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Anakinra Reduces Inflammation Following Aneurysmal Subarachnoid Haemorrhage: Results of the SCIL-SAH Study

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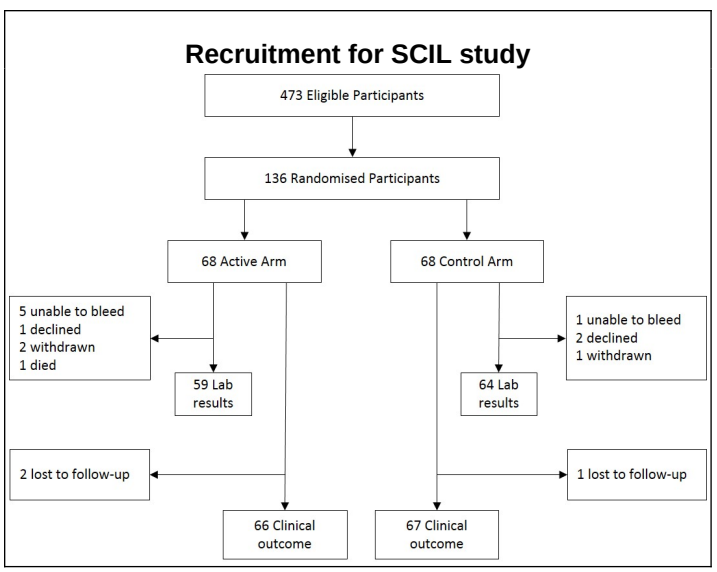
Introduction

Aneurysmal subarachnoid haemorrhage (aSAH) is a devastating cerebrovascular event with significant long term morbidity. There is evidence implicating the proinflammatory cytokine interleukin-1 (IL-1) in neurodegeneration (1) and suggesting that haem-mediated toxicity is IL-1 dependent (2). Interleukin-1 receptor antagonist (IL-1Ra), its naturally occurring antagonist, reverses the deleterious role of IL-1 in vitro and in animal models of cerebrovascular disease. We hypothesised that subcutaneous (SC) anakinra, a methylated-synthetic analogue of IL-1Ra, lowers plasma markers of inflammation associated with poor outcome following aSAH.

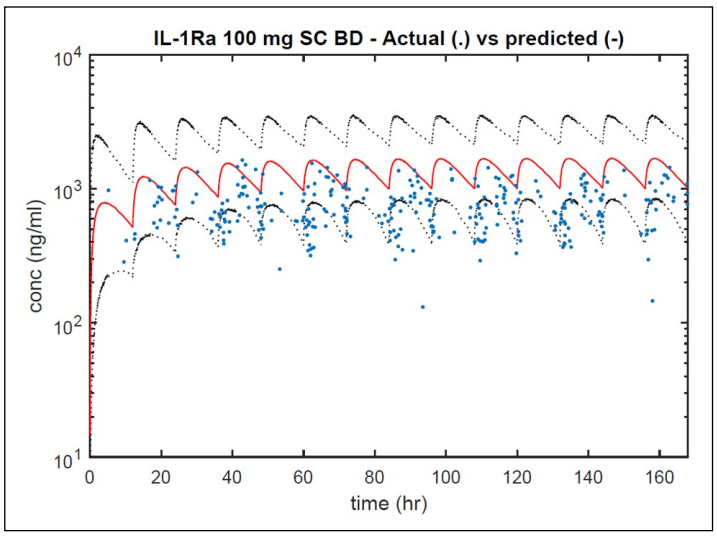
Methods

An open-label, randomised controlled multi-centre trial of IL-1Ra in 136 patients with confirmed SAH. 100mg SC IL-1Ra in treatment group was first administered within 72 hours of confirmed ictus and then twice daily for up to 21 days (or discharge if sooner). Plasma inflammatory markers were measured at baseline, days 3 to 8, 14 and 21 post ictus. Primary outcome was difference in plasma IL-6 (area under curve [AuC]) between days 3 to 8 adjusted for baseline.

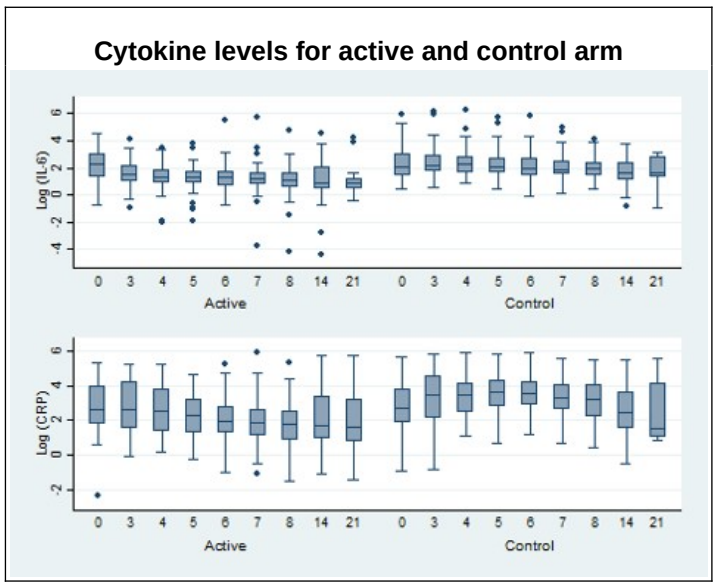


Results

123 patients (mean age 52 yrs, 27 male) provided sufficient data for primary analysis. Observed concentration profiles of IL-1Ra were within the predicted intervals from our pharmacokinetic model.



IL-6 and CRP AuC concentrations were significantly lower in the treated group ($p<0.001$). A less marked effect was seen for fibrinogen ($p=0.002$). There was no evidence of an effect on IL-8.



Administration of SC IL-1Ra BD was feasible and well tolerated. There was no significant difference in adverse events between the two groups. The number of infections in our cohort was 48 and 42 patients had vasospasm.

Three patients were lost to follow-up. GOSE was better in the active group than in controls: odds ratio (95% CI) = 0.92 (0.52 to 1.7); p=0.80. Our study was not powered for this comparison.

Clinical outcome (GOS-E) in SCIL study

Grade	Active (n=66)	Control (n=67)
Dead	6 (9%)	6 (9%)
PVS	0 (0%)	1 (1%)
Lower Severe Disability	5 (8%)	8 (12%)
Upper Severe Disability	12 (18%)	6 (9%)
Lower Moderate Disability	1 (2%)	0 (0%)
Upper Moderate Disability	6 (9%)	9 (13%)
Lower Good Recovery	9 (14%)	12 (18%)
Upper Good Recovery	27 (41%)	25 (37%)

Conclusions

This study provides proof of efficacy, safety and feasibility for the use of SC IL-1Ra to dampen IL-1 mediated inflammation following aSAH. It will inform an upcoming phase III trial of SC IL-1Ra to compare clinical outcome at 6 months for patients with aSAH.

References

1. Galea, J. & Brough, D. The role of inflammation and interleukin-1 in acute cerebrovascular disease. J Inflamm Res 6, 121–128 (2013).
2. Greenhalgh, A. D. et al. Interleukin-1 receptor antagonist is beneficial after subarachnoid haemorrhage in rat by blocking haem-driven inflammatory pathology. Dis Model Mech 5, 823–833 (2012).

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