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Fight INflammation to Improve outcome after aneurysmal Subarachnoid HEmorRhage (FINISHER) trial: Study protocol for a randomized controlled trial

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Abstract

Rationale: Aneurysmal subarachnoid hemorrhage (SAH) has high morbidity and mortality. While the primary injury results from the initial bleeding cannot currently be influenced, secondary injury through vasospasm and delayed cerebral ischemia worsens outcome and might be a target for interventions to improve outcome. To date, beside the aneurysm treatment to prevent re-bleeding and the administration of oral nimodipine, there is no therapy available, so novel treatment concepts are needed. Evidence suggests that inflammation contributes to delayed cerebral ischemia and poor outcome in SAH. Some studies suggest a beneficial effect of anti-inflammatory glucocorticoids, but there are no data from randomized controlled trials examining the efficacy of glucocorticoids. Therefore, current guidelines do not recommend the use of glucocorticoids in SAH.

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Aim: The Fight INflammation to Improve outcome after aneurysmal Subarachnoid HEmorRhage (FINISHER) trial aims to determine whether dexamethasone improves outcome in a clinically relevant endpoint in SAH patients.

Methods and design: FINISHER is a multicenter, prospective, randomized, double-blinded, placebo-controlled clinical phase III trial which is testing the outcome and safety of anti-inflammatory treatment with dexamethasone in SAH patients.

Sample size estimates: In all, 334 patients will be randomized to either dexamethasone or placebo within 48 h after SAH. The dexamethasone dose is 8 mg tds for days 1–7 and then 8 mg od for days 8–21.

Study outcome: The primary outcome is the modified Rankin Scale (mRS) at 6 months, which is dichotomized to favorable (mRS 0–3) versus unfavorable (mRS 4–6).

Discussion: The results of this study will provide the first phase III evidence as to whether dexamethasone improves outcome in SAH.

Keywords
Dexamethasone, glucocorticoid, aneurysm, subarachnoid hemorrhage, inflammation, clinical trail

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Introduction and rationale

Despite some improvement over the last decades, the overall case fatality rate in aneurysmal subarachnoid hemorrhage (SAH) is still extremely high and the outcome is still poor.[1,2] To date, beside the aneurysm treatment to prevent re-bleeding and the administration of oral nimodipine, there is no causal therapy available, so that novel treatment concepts are desperately needed.[3]

While the primary injury results from the initial bleeding cannot be influenced, secondary injury during the course of the disease might be a target for intervention in order to improve outcome. There is almost no evidence-based treatment option to prevent the complication of delayed cerebral ischemia (DCI), which typically occurs during days 3–14 after SAH substantially contributing to poor outcome. Only treatment with the calcium channel blocker nimodipine has been shown to moderately improve outcome due to a neuroprotective effect.[2]

There are strong indications that inflammation contributes to poor outcome. Different inflammatory mediators including interleukin 6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor alpha (TNF-α) correlate with or even cause vasospasm and DCI.[4,5] Moreover, systemic inflammation and immune dysregulation have been described and proposed to impact on the brain injury pathogenesis in SAH. This includes a reduction in regulatory T cells (T regs) that have been described to be protective in SAH.[5] Thus, an anti-inflammatory treatment increasing the number and function of T regs is currently discussed as a promising approach to reduce vasospasm, DCI, and finally an unfavorable outcome. In addition, markers of inflammation including CRP, procalcitonin (PCT), and high mobility group box 1 (HMGB-1) are increased in SAH patients on initial admission.[6–9]

All these above-described immune mediators are discussed as potential promising targets (e.g. interleukin 1 beta (IL-1β), IL-6, and TNF-α). Many of these immune mediators have been proven to be influenced by glucocorticoids (GC): GC have been shown to expand the number of T regs in peripheral blood and to reduce inflammatory cytokines such as IL-1β, IL-6, and TNF-α. Thus, GC not only are inhibiting a single immune mediator that is claimed to be involved in SAH pathophysiology but also possess a variety of anti-inflammatory effects by the suppression of many different inflammatory cytokines as well as immune cell functions. In line with this, data from a retrospective study and also a prospective pilot-trial suggest a beneficial effect of GC, such as methylprednisolone and dexamethasone (DEX), in SAH.[10–12] Therefore, the Fight INflammation to Improve outcome after aneurysmal Subarachnoid HEmorRhage (FINISHER) aims to answer the question whether GC improve outcome in the general population of SAH patients.

Methods

Design

FINISHER resembles a multicentric, prospective, randomized, double-blinded, placebo-controlled clinical phase III trial (Figure 1). This trial is conducted in accordance with the Declaration of Helsinki and received approval from all participating sites' ethical committees as well as the German Federal Institute for Pharmaceuticals and Medical Products.

The trial will be conducted in 14 centers in Germany (Figure 2). All patients included in the study will initially receive standard treatment according to the institutional guidelines of each participating site. In the experimental arm, patients will receive three times 8 mg DEX from days

Figure 1. FINISHER logo.

1–7 starting within 48 h after SAH and one time 8 mg DEX from days 8–21. In the control arm, patients will receive a placebo, respectively. Follow-up is 12 months.

Patient population

In all, 334 subjects will be allocated to the trial and 304 subjects (152 in each treatment arm) are expected to complete the trial.

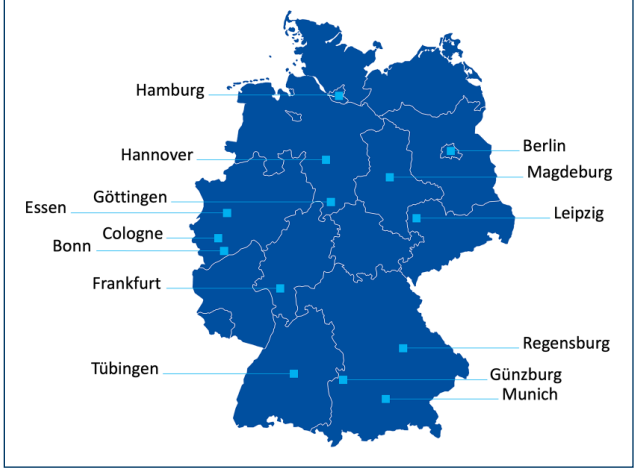
Inclusion criteria

- Aneurysmal SAH (World Federation of Neurosurgical Societies Grades I–V) and onset within 48 h before inclusion.
- Male or female subjects, ⩾18 years old.
- Written consent to participate in the study.

Exclusion criteria.

- SAH due to any other cause than aneurysm rupture (e.g. traumatic, arteriovenous malformation).
- Any condition that could impose hazards to the patient if study therapy is initiated or affects the participation of the patient in the study.
- Patients with obvious evidence of irreparable brainstem or thalamic injury.
- Patients with foreseeable difficulties to attend follow-ups adequately.
- Physical or psychiatric condition which may put the subject at risk, may confound the trial results, or may interfere with the subject's participation in this clinical trial.
- Pregnancy.
- Known history of hypersensitivity to the investigational drug or to drugs with a similar chemical structure.
- Severe infectious diseases.
- Known angle-closure or open angle glaucoma.
- Known ulceration in the gastro-intestinal tract.
- History of gastro-intestinal bleeding.
- Long-term treatment with corticosteroids prior SAH.

Figure 2. Participating sites in Germany.



Randomization

Patients will be randomized in a 1:1 ratio stratified by the center via permuted blocks within each stratum.

Treatment

- *Experimental arm*: three times 8 mg DEX (2 mL) daily for days 1–7 and one time 8 mg DEX (2 mL) daily for days 8–21.
- *Control arm*: three times 2 mL placebo daily for days 1–7 and one-time 2mL placebo daily for days 8–21.

Primary outcomes

The primary target variable on a subject level is the modified Rankin Scale[13] (mRS) 6 months after SAH, dichotomized in the classes "favorable" (mRS 0–3) versus "unfavorable" (mRS 4–6) outcome.

Secondary outcomes and exploratory readouts

- Outcome (ordinal mRS) at discharge, 3 months, 6 months, and 12 months.
- Mortality.
- Length of intensive care unit (ICU) stay and hospitalization after SAH.
- Delayed ischemic neurological deficit (DIND).
- Symptomatic vasospasm.
- Inflammation parameters (such as CRP, PCT, white blood cells (WBC), and IL-6) in serum.
- Quality of life (36-Item Short Form Survey and European Quality of Live 5 Dimensions scores).
- AEs by number, severity, and relationship.
- Analysis of 20 cytokines and soluble in serum and cerebrospinal fluid (CSF).

- Analysis of metabolomics level in serum, CSF, and stool.
- Comparison of cognitive abilities, hypersensitivity to stimuli, anxiety, depression, fatigue, social roles, personality change, language, vision, taste, smell, hearing, headache, and sexual function measured by the questionnaire for the screening of symptoms in aneurysmal subarachnoid hemorrhage as an electronic patient-reported outcome measure.[14]

Time points of all assessments are shown in the time schedule (Table 1).

Data monitoring body

The Data Safety Monitoring Board (DSMB) will review all serious adverse events (SAEs) of all patients so far recruited to the trial regularly. The DSMB will include at least three members with experience in the conduct of study and individual expertise in the field of neurology and biometrics. The data provided to the DSMB for review may also include so far unmonitored data.

The DMSB is free to suggest any modifications regarding the trial (e.g. stopping of the trial, modifications of the protocol). The DSMB is charged with reviewing safety data in both arms of the trial. The DSMB will be empowered to stop the study for evidence of harm but not for evidence of lack of efficacy. The DSMB has been appointed to review the conduct and results every 6 months.

Sample size estimates

The sample size/power calculation is based on the existing retrospective and prospective clinical data.[11,12] Taken the information together, an unfavorable outcome according to mRS 4–6 is to be expected in about 40% of the study population. The GC treatment is reported to improve the unfavorable outcome from 50% to 20% or from 35% to 15%. We make the conservative assumption that the GC treatment improves the unfavorable outcome from 40% to 25%. Using the Chi-square test, as intended, this requires a sample size of 152 patients per study arm for a power of at least 80% to detect the difference. With 10% estimated dropouts, two times 167 patients will be allocated to the trial.

Study organization

FINISHER is an investigator-initiated trial (IIT) Full study protocol is available as supplemental material.

Statistical analyses

The analysis of the primary endpoint will be performed within the intention-to-treat and per-protocol population. The rate of unfavorable outcomes will be compared between the study arms with a Cochran–Mantel–Haenszel test at a level of 5% stratified by centers.

In the secondary analysis of the primary endpoint, logistic regression models will be fitted to estimate the combined effect of other risk factors (e.g. inflammation parameters) and the therapy of the dichotomized primary outcome criterion (also accounting for strata). A sensitivity analyses using clinically meaningful sliding cutoff will be performed. Analysis of outcome via mRS without dichotomization using a proportional odds model as well as the analysis of the complete time course by means of generalized estimating equations and, in addition, a corresponding rank test on the 6-months data will be performed.

Descriptive analysis of the secondary and exploratory endpoints will be applied.

Subgroup of patients with and without initial inflammation will be compared regarding their outcome. The signature will be defined based on cutoff values of the inflammatory parameters.

Discussion

As there is a lack of outcome improving treatments in SAH, especially to treat the secondary complications, leading to a poor patient outcome and to socioeconomic issues,[15] novel treatment options are desperately required. Promising pilot data suggest a major role of neuroinflammation and thus suggest outcome improvement of anti-inflammatory drugs in SAH, especially GC.[4,11,12] However, there are no data from randomized controlled trials proving or disproving the beneficial effect of GC, so that current guidelines do not recommend the routine use of GC in SAH.[3]

In the experimental arm, three times 8 mg DEX will be applied over 7 days followed by a dose of one time 8 mg over 14 days. We chose therewith a dosage within the range that has been claimed to show an effect but is not the highest reported dose to avoid unnecessary side effects.[10–12]

As we will analyze SAH patients with or without an initial inflammatory signature in peripheral blood, this trial will generate in a secondary analysis whether the initial inflammatory state of SAH patients defines a subgroup that particularly responds to a treatment with GC.

Summary and conclusions

FINISHER will generate the first confirmatory data in a controlled randomized fashion that DEX improves the outcome in a clinically relevant endpoint in SAH patients. Moreover, this trial will generate first data in a secondary analysis: whether the initial inflammatory state of SAH patients defines a subgroup that particularly responds to a treatment with DEX.

As there is no recommendation for GC application in SAH patients in the current guidelines so far, the results of

Table 1. Time schedule.

	Day 1 (0–48 h after bleeding)		Days 2–21			90d ± 14d	180d ± 14d	270d ± 14d	365d ± 30d
	V1	V2	V3	V4–V22	V23	V24	V25	V26	V27
Visit window	Screening	1st treatment (as soon as possible after randomization, but max. 48 h after SAH)	Within 24 h after aneurysm repair	Daily	Discharge from hospital	Follow-up (Telephone)	End of study (EOS)	Only digital visit	Long-term Follow-up
Aneurysm repair		√							
Informed consent	√								
Including/excluding criteria	√								
Demographic data	√								
Medical history/anamnesis	√								
CCT or MRI	√*		√*	√*			√*[a]		
Vital signs	√	√	√	√	√				
Randomization	√								
IMP application		√	√	√					
Best medical treatment	√	√	√	√	√				
Details of ICU therapy					√				
Laboratory parameters (including standard inflammation parameters)	√		√	√	√		√[a]		
Pregnancy (e.g. serum β-HCG level, local lab)	√			√[b]					
Inflammation marker/cytokines (exploratory)	√		√	√[c]			√[a,d]		
Metabolomics	√			√[e]					√[a,d]
mRS Score (if reasonable surveyed via telephone call)	√				√	√	√		√
Physical examination	√				√		√[a]		
QoL questionnaires (SF36 and EQ-5D)					√	√	√		√
SOS-SAH PROM (exploratory)						√	√	√	√
AEs/SAEs, CoMed		√	√	√	√				

SAH, subarachnoid hemorrhage; CCT, cranial computed tomography; IMP, Investigational Medicinal Product; MRI, magnetic resonance imaging; ICU, intensive care unit; mRS, modified Rankin Scale; QoL, Quality of Life; AEs, adverse events; SAEs, serious adverse events.
[a]Optional, if on site visit is reasonable.
[b]On last day of IMP application.
[c]On Visit 6, 10, 15, 20.
[d]Serum only.
[e]On Visit 7.
*Whenever imaging is performed for clinical purposes, images are collected for secondary readouts.

this study may contribute to novel treatment options and modification of the current guidelines.

Declaration of conflicting interests

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Trial registration

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Supplemental material

Supplemental material for this article is available online.

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