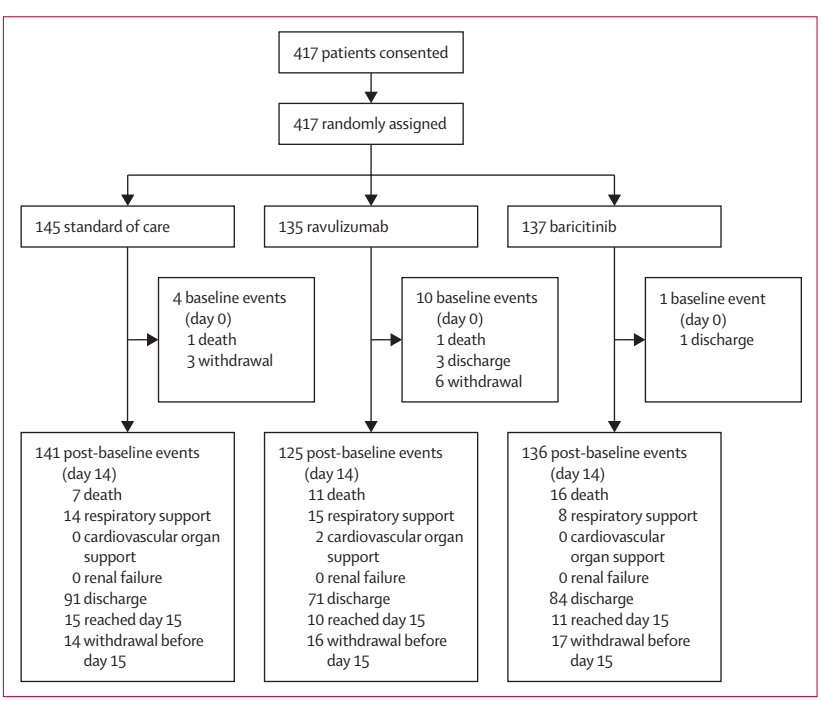

Figure 1: **Trial profile**

	Standard of care	Ravulizumab	Baricitinib
Participants, n	145	135	137
Mean age, years	59·9 (13·0)	62·2 (11·1)	61·4 (12·4)
Median age, years	60 (51·0–68·0)	62 (53·5–69·5)	61 (54·0–70·0)
Sex			
Male	98 (68%)	92 (68%)	108 (79%)
Female	47 (32%)	43 (32%)	29 (21%)
Ethnicity, n	145	135	136
Asian or Asian British	18 (12%)	16 (12%)	14 (10%)
Black or Black British	15 (10%)	10 (7%)	16 (12%)
Mixed	1 (1%)	0	0
White	102 (70%)	100 (74%)	96 (71%)
Other ethnic group	9 (6%)	9 (7%)	10 (7%)
BMI, n	133	121	122
Mean BMI (SD)	33·6 (10·2)	32·2 (7·4)	31·5 (6·0)
Median BMI (IQR)	30·8 (27·8–36·2)	31·1 (27·1–35·3)	30·4 (27·4–35·2)
Comorbidities			
Hypertension	60 (41%)	71 (53%)	68 (50%)
Diabetes	41 (28%)	43 (43%)	41 (30%)
7-point ordinal scale, n			
1 (death)	0	0	0
2 (IMV or ECMO)	2 (1%)	0	0
3 (non-invasive ventilation or high-flow oxygen)	70 (48%)	73 (54%)	69 (50%)
4 (low-flow oxygen)	65 (45%)	52 (39%)	65 (47%)
5 (hospitalised, no supplemental oxygen)	8 (6%)	10 (7%)	3 (2%)
6 (discharged, normal activities not resumed)	0	0	0
7 (discharged, normal activities resumed)	0	0	0
Baseline dyspnoea score, n	122	115	112
1 (not troubled by breathlessness except on strenuous exercise)	34 (28%)	21 (18%)	24 (21%)
2 (short of breath when hurrying on the level or walking up a slight hill)	8 (7%)	9 (8%)	7 (6%)
3 (walks slower than most people on the level, stops after a mile or so)	12 (10%)	9 (8%)	18 (16%)
4 (stops for breath after walking about 100 m or after a few minutes on level ground)	14 (11%)	17 (15%)	14 (12%)
5 (too breathless to leave the house or breathless when undressing)	54 (44%)	59 (51%)	49 (44%)
Baseline ECOG, n	122	115	112
0 (fully active; pre-disease performance without restriction)	31 (25%)	20 (17%)	21 (19%)
1 (restricted in physically strenuous activity but ambulatory and able to carry out work of light and sedentary nature)	10 (8%)	11 (10%)	6 (5%)
2 (ambulatory and capable of all self-care but unable to carry out any work activities; up and about >50% of waking hours)	13 (11%)	10 (9%)	20 (18%)
3 (capable of only limited self-care; confined to bed or chair >50% of waking hours)	40 (33%)	51 (44%)	47 (42%)
4 (completely disabled; cannot carry out any self-care; totally confined to bed or chair)	28 (23%)	23 (20%)	18 (16%)
5 (dead)	0	0	0
Severity risk score, n	145	135	137
Mean risk score (SD)	4·77 (1·18)	4·87 (1·08)	4·93 (1·01)
Median risk score (IQR)	5 (4–6)	5 (4–5)	5 (4–6)

(Table 1 continues on next page)

of efficacy, futility, or a safety signal. The final analysis was frequentist to avoid any issues with the choice of prior probability distribution and to be readily interpretable. As there were no preceding interim analyses, there was no requirement to account for multiple looks at the data and the comparison was between the two groups versus the standard-of-care treatment, as if the trial had been run as a three-arm conventional trial (with no added or dropped groups). Simulation studies of this blend of Bayesian interim and final frequentist analysis were done and showed satisfactory frequentist operating characteristics, in terms of type I error and power.

The chosen event rate of 20% was based on data from the first 200 admissions with COVID-19 at Kings College Hospital (James Galloway, unpublished). Aside from reaching the end of the 14-day follow-up period, censoring was assumed to be negligible. The trial did not have a fixed sample size.[13] The decision about timing for interim analysis was based on a provisional sample size. This provisional sample size was based on a theoretical study that compared treatment to standard of care with a fixed sample size for two groups. Using 80% power to detect a clinically relevant difference in the primary outcome (one-sided α 0·025), the required sample sizes per group were calculated to be 125 to detect an effect size of 0·5, 229 to detect an effect size of 0·6, and 469 to detect an effect size of 0·7. The statistical properties of the Bayesian interim analysis, stopping guidelines, and sample sizes, in terms of type 1 error and power, were studied subsequently using simulation techniques.

For the primary endpoint, we compared standard of care alone with standard of care plus either baricitinib or ravulizumab using a frequentist Cox proportional hazards model, adjusting for a random-site effect. We applied proportional hazards tests and diagnostics based on weighted residuals to check the assumption of constant HRs.[15] The predictors and subgroups were all binary variables and, therefore, there was no linearity assumption. An intention-to-treat paradigm was adopted and the population included all patients who were randomly assigned, which excluded deaths, discharges, or withdrawals before randomisation. The Fine-Gray method was used to handle the competing event of discharge.[16] The model was fitted across all three groups simultaneously. Each active investigational medicinal product group (baricitinib or ravulizumab) was compared, independently, with standard-of-care treatment. No adjustment for multiple testing of the two active treatment groups was done because, conceptually, two individual studies could have been done to compare each group with standard of care with no adjustment to their statistical significance level. For secondary endpoints, we used a hierarchical approach within each comparison of the active treatment groups to standard of care, with the endpoints ordered as described under Outcomes, and formal statistical

significance was claimed for an endpoint only if all the preceding endpoints were also significant.

We analysed the time-to-event secondary endpoints using Cox proportional hazards models, with the exception of duration of hospitalisation, which estimated the absolute difference of restricted mean survival time up to 14 days from hospital admission. We analysed the 7-point ordinal scale at day 14 using proportional odds logistic regression, adjusting for the baseline value and a random site-level intercept. The risk of AESI was compared by estimating the relative risk (RR). The medians of all possible pairwise differences were tested by Mann-Whitney U test. We performed subgroup analyses for the components of the risk score used to determine eligibility, dichotomised using the thresholds from the risk score. Covariates were individually included as adjusters in the regression model and treatment effects were estimated within each subgroup. We calculated the RRs (95% CI) of AESI according to Altman.[17]

We used R (version 4.1.0) for all analyses and Stan (version 2.21.1) for the Bayesian component. The interim and the final trial statistical analysis plans and reports are provided in appendix 2 (pp 54–82; pp 83–115).

	Standard of care	Ravulizumab	Baricitinib
(Continued from previous page)			
Radiographic score, n	141	127	133
Mean radiographic score (SD)	5·07 (1·63)	4·89 (1·65)	5·17 (1·64)
Median radiographic score (IQR)	5 (4–6)	5 (4–6)	5 (4–7)
Neutrophil-to-lymphocyte ratio, n	144	134	137
Mean ratio (SD)	11·09 (10·61)	9·56 (7·22)	11·12 (13·59)
Median ratio (IQR)	7·6 (5·0–14·3)	7·4 (4·8–11·6)	8·2 (5·2–12·6)
C-reactive protein, n	145	134	137
Mean C-reactive protein concentration (SD), mg/L	128 (72·7)	125 (73·4)	113 (68·1)
Median C-reactive protein concentration (IQR), mg/L	120 (70–169)	118 (66–170)	104 (59–155)
Use of standard-of-care treatment, n	145	135	137
Dexamethasone	124 (86%)	120 (89%)	119 (87%)
Prednisolone	16 (11%)	9 (7%)	14 (10%)
Interleukin-6 receptor blocker	10 (7%)	3 (2%)	7 (5%)
Remdesivir	65 (45%)	57 (42%)	57 (42%)

Data are mean (SD) for normally distributed variables, median (IQR) for variables with a skewed distribution, or n (%) for categorical variables. ECMO=extracorporeal membrane oxygenation. ECOG=Eastern Cooperative Oncology Group performance status. IMV=invasive mechanical ventilation.

Table 1: **Baseline characteristics of the consented trial population and medications given as standard of care for COVID-19**

Role of the funding source

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

Results

Enrolment into TACTIC-R started on May 8, 2020, and was closed on May 7, 2021. We recruited 417 patients across 22 sites in the UK, 145 to the standard-of-care alone group, 137 to the baricitinib group, and 135 to the ravulizumab group (figure 1). The majority of patients (387 [93%] of 417) were recruited during the second wave of the pandemic, in early 2021, by which point dexamethasone had been incorporated into the standard of care.[18,19] Participating sites were not required to complete an eligibility log due to ongoing clinical pressures on staff. Baseline demographics, 7-point scale distribution, dyspnoea score, ECOG performance status, inflammatory blood values, and use of standard-of-care immunosuppressives and antiviral medications were similar between the groups (table 1).

A total of 15 (10%) of 145 in the standard-of-care group, ten (7%) of 135 in the ravulizumab group, and 11 (8%) of 137 in the baricitinib group reached day 15 (censored) of the study (figure 1). The number of patients who were withdrawn at baseline or otherwise before day 15 in each group are shown in figure 1. The reasons for withdrawal were loss to daily follow-up before day 15 (12 in the standard-of-care group, nine in the ravulizumab group, and four in the baricitinib group), withdrawal of patient consent (two in the standard-of-care group, eight in the ravulizumab group, and two in the baricitinib group), diagnosis revised (ie, patient no longer considered to have COVID-19-related disease; one in the standard-of-care group, one in the ravulizumab group, and four in the baricitinib group), withdrawal due to clinical decision (two in the standard-of-care group, two in the ravulizumab group, and one in the baricitinib group), progression to primary endpoint before dosing with investigational medicinal product (one in the ravulizumab group and two in the baricitinib group), occurrence of SARs or SUSARs (none in the standard-of-care group, none in the ravulizumab group, and two in the baricitinib group), confirmed new deep vein thrombosis or pulmonary embolus (two in the baricitinib group; relevant to baricitinib treatment only), and withdrawal due to an adverse event (none in the standard-of-care group, one in the ravulizumab group, and none in the baricitinib group).

Baricitinib was administered daily in tablet form, but only 54 (39%) of 137 patients in the baricitinib group received the maximum 14-day course. Of the 83 (61%) patients who received less than the maximum 14-day course, 40 (48%) received less than five dose day equivalents. 132 (98%) of 135 patients in the ravulizumab group received the intended dose (appendix 1 p 7).

The primary interim analysis was triggered when 125 datasets were available to day 14 in each study group. The data were reviewed by the independent data monitoring committee. The criteria for efficacy were not breached. However, the trial was stopped early for futility since the posterior probability of a negative treatment effect exceeded 80%, in accordance with the protocol.[13] This finding enabled us to conclude that neither investigational medicinal product (as administered in this study) improved treatment compared with standard of

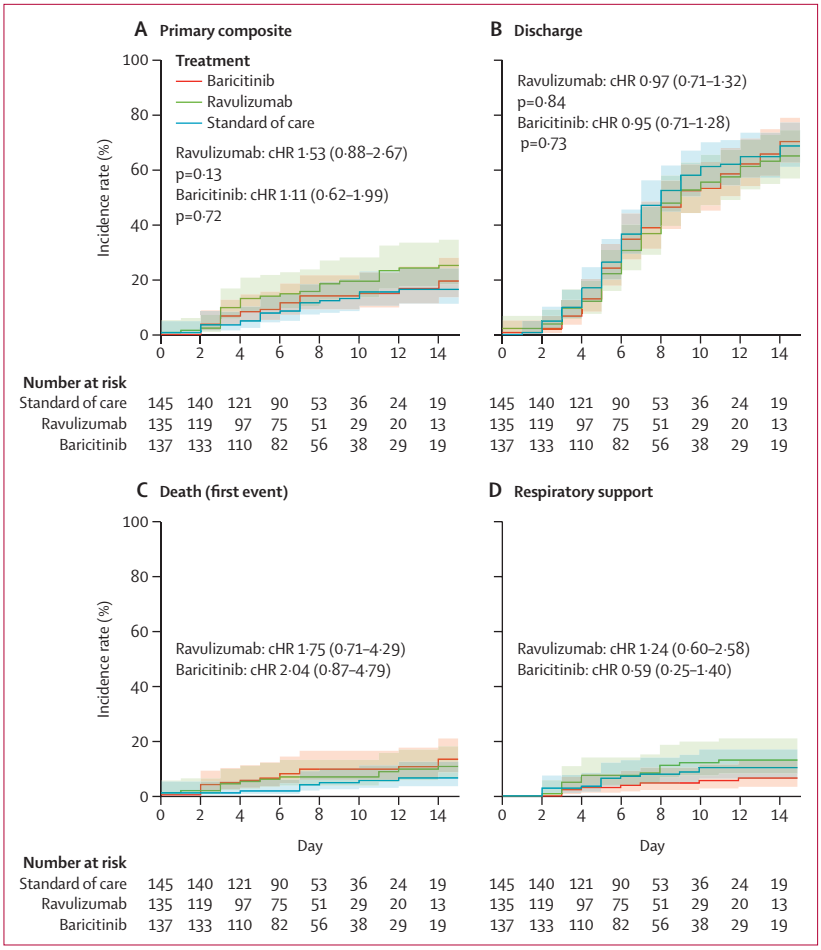

Figure 2: **Cumulative incidence for the primary endpoint and discharge**
(A) Cumulative incidence of the composite primary endpoint: time to incidence (up to and including day 14) of the first event of death, IMV, ECMO, cardiovascular organ support, or renal failure. (B) Cumulative incidence of discharge without a primary endpoint event being reached (to day 14). (C) Cumulative incidence of death, a component of the composite primary endpoint (to day 14). (D) Cumulative incidence of IMV or ECMO, components of the composite primary endpoint (to day 14). There were no cases of renal failure and only two cases of cardiovascular organ support, and these components of the primary composite endpoint are not shown. The inset in each graph shows the conditional hazard ratio for the two investigational medicinal product study groups, each compared with standard of care, adjusting for site. cHR=conditional hazard ratio. ECMO=extracorporeal membrane oxygenation. IMV=invasive mechanical ventilation.

care alone. In addition, the recruitment rate was slowing, making recruitment to a second interim point difficult. This combination of factors prompted the data monitoring committee to recommend termination of the study.

A total of 141 patients in the standard-of-care group, 135 in the ravulizumab group, and 136 in the baricitinib group were included in the primary endpoint after randomisation (figure 2). The median follow-up time to the primary event was 7 (IQR 5–11) days for the standard-of-care group, 7 (4–12) days for the ravulizumab group, and 6 (4–11) days for the baricitinib group. The HR for the primary composite endpoint (time to the first event of death, IMV, ECMO, cardiovascular organ support, or renal failure) was 1·53 (95% CI 0·88–2·67) for the ravulizumab group and 1·11 (0·62–1·99) for the baricitinib group. Figure 2 also displays the breakdown of the primary endpoint into subcomponents. The HR for death was 1·75 (95% CI 0·71–4·29) for the ravulizumab group and 2·04 (0·87–4·79) for the baricitinib group. The HR for respiratory support was 1·24 (95% CI 0·60–2·58) for the ravulizumab group and 0·59 (0·25–1·40) for the baricitinib group. There were no cases of renal support and only two cases of cardiovascular support (in the ravulizumab group). The HR for the competing endpoint, discharge, was 0·97 (0·71–1·32) for the ravulizumab group and 0·95 (0·71–1·28) for the baricitinib group.

The median follow-up of patients in each group was 90 (IQR 61–94) days for the standard-of-care group, 89 (28–92) days for the ravulizumab group, and 90 (28–93) days for the baricitinib group. Analysis of change in the pulmonary 7-point scale revealed no efficacy in either treatment group (appendix 1 p 8). Subgroup analysis of patients reaching the composite primary endpoint did not reveal any significant interaction with sex, ethnicity, baseline severity of risk or radiological scores, presence of diabetes or hypertension, baseline C-reactive protein of more than 40 mg/L, or neutrophil count of more than 8×10^9 per L (appendix 1 pp 9–10). However, the numbers of participants in each subgroup analysed were low, resulting in wide CIs. Further secondary endpoint analyses showed comparable outcomes between the groups (table 2). We noted an improvement in both dyspnoea and ECOG scores between screening (shortly after admission) and baseline data collection (appendix 1 pp 11–12). The low granularity of these scores, together with the relatively low participant numbers in this study, rendered comparison between the investigational medicinal product groups and the standard-of-care group inconclusive.

Analysis of SAEs revealed a total of 35 (21 deaths) SAEs in the standard-of-care group compared with a total of 42 (24 deaths) in the baricitinib group and 41 (18 deaths) in the ravulizumab group (table 3). Progression of COVID-19 pneumonia was more frequently reported as an SAE in the active treatment groups (21 [16%] of 135 patients in the ravulizumab group and 25 [18%] of 137 in the baricitinib group) than in the standard-of-care group (12 [8%] of 145). Superadded bacterial infection was similar in all groups (four [3%] of 145 in the standard-of-care group, three [2%] of 135 in the ravulizumab group, and none in the baricitinib group). No new safety signal emerged (figure 3). The AESI were formally compared between each active treatment group and the standard-of-care group. Three (2%) patients had venous thromboembolic events in the standard-of-care group, compared with ten (7%) in the baricitinib group and four (3%) in the ravulizumab group. The number of events was too few to estimate RR. The RR of new infections requiring antimicrobials was 1·17 (95% CI 0·66–2·10) in the baricitinib group and 1·02 (0·55–1·86) in the ravulizumab group.

Discussion

In this trial, which sought to clarify the effect of JAK1/2 or complement C5 inhibition in severe COVID-19, we found no evidence for efficacy of the JAK1/2 inhibitor baricitinib, but moderate evidence for inefficacy of the long-acting complement C5 inhibitor ravulizumab, when compared with standard of care.

Subgroup analyses for the primary outcome measure should be interpreted in the context of the small patient numbers in each subgroup. The wide CIs for the HR estimates suggest possible bias due to sparse data. There were no differences between the groups in the secondary outcome measures, including change in disease severity (measured with a 7-point ordinal scale) and days to discharge. All-cause mortality was comparable between groups at the end of the trial. However, this study was designed to screen for clinically meaningful efficacy and was not powered to detect small effects.

The efficacy of baricitinib in patients hospitalised with COVID-19 has been suggested in three phase 3 trials: RECOVERY,[20] ACTT2,[21] and COV-BARRIER.[22] ACTT2 (with 1033 participants reported that baricitinib plus remdesivir (*vs* remdesivir alone) reduced median time to recovery in all patients hospitalised with COVID-19 from 8 (95% CI 7–9) to 7 (6–8) days (12·5% improvement; p=0·03).[21] In COV-BARRIER (1630 participants), which recruited adults hospitalised with COVID-19 and randomly assigned them to receive either baricitinib or placebo, all-cause mortality was reduced in the baricitinib group up to 28 days and 60 days.[22] RECOVERY (8156 participants) reported that 28-day mortality was 12% in those given baricitinib compared with 14% in those who received standard of care (age-adjusted rate ratio 0·87; 95% CI 0·77–0·98; p=0·026).[20] A meta-analysis of RECOVERY plus eight earlier trials of a JAK inhibitor in COVID-19 indicated a 20% proportional reduction in mortality (rate ratio 0·80; 95% CI 0·71–0·89). The efficacy of baricitinib in the RECOVERY study was reported to be irrespective of treatment with corticosteroid, remdesivir, or an interleukin-6 (IL-6) receptor-blocking monoclonal antibody. The antiviral remdesivir was used in 100% of the ACTT2 trial population[21] and about 20% of patients in the COV-BARRIER[22] and RECOVERY[20] cohorts.

A retrospective cohort study with eculizumab (a monoclonal antibody inhibiting complement C5 activation, with the same binding site as ravulizumab) reported improved respiratory function in all ten patients requiring continuous positive airway pressure respiratory support, compared with 65 contemporary controls from the same centre.[23] However, a phase 3 trial of ravulizumab with 202 patients, recruited between May, 2020, and January, 2021, with severe COVID-19 and requiring mechanical ventilation did not meet its primary endpoint (all-cause mortality up to day 29).[24] A macrocyclic peptide inhibitor of complement C5 activation, zilucoplan, was investigated in an open-label, randomised controlled trial in patients with moderate-to-severe COVID-19.[25] In this trial, 81 patients were randomly assigned in a 2:1 ratio to zilucoplan (55 patients) or standard-of-care (26 patients) groups and there was no significant difference in outcomes between the groups and no safety signal emerged.

An alternative approach to blocking the activation of complement C5 is to block the activity of C5a, one of the complement C5 activation products, which amplifies the acute inflammatory response, being a potent chemo-attractant for neutrophils and macrophages. Between May, 2020, and January, 2021, 207 patients hospitalised with COVID-19 were recruited and randomly assigned to

	Ravulizumab *vs* standard of care	Baricitinib *vs* standard of care	Standard of care
Clinical status assessed on 7-point ordinal scale at day 14			
Proportion with 7-point scale ≤5	34%	29%	28%
Comparison of score on 7-point ordinal scale, common OR (95% CI)	0·79 (0·49 to 1·27)	0·97 (0·61 to 1·55)	..
Time to discharge from hospital			
Proportion not discharged at day 14 (95% CI)	18% (11 to 30)	17% (11 to 27)	21% (14 to 32)
Comparison of time to discharge, HR (95% CI)	0·97 (0·71 to 1·32)	0·95 (0·71 to 1·28)	..
All-cause mortality			
Proportion of deaths at day 28 (95% CI)	14% (8 to 20)	14% (8 to 19)	12% (7 to 18)
Comparison of all-cause mortality, HR (95% CI)	0·99 (0·52 to 1·87)	1·32 (0·73 to 2·40)	..
Time to SpO_2 >94% on room air			
Proportion with SpO_2 >94% on room air at day 14 (95% CI)	68% (59 to 78)	79% (72 to 87)	76% (68 to 85)
Comparison of SpO_2 >94% on room air, HR (95% CI)	0·93 (0·70 to 1·22)	0·95 (0·73 to 1·24)	..
Duration of oxygen therapy, days			
Mean duration of oxygen therapy (SD)	4·37 (3·72)	5·02 (3·82)	4·70 (3·68)
Median difference in duration of oxygen therapy (95% CI)	0·00 (0·00 to 1·00)	0·00 (–1·00 to 1·00)	..
Clinical improvement (defined as >2 point improvement from day 1 on 7-point ordinal scale)			
Proportion with clinical improvement at day 14 (95% CI)	25% (18 to 35)	17% (12 to 25)	17% (11 to 24)
Comparison of clinical improvement, HR (95% CI)	0·93 (0·68–1·27)	0·98 (0·73–1·31)	..
Risk of adverse events of special interest			
Venous thromboembolism (too few events for risk estimate)	NA	NA	NA
Proportion of patients with new infection requiring antimicrobials	10 (7%) of 135	11 (8%) of 137	10 (7%) of 145
Comparison of new infection requiring antimicrobials, RR (95% CI)	1·02 (0·55–1·86)	1·17 (0·66–2·10)	..
Duration of hospitalisation (time to death, discharge, or primary event), days			
Mean duration of hospitalisation (SE)	10·7 (1·1)	11·5 (1·0)	12·1 (1·3)
Difference in restricted mean survival time (95% CI)	0·03 (–0·91 to 0·98)	0·64 (–0·29 to 1·56)	..
First negative SARS-CoV-2 PCR			
Proportion with first negative SARS-CoV-2 PCR at day 14 (95% CI)	18% (9 to 35)	23% (14 to 38)	26% (16 to 42)
Comparison of time to first negative SARS-CoV-2 PCR, HR (95% CI)	1·1 (0·72–1·69)	0·88 (0·56–1·36)	..

Secondary outcome measures are reported as OR (95% CI), HR (95% CI), RR (95% CI), proportion of patients (95% CI) or difference in days in restricted mean survival time (95% CI), unless stated otherwise. HR=hazard ratio. NA=not applicable. OR=odds ratio. RR=relative risk. SpO_2=pulse-oximetric oxygen saturation.

Table 2: **Secondary endpoints**

avdoralimab (a monoclonal antibody specific for C5a receptor type 1) or placebo in an open-label study (FORCE).[26] There was no significant difference in change in the WHO clinical scale score at 14 days or 18 days after administration of avdoralimumab or placebo. Mortality at day 28 was higher in the avdoralimab group (20 [19%] of 103 patients) compared with the placebo group (ten [10%] of 104). An anti-C5a antibody (vilobelimab) was evaluated in PANAMO (368 participants), a randomised, double-blind, placebo-controlled trial that recruited patients with severe COVID-19 between October, 2020, and October, 2021.[27] In contrast to the other trials of complement blockade, PANAMO reported efficacy of vilobelimab with a reduction in all-cause mortality at 28 days (HR 0·67; 95% CI 0·48–0·96).

A phase 3 trial of ravulizumab in patients with severe COVID-19[24] supports the conclusion from TACTIC-R that wholesale blockade of terminal complement activation is ineffective in the context of a standard-of-care regimen that includes dexamethasone and IL-6 receptor blockade. TACTIC-R recruited patients with less severe COVID-19 than the ICU-based trial;[24] findings from both trials indicate that ravulizumab is ineffective across the spectrum of disease severity in patients who are hospitalised with COVID-19. Ravulizumab differs from zilucoplan, avdoralimab, and vilobelimab in that it blocks the activation of complement component C5 and, therefore, the production of both C5a and C5b. It is plausible that blockade of C5a has at least some benefit in COVID-19—eg, by reducing aberrant neutrophil recruitment and activation. However, global inhibition of C5a and C5b (and membrane attack complex) formation might promote viral persistence or secondary bacterial pneumonia.

Systemic inflammation, with a prominent rise in IL-6 concentration, has been recognised to be associated with severe COVID-19 from early in the pandemic.[4] Deep immunophenotyping has recently demonstrated the strong association of an early increase in IL-6 levels with severe disease.[28] Longitudinal immunophenotyping has also shown that complement activation is implicated early in the pathogenesis of COVID-19.[28] In individuals who subsequently developed severe COVID-19, higher levels of early complement activation were detected. Therefore, it remains plausible that a subset of patients with early, excessive IL-6 levels or complement activation might benefit from inhibition of either IL-6 signalling pathways or C5a activity, respectively. Blockade of these pathways might be beneficial earlier in the disease trajectory than was possible in patients who had been hospitalised, before the prescription of corticosteroids, or in individuals with detrimental IL-6 production or complement activation.

	Standard of care (n=145)	Ravulizumab (n=135)	Baricitinib (n=137)
Serious adverse events	35 (24%)	41 (30%)	42 (31%)
Serious adverse reactions	..	6 (4%)	10 (7%)
Suspected unexpected serious adverse reactions	..	0	0
Progression of COVID-19 pneumonia	12 (8%)	21 (16%)	25 (18%)
Superadded bacterial pneumonia	4 (3%)	3 (2%)	0
Non-respiratory infection	4 (3%)	6 (4%)	3 (2%)
Other pulmonary complications (non-embolic)	5 (3%)	5 (4%)	1 (1%)
Cardiac complications	2 (1%)	2 (1%)	4 (3%)
Tumours	2 (1%)	3 (2%)	1 (1%)
Gastrointestinal and hepatobiliary complications	1 (1%)	1 (1%)	4 (3%)
Renal impairment	1 (1%)	2 (1%)	1 (1%)
Death	21 (14%)	18 (13%)	24 (18%)
Other	6 (4%)	7 (5%)	4 (3%)
Adverse events of special interest	21 (14%)	19 (14%)	29 (21%)
New infection requiring antimicrobial treatment	19 (13%)	18 (13%)	21 (15%)
Venous thromboembolism	3 (2%)	4 (3%)	10 (7%)

Table 3: **Summary of adverse events**

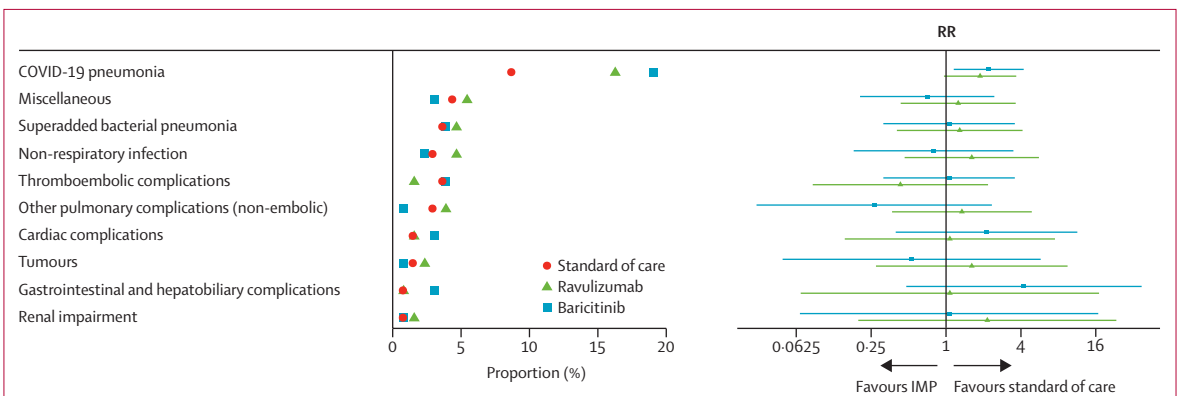

Figure 3: **Serious adverse events in the ravulizumab and baricitinib treatment groups**
Proportions of each category of serious adverse events are reported for each group. RRs of each category of serious adverse event are shown for the ravulizumab and baricitinib groups. IMP=investigational medicinal product. RR=relative risk.

There were no new safety signals with the addition of either baricitinib or ravulizumab to the standard-of-care regimen, as assessed through analysis of SAEs and AESI. There were more occurrences of venous thromboembolism in the baricitinib group than in either of the other groups, but the numbers were too small for significance testing. Despite anticipated immunosuppression associated with baricitinib and ravulizumab, no increase in infections requiring antimicrobials was noted. With respect to terminal complement blockade, no cases of meningococcal meningitis emerged.

The advantages of the TACTIC-R trial included the randomised design, with no element of clinician selection of the trial group. The 22 recruiting sites included a range of secondary and tertiary hospitals, and randomisation was stratified by site to control for any site-related variation in outcomes. TACTIC-R was also designed to select patients admitted to hospital with COVID-19 who had a high risk of severe disease, which was done by using a threshold on a clinical risk score indicating approximately a 40% risk of admission to an ICU or death.[15] This trial collected all SAEs and two AESI. Venous thromboembolic events were of particular interest in patients who received baricitinib in view of reports of increased venous thromboembolic events in patients with rheumatoid arthritis who were treated with JAK inhibitors and the recognised prothrombotic state in severe COVID-19. The incidence of infection was relevant to both interventions due to their immunosuppressive properties.

There are some important limitations associated with the TACTIC-R dataset. Patients were recruited across two waves of the pandemic, with 387 (93%) of 417 participants recruited in the second wave. The nature of the eligible patient group and viral strains changed during the course of the trial. The standard of care also evolved during this period. The use of corticosteroids in severe COVID-19 became prevalent from June, 2020,[20] and tocilizumab was added to standard of care in January, 2021.[29] TACTIC-R had been designed in a landscape with no effective treatments for COVID-19. However, it was conducted with standard-of-care glucocorticoids and during rollout of the first dose of anti-SARS-CoV-2 vaccines. The TACTIC-R dataset suggests the rapid effect of dexamethasone, given the improvement in ECOG and dyspnoea scores between screening (shortly after admission) and baseline datasets. This result would be expected to decrease the power of the study to specifically detect an effect of inhibition of proinflammatory cytokines or of complement activation, since these pathways would already have been inhibited by corticosteroids.[30] The number of patients recruited (417) further reduced the power of the TACTIC-R trial relative to ACTT2 (1033 patients), COV-BARRIER (1630) and, most strikingly, RECOVERY (8156).[21]

Less than 40% of patients in the baricitinib group received the maximum 14-day course. The main reason for this was that many patients were discharged rapidly, particularly during the pandemic peak. Discharge was often within the first few days after random assignment into the trial. The patients in the baricitinib group of TACTIC-R received less of the drug compared with 73 (14%) of the 515 patients given baricitinib in ACTT2 and 120 (16%) of 764 in COV-BARRIER. In the RECOVERY trial, baricitinib was administred for 10 days, or until discharge; dose day equivalents received was not reported. Since ravulizumab was administered as a single intravenous infusion, this limitation did not affect the ravulizumab group (132 [99%] of 135 patients received 100% of the intended dose).

TACTIC-R reports that neither baricitinib nor ravulizumab, as administered in this study, was effective in the reduction of disease severity in patients selected for severe COVID-19. However, baricitinib has been reported to be effective in three other trials. The discrepancy might be related to the short dosing period in more than 50% of the TACTIC-R baricitinib group. It remains possible that inhibition of selected effectors in the complement cascade has benefits in other patient subgroups, such as those earlier in the disease course, patients intolerant of corticosteroids, or patients selected on the basis of aberrant complement activation.

Contributors

FCH, JC, APC, JG, IW, SB, SN, and DRJ were responsible for the conceptualisation of the study. FCH, JC, APC, JG, IW, and DRJ contributed to funding acquisition. FCH, JC, APC, JG, IW, and SB were responsible for the study design and methodology. FCH, JC, JG, IW, SB, APC, JU, MK, HB, WGP, and TS contributed to project administration. FCH, JC, APC, JG, IW, DRJ, EB-H, JU, MK, HB, WGP, TS, and MN contributed to resource acquisition and management. FCH, JC, APC, JG, IW, EB-H, HB, MK, WGP, TS, and JU conducted the investigation of the project. FCH, APC, JG, SB, and MN contributed to data curation. SB and MN undertook the formal analysis. SB and MN contributed to software selection and coding. SB, SN, and MN were responsible for data validation. FCH, APC, JG, and SB for data visualisation. FCH, JC, JG, IW, APC, JU, MK, HB, WGP, and TS contributed to supervision. FCH, SB, SN, DRJ, and WGP wrote the original draft of the manuscript. FCH, JC, APC, JG, IW, EB-H, SB, MN, DRJ, HB, MK, WGP, TS and JU reviewed and edited the paper, with contributions from other members of the TACTIC-R Investigators' Group. FCH and SB accessed and verified the data. All authors had full access to all the data in the study. FCH had final responsibility for the decision to submit for publication.

Declaration of interests

FCH has received contributions towards trial running costs from Alexion Pharmaceuticals and Eli Lilly and Company; towards randomisation and investigational medicinal product distribution from UK Research and Innovation (UKRI); and towards research infrastructure from the UK National Institute for Health and Care Research (NIHR). FCH reports payment for weekend shifts for Clinical Investigators from Addenbrooke's Charitable Trust. JC has received funding (via his institution) from Alexion and Lilly, as well as UKRI, for partial funding of the TACTIC-R trial, and funding from AstraZeneca and GSK for other clinical trial work. APC has received support for the current manuscript in the form of funding for drugs from Lilly and Alexion. JG has received payment for the delivery of an educational talk on rheumatoid arthritis from Eli Lilly and Company (manufacturer of baricitinib). IW has received payments (via his institution) from UKRI and NIHR. EB-H is employed by the UK National Health Service; however, 50% of his time is seconded to GSK. MK received a monthly consulting fee for the design and conduct of early-phase trials (not associated with this trial or COVID-19) and is an investigator for GSK (not including any therapeutic or vaccine trials for

COVID-19). MK is also co-founder and 50% shareholder of Cambridge Early Phase Clinical Trials (which has not undertaken any work for the trial). WGP has received speaker honoraria from Novartis. JU holds a UK Medical Research Council grant investigating blood–brain barrier dysfunction following bloodstream infection and COVID-19, and has received honoraria from Gilead Sciences (manufacturer of remdesivir) for educational material and from Celltrion Healthcare for participation on an advisory board regarding regdanvimab, an antibody treatment for COVID-19 (unavailable in the UK). DRJ has received consulting fees from AstraZeneca, GSK, Roche, Takeda, UCB, and Vifor; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational services from UCB and Vifor; and holds stock or stock options in Aurinia. All other authors declare no competing interests.

Data sharing

Full individual participant data (deidentified) will be available to researchers who provide a methodologically sound proposal, available for 24 months after publication of the trial. Proposals should be directed to Dr Frances C Hall (fch22@medschl.cam.ac.uk). Data requestors will need to sign a data access agreement. Data will be shared via a secure data access system.

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