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IRIS, a randomised, double-blind, placebo-controlled trial of interleukin-6 receptor inhibition undergoing endovascular treatment in acute anterior circulation ischaemic stroke: study rationale and design

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ABSTRACT

Rationale Neuroprotective strategies based on reperfusion therapy hold substantial promise for acute ischaemic stroke (AIS). Preclinical research indicates that tocilizumab, an interleukin-6 receptor antagonist, can attenuate ischaemia-reperfusion damage by exerting anti-inflammatory and neuroprotective effects.

Aim To determine tocilizumab's efficacy and safety when combined with endovascular thrombectomy (EVT) in patients with acute anterior circulation large vessel occlusion (LVO).

Sample size estimates To determine a 30% decrease in average infarct core volume comparing the intervention and historical control groups (mean increase of 18.7 mL (SD=9.7 mL) post-thrombectomy) via a two-sided test (alpha=0.05, power=80%), accounting for a 10% drop-out rate, we plan to recruit 108 participants.

Methods and design This trial is designed as a randomised, multicentre, double-blind, placebo-controlled trial. Patients will be randomly and evenly allocated to the tocilizumab or placebo groups.

Study outcomes The primary endpoint is the change in infarct core volume between baseline and 72 hours post-treatment. Secondary outcomes include the 90-day modified Rankin scale score (0–2, indicating functional independence). The key safety endpoints include 90-day mortality and symptomatic intracerebral haemorrhage within 72 hours after EVT.

Discussion Administering tocilizumab within 24 hours of stroke as an adjunct to EVT may effectively reduce the infarct core volume for patients experiencing AIS with anterior circulation LVO, potentially improving functional outcomes in these patients.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Preclinical research indicates that tocilizumab may mitigate reperfusion damage and offer neuroprotective effects. However, the efficacy and safety of tocilizumab in patients with acute ischaemic stroke (AIS) undergoing endovascular thrombectomy (EVT) remain to be elucidated.

WHAT THIS STUDY ADDS

⇒ This is the first trial to investigate the use of tocilizumab as an adjunctive therapy to thrombectomy in patients with AIS.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study will provide insightful data on tocilizumab use alongside EVT in patients with AIS.

INTRODUCTION AND RATIONALE

Recent advances in endovascular thrombectomy (EVT) have substantially improved reperfusion rates among patients with acute ischaemic stroke (AIS) secondary to large vessel occlusion (LVO); nevertheless, five landmark EVT studies have indicated poor functional outcomes (>50%).[1] This discrepancy may be associated with futile recanalisation and ischaemia-reperfusion injury driven by the inflammatory response[2] mediated by interleukin-6 (IL-6), an immune cell pleiotropic cytokine. Increased serum IL-6 levels predict larger infarct sizes and poorer outcomes in patients who had a stroke.[3]

Tocilizumab, a humanised monoclonal antibody that targets the IL-6 receptor (both membrane-bound and soluble), inhibits IL-6 signalling and the resulting inflammatory cascade.[4] Tocilizumab has a half-life ranging from 5 to 13 days, and its clearance is dose-dependent, being non-linear at lower doses and linear at higher doses. This pharmacokinetic profile allows for sustained IL-6 inhibition.[5] During stroke reperfusion, inflammation contributes significantly to

worsening brain damage. The migration of activated peripheral leucocytes into brain tissue contributes to the blood–brain barrier (BBB) disruption, cerebral oedema and microcirculatory impairment, ultimately leading to further brain damage.[6] Neutrophils and macrophages are a significant source of matrix metalloproteinases, which degrade the vascular basement membrane, exacerbating BBB disruption, haemorrhagic transformation (HT) and cerebral oedema.[7] By inhibiting IL-6 signalling, tocilizumab may reduce inflammatory cell activation, decrease MMP release and mitigate BBB disruption, thus lowering the risk of oedema and HT while providing neuroprotective effects.

Preclinical research has demonstrated that tocilizumab decreases infarct volume and improves disease severity in rodent transient middle cerebral artery occlusion models.[8 9] Given the strong influence of infarct volume on clinical outcomes in patients with AIS, we hypothesise that tocilizumab may improve outcomes by reducing infarct volume.

Until now, no clinical study has demonstrated the efficacy and safety of tocilizumab in AIS patients postrecanalisation. The IRIS (Interleukin-6 Receptor Inhibition in Stroke) trial will evaluate the efficacy and safety of tocilizumab in patients with AIS experiencing anterior circulation LVO and undergoing thrombectomy.

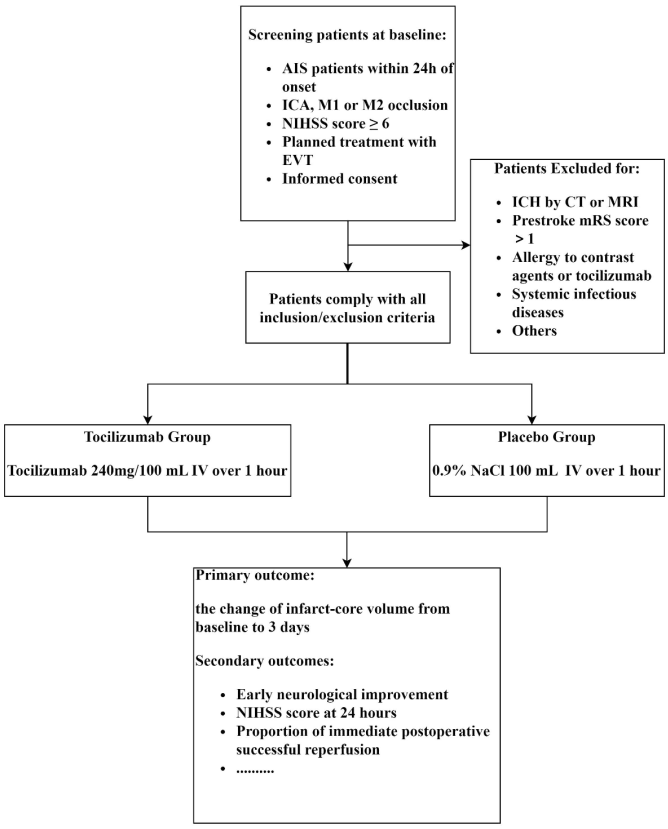

Figure 1 Study flow chart. AIS, acute ischaemic stroke; EVT, endovascular therapy; ICA, intracranial carotid artery; ICH, intracranial cerebral haemorrhage; M1, first segment of the middle cerebral artery; M2, second segment of the middle cerebral artery; mRS, modified Rankin scale; NIHSS score, National Institute of Health Stroke Scale.

METHODS

Trial design

IRIS is a phase 2, multicentre, randomised, double-blind, placebo-controlled trial assessing the efficacy and safety of early adjunctive tocilizumab in patients with anterior circulation LVO stroke undergoing thrombectomy. Informed consent for participation in this study was gained from all participants or their legal representatives. Figure 1 shows the patient flow diagram.

Patient population

Inclusion criteria

1. Between 18 and 80 years old.
2. AIS due to intracranial carotid, M1 or M2 middle cerebral artery occlusion.
3. National Institute of Health Stroke Scale (NIHSS) score of ≤6.
4. Meeting the criteria for EVT.
1. Alberta Stroke Programme Early CT Score (ASPECTS) of ≥6, EVT within 6 hour of onset.
2. Onset 6–16 hours, fulfilling the specifications of either DEFUSE-3 (infarct core <70 mL, mismatch ratio ≥1.8 and mismatch volume >15 mL) or DAWN (NIHSS ≥10 with infarct core <31 mL or NIHSS ≥20 with infarct core 31–51 mL).
3. Onset 16–24 hours, meeting the DAWN inclusion criteria.
4. For ASPECTS<6, eligibility requires meeting one of these criteria: RESCUE-Japan LIMIT: ASPECTS 3–5; and (onset ≤6 hours or 6–24 hours with no fluid-attenuated inversion recovery (FLAIR) changes); ANGEL-ASPECT: (onset ≤24 hours and ASPECTS 3–5) or (onset ≤24 hours, ASPECTS 0–2 and core 70–100 mL) or (onset 6–24 hours, ASPECTS>5 and core 70–100 mL); SELECT2: ASPECTS 3–5 or core >50 mL
1. Administration of experimental drug is possible ≤24 hours poststroke.
2. Informed consent is obtained from all participants and/or their legally authorised representatives.

Exclusion criteria

1. Any intracranial haemorrhage on head CT (including epidural, subdural, intraventricular or subarachnoid).
2. Prestroke modified Rankin scale (mRS) rating>1.
3. Allergic reaction to tocilizumab or any of its inactive ingredients.
4. Iodinated contrast agents allergy.
5. Potential difficulties completing EVT secondary to vascular tortuosity.
6. History of any bleeding disorders (congenital or acquired), coagulopathy or thrombocytopenia.
7. Uncontrolled hypertension despite treatment (systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg).
8. Neutrophils $<2\times10^9$/L.

9. Platelets <100×10^9/L.
10. Blood glucose <2.8 mmol/L (50 mg/dL) or >22.2 mmol/L (400 mg/dL).
11. Elevated liver enzymes (alanine aminotransferase or aspartate aminotransferase >1.5 times the upper limit of normal).
12. Impaired renal function (serum creatinine >1.5 times the upper limit of normal or estimated glomerular filtration rate <60 mL/min).
13. Pregnant, breast feeding or intending to become pregnant within 90 days.
14. Severe mental disorders or dementia preventing informed consent or follow-up compliance.
15. A life expectancy not exceeding 90 days due to a concurrent malignancy or severe systemic disease.
16. Autoimmune diseases or use of immunosuppressive drugs.
17. Active, chronic or recurrent infectious disease, including tuberculosis, HIV or hepatitis B/C.
18. Enrolment in an interventional clinical study during the 30 days prior to randomisation.

Randomisation

Eligible participants are randomized 1:1 via interactive web-based response system to receive either intravenous tocilizumab or placebo. Allocation is based on a computer-generated, unpredictable sequence, initiated after eligibility verification. Randomisation is stratified by the participating centre. Participants receive a unique serial number by order of randomisation and are administered the respective blinded medications.

Treatments

Eligible patients receive a single-dose intravenous infusion of tocilizumab (20 mg/mL tocilizumab (240 mg in 12 mL 0.9% NaCl) plus 88 mL of 0.9% NaCl) or placebo (100 mL of 0.9% NaCl) for >1 hour. Tocilizumab and placebo solutions exhibit similar appearances. Both treatments are blindly administered within 1 hour after randomisation. Intravenous thrombolysis with alteplase is allowed if indicated. Thrombectomy should be performed promptly in all patients without requiring specific procedures or equipment. On thrombectomy failure, the attending physician may employ salvage techniques tailored to the patient's clinical presentation. Perioperative management is performed according to the American Heart Association/The American Stroke Association (AHA/ASA) guidelines. Patients, investigators and study staff are blinded to treatment allocation.

Study schedule

At treatment, baseline data are collected, including patient demographics, medical history, laboratory results, stroke severity and neurological deficits. Recorded data include pretreatment and post-treatment imaging, procedural details (EVT characteristics, complications and time metrics), presumed stroke cause and 90-day functional outcomes (table 1).

Imaging

Imaging is performed (either CT+CT angiography (CTA)+CT perfusion or MRI+MR angiography (MRA)) at each participating site. MRI scans include T1-weighted, T2-weighted, diffusion-weighted imaging, apparent diffusion coefficient and FLAIR sequences (online supplemental material 1).

Efficacy endpoints

The primary endpoint is the difference in infarct core volume between baseline to 72 hours post-treatment.

Secondary endpoints include:

1. Early neurological improvement: NIHSS improvement ≥8 points or a score ≤2 within 24 hours.
2. 24 hours NIHSS score.
3. Rate of immediate postoperative modified Thrombolysis in Cerebral Infarction (mTICI) 2b/3 reperfusion.
4. 72 hours recanalisation rate (CTA/MRA).
5. NIHSS score at 7 days.
6. 90-day functional independence rate (mRS≤2).
7. 90-day mRS shift analysis.
8. 90-day Barthel Index.
9. 90-day EuroQol 5 Dimensions (EQ-5D).

Safety endpoints

Safety endpoints include the incidence of cerebral haemorrhage and symptomatic cerebral haemorrhage at 72 hours postprocedure, incidence of stroke-associated pneumonia and decompressive craniectomy at 7 days and mortality rate at 90 days. Serious adverse events (SAEs) and AEs are documented throughout the study.

Data safety and monitoring board

Trial safety and progress are monitored by an independent data safety monitoring board (DSMB), including neurologist, neuroradiologist and methodologist, none of whom are affiliated with the study investigators. All SAEs are reviewed and evaluated by the DSMB, which advises the Steering Committee on whether to continue, pause or terminate the trial.

Sample size estimates

Sample size was calculated for a two-sided test (α=0.05, power=80%) comparing two independent means using PASS software. Based on a mean post-thrombectomy infarct core volume increase of 18.7 mL (variance 9.7) in historical controls and an observed infarct volume reduction of approximately 30% in a pilot study using the same tocilizumab dose (unpublished data), 48 participants per group (n=96 total) are required to detect a similar reduction. Accounting for a ≤10% drop-out rate, the final estimated sample size is 108.

Statistical considerations

The primary endpoint, core infarct volume change at 72 hours post-treatment, will be analysed applying a mixed linear effects model in the intention-to-treat population. Results will be reported as mean differences with 95% CIs. Outcomes will be adjusted for centre-specific effects

Table 1 Assessment flow chart

	Screening		Follow-up					
	Baseline	Randomisation	Immediately postoperative	24±6 hours	48±12 hours	72±12 hours	7 days±12 hour or at discharge	90±7 days
Inclusion/ exclusion criteria	x							
Informed consent	x							
Randomisation		x						
Demographics	x							
Medical history	x							
Previous medication	x							
Vital signs	x		x	x	x	X	x	
Physical examination	x							
Laboratory tests	x			x	x	X	x	
Prestroke mRS	x							
mRS								x
NIHSS score	x			x		X	x	
Brain CT plus CTP/MRI	x							
CTA/MRA/DSA	x					X		
Brain CT/MRI						X		
ASPECTS	x							
mTICI score			x					
AOL grade						X		
Comedication			x	x	x	X	x	x
Barthel index								x
EQ-5D								x
AE/SAE			x	x	x	X	x	x

AE, adverse event; ASPECTS, Alberta Stroke Programme Early CT Score; CTA, CT angiography; CTP, CT perfusion; DSA, digital subtraction angiography; EQ-5D, EuroQol 5 Dimensions Questionnaire; AOL grade, American Society of Interventional and Therapeutic Neuroradiology (ASITN)-Society of Interventional Radiology (SIR) Grading System for Thrombolysis in Acute Ischaemic Stroke; MRA, MR angiography; mRS, modified Rankin scale; mTICI, modified Thrombolysis in Cerebral Infarction; NIHSS, National Institute of Health Stroke Scale; SAE, serious adverse event; TOAST, Trial of Org 10 172 in Acute Stroke Treatment classification.

by including centre as a random variable. For missing data due to stroke-related deaths, the maximum 72 hours core infarct volume is imputed. For other missing data, ≥100 imputations will be performed, including baseline age, NIHSS score, ASPECTS and treatment-related information as covariates. Each imputed dataset will be analysed independently, and Rubin's rules will be applied to combine the results and obtain the final estimates and standard errors. A prespecified subgroup analysis will assess treatment effect heterogeneity based on age (≤70 vs >70 years), baseline ASPECTS (≤5 vs >5), baseline NIHSS (<20 vs ≥20), and intravenous thrombolysis (yes vs no). Additionally, a per-protocol sensitivity analysis will assess the impact of protocol adherence.

Other continuous outcomes (including NIHSS score at 24 hours and 7 days, 90-day Barthel Index, 90-day EQ-5D) will be analysed using the same mixed linear model employed for the primary endpoint. For variables with severe departures from normality, data transformation or more robust methods, including generalised estimating equations, will be considered.

Binary outcomes (including early neurological improvement, proportion of immediate postoperative successful reperfusion, 72 hours recanalisation rate (CTA/MRA), rate of cerebral haemorrhage or symptomatic cerebral haemorrhage at 72 hours, 7 day stroke-associated pneumonia rate, 7-day decompressive craniectomy rate, rate of patients achieving functional independence, mortality

at 90 days and AE/SAEs at 90 days) will be analysed using log-binomial regression models and presented as relative risk. A robust Poisson regression will be used for non-convergent models.

An ordinal logistic regression model will be applied to analyse the 90-day mRS score (ordinal). Results will be presented as ORs with 95% CIs. If the proportional-odds assumption is violated, partial proportional odds models or other nonparametric methods will be considered.

All tests will be analysed by using SAS V.9.4 with a two-tailed α=0.05.

Version

This study protocol is currently at V.1.1.

Data access policy

Data access requests should be submitted to the corresponding author and will be subject to review by the study team.

DISCUSSION

Although immunomodulatory therapies have shown promise in treating AIS, their efficacy remains unclear. For example, the sphingosine-1-phosphate receptor modulator fingolimod demonstrated potential benefits only in a small clinical trial; thus, larger studies are needed.[10] Similarly, ApTOLL, a Toll-like receptor 4 antagonist and edaravone dexborneol, an antioxidant/anti-inflammatory compound, are promising anti-inflammatory treatments that warrant further investigation.[11 12] However, in a large randomised controlled trial, methylprednisolone did not improve overall disability in patients with AIS with LVO undergoing EVT.[13] Varied drug targets and study populations likely contributed to inconsistent findings in previous studies. Nevertheless, these findings highlight the potential of anti-inflammatory and immunomodulatory therapies for AIS, particularly in patients undergoing reperfusion therapy.

IL-6 levels rapidly increase after ischaemic brain injury and contribute to various pathological processes, including inflammation, BBB disruption and neuronal apoptosis.[14 15] Clinical studies indicate that serum IL-6 levels in patients with AIS increase ≥24 hours postonset and are significantly correlated with infarct size and mortality.[16 17] Tocilizumab is fast-acting and has relatively mild AE.[18] The inflammatory response initiates within hours of ischaemia and persists for days to weeks.[19] Therefore, this study employs a single intravenous dose of tocilizumab to achieve sustained IL-6 pathway inhibition during the critical inflammatory phase, thereby promoting prolonged anti-inflammatory and neuroprotective effects. To rigorously assess the efficacy and safety of tocilizumab, a placebo-controlled design is employed. Despite the potential concerns about withholding active treatment in a life-threatening condition, all patients in the study received standard care as per current guidelines, including EVT and secondary prevention strategies. The placebo control allows for a clear differentiation between the true therapeutic effects of tocilizumab and any placebo effect, ensuring that the results are both scientifically robust and clinically meaningful.

Several clinical trials have indicated EVT to be effective and safe for patients with AIS exhibiting large core infarcts from anterior circulation LVO.[20–22] The purpose of this study is to comprehensively estimate the efficacy of tocilizumab and provide new treatment strategies for patients with AIS and large core infarcts, a population at higher risk of postprocedure complications.[23] Changes in infarct core volume by tocilizumab is the primary endpoint, which may have important implications for further investigation. [24 25]If the combination of tocilizumab and EVT proves effective and safe in patients with acute anterior circulation LVO, it could provide critical evidence for the application of anti-inflammatory therapies in patients undergoing vascular recanalisation. Such findings could fill an existing therapeutic gap and have profound implications for stroke management strategies, potentially influencing updates to clinical guidelines. Thus, we plan to conduct a larger phase 3 clinical trial to further validate the efficacy and safety of tocilizumab.

SUMMARY AND CONCLUSIONS

If the IRIS hypothesis is confirmed, combining tocilizumab and EVT can reduce infarct volume in patients with anterior circulation LVO within 24 hours poststroke, potentially improving functional outcomes.

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Contributors The manuscript was drafted by XC. ZM, YL, JS, NW, ChaoqunL, XF, JL and BW conducted the study, while CZ, ChuanhuiL, WZ, XJ, ZM and CW designed it. XC and ZM contributed equally to this paper. All authors critically reviewed and revised the manuscript. CW is the guarantor.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Beijing Institute of Brain Disorders, Capital Medical University, 2024001. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Data access requests should be submitted to the corresponding author and will be subject to review by the study team.

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