EARLY ORAL SWITCH THERAPY IN LOW-RISK STAPHYLOCOCCUS AUREUS BLOODSTREAM INFECTION

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bacterial infectious disorders
Study type	Interventional

Summary

ID

NL-OMON44940

Source
ToetsingOnline

Brief title
SABATO: Staphylococcus aureus Bacteremia Antibiotic Treatment Options

Condition

- Bacterial infectious disorders

Synonym
bacterial infection, resistant bacteria

Research involving
Human

Sponsors and support

Primary sponsor: University of Düsseldorf

Source(s) of monetary or material Support: Deutsche Forschungsgemeinschaft

Intervention

Keyword: Bloodstream, Infection, Staphylococcus aureus, Therapy

Outcome measures

Primary outcome

The primary endpoint measure, SAB-related complication, reflects the failure rate of antimicrobial therapy in preventing late complications. This includes both, relapsing SAB and deep-seated S. aureus infection within 90 days and is thus the most appropriate clinical outcome measure.

Microbiological success is sometimes demonstrated by a negative blood culture as a test of cure at EOT. Since patients in this trial have already been treated for seven days with antimicrobials before randomization, >99% of blood cultures obtained at EOT are expected to yield a negative result. Therefore, microbiological success has not been chosen as an endpoint. Death unrelated to SAB is expected at about 5% within 30 days. It was not included in the primary endpoint because this would compromise the power of the trial by variance inflation. However, SAB-related and all-cause mortality will be carefully assessed and compared (secondary/safety endpoints).

Secondary outcome

The secondary endpoint, length of hospital stay, reflects the potential benefits for patients who have been switched to oral medication. Furthermore, 14- and 30-day survival and complications related to i.v. therapy, e.g. chemical or septic (thrombo-)phlebitis will be measured.

The safety of study drugs is assessed by monitoring Clostridium difficile

associated diarrhea (CDAD), AEs and SAEs.

Study description

Background summary

Increasing resistance to antimicrobial agents has been recognized as a major health problem worldwide that will even aggravate due to the lack of new antimicrobial agents within the next decade. This threat underscores the need to maximize clinical utility of existing antimicrobials, through more rational prescription, e.g. optimizing duration of treatment. Staphylococcus aureus bloodstream infection (SAB) is a major cause for prolonged antimicrobial therapy. With an approximate incidence of 25 cases per 100,000, about 200,000 cases occur annually in Europe. Recent data for Western Europe demonstrate a crude mortality of 20-30% (in-hospital or 30-day mortality) in patients with SAB. In many cases SAB can be cured by antimicrobial therapy. However, SAB differs from other bloodstream infections with respect to SAB-related complications: relapses, local extension and distant metastatic foci are relatively common events and occur in about 2-25% of infections. Therefore, antbiotic therapy is considered to be especially important in this disease and standard treatment schedules are significantly longer than in other bloodstream infections. A course of at least 14 days of intravenous antimicrobials is considered standard therapy in *uncomplicated SAB*. Generally, *uncomplicated SAB* is defined by absence of: community acquisition, skin examination findings suggesting acute systemic infection, positive follow-up blood cultures and persistent fever at 72h. Shorter courses of intravenous treatment are currently not recommended due to the lack of sound clinical evidence. The SABATO trial will specifically address this issue and examine the effectiveness and safety of an abbreviated course of intravenous therapy in patients that have a low-risk of SAB-related complications. This trial poses specific risks for the patient. A shorter course of effective antimicrobial therapy may lead to relapsing SAB, local spread of the infection, or hematogenous dissemination of S. aureus with resulting deep-seated infection. To minimize the risk, a population of patients with a very low-risk of SAB-related complications is described by inand exlusion criteria. This population has been validated by using data from two prospective cohort studies. Data from the INSTINCT (Invasive Staphylococcus aureus Infection Cohort) study (10) shows a low incidence of SAB-related complications in low-risk patients (3%; 4 of 135 patients). A pilot study for the SABATO trial with 236 SAB patients from 10 German study centers provided further evidence for a very low risk of complications in these patients: Only 1 of 89 patients had a SAB-related complication. Abbreviated or early i.v. to oral switch treatment strategies

have been successfully applied to other infectious diseases such as nosocomial pneumonia, meningococcal disease, and febrile neutropenia. These strategies allow shorter intravenous antimicrobial therapy and offer options for early discharge from hospital. This, in turn, increases the patients* quality of life, decreases treatment costs, reduces the risk of nosocomial infections and may help to diminish antimicrobial resistance development and spread. The SABATO trial is the first randomized controlled trial addressing early oral switch therapy in SAB.

Study objective

The hypothesis is that a switch from intravenous to oral antimicrobial therapy is non-inferior to standard intravenous therapy in patients with low-risk SAB. Therefore, the primary objective of the trial is to demonstrate, that oral switch therapy (OST) is as safe and effective as intravenous standard therapy (IST). This will be achieved by comparing the rate of SABrelated complications (relapsing SAB, deep-seated infection with S.aureus, or mortality attributable to SAB) within 90 days. Low-risk SAB manifests itself typically in patients with comorbidities. Therefore, survival is
largely determined by the underlying disease (18) and was not chosen as a primary endpoint. However, death related to SAB is comprised in the primary endpoint. Death unrelated to SAB will be carefully evaluated and compared.

The secondary objective is to measure the potential benefit for the patient. This is achieved by evaluating the length of hospital stay after the first positive blood culture and complications of intravenous therapy. A considerable number of patients on OST are expected to be discharged earlier from hospital, since hospital stay due to intravenous therapy is no longer required. This will reduce the risks associated with hospitalization and i.v. therapy (catheter-related infection, venous thrombosis, and septic thrombophlebitis) and is likely to improve patients* quality of life.

Study design

Phase III, multicenter, open-label, randomized, controlled, non-inferiority trial with a total of 430 patients enrolled.

The trial starts with the first patient visit and ends with the last visit of the last patient. Individual patients go through a screening, intervention and follow-up phase.

Intervention

First, patients with SAB are reported from the microbiological department to the principle investigator. Then, individual patients with SAB are screened for possible enrolment by the principle investigator. The intervention phase (7-9

days) starts when patients have given informed consent and all in- and exclusion requirements are fulfilled.The length of the intervention phase depends on how long patients have received appropriate pre-randomization antimicrobials. All patients will receive an overall course of 14 days appropriate antimicrobial therapy, e.g. patients having received five days of appropriate pre-randomization antimicrobials will receive nine days of OST or IST. Patients on OST can be discharged before end of therapy (EOT) according to clinical and psychosocial criteria. Patients on IST can only be discharged when an OPAT (outpatient parenteral antimicrobial therapy) service is in operation at the local study site. The follow-up phase starts at EOT and ends 90 days after the first positive blood culture. Patients that are still in hospital will be visited on the ward to collect follow-up information. Discharged patients are followed by a structured telephone interview at day 85-99.

Study burden and risks

This trial poses specific risks for the patient. A shorter course of effective antimicrobial therapy may lead to relapsing SAB, local spread of the infection, or hematogenous dissemination of S. aureus with resulting deep-seated infection. To minimize the risk, a population of patients with a very low-risk of SAB-related complications is described by inand exlusion criteria.

In turn, the patients' increases quality of life, decreases treatment costs, reduces the risk of nosocomial infections and may help to diminish antimicrobial resistance development and spread.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

> 18 years, not legally incapacitated, written consent, blood culture positive for S. aureus not considered to represent contamination
Negative follow-up blood culture within 24-96 hours after start of adequate antimicrobial therapy
5-7 full days of appropiate i.v. antimicrobial therapy prior to randomization

Exclusion criteria

Polymicrobial bloodstream infection
Recent history of prior SAB (within 3 months)
In vitro resistance of S.aureus to all oral or all i.v. drugs
Previously planned treatment with active drug against S. aureus during intervention phase (e.g. cotrimoxazol prohylaxis)
Signs and symptoms of complicated SAB (deep-seated focus, septic shock within 4 d, prolonged bacteremia, fever(>38C) twice within 48h before randomization
Presence of the following non-removable foreign bodies (if not removed 2 days or more before randomization): prosthetic heart valve, ascular graft, ventriculo-atrial shunt
Presence of a prosthetic joint (if not removed 2 days or more before randomization). This is not an exclusion criterion, if all of the following conditions are fulfilled:prosthetic joint was implanted at least 6 months prior and catheter-related infection, skin and soft tissue infection or surgical wound infection is present and joint infection unlikely (no clinical or imaging signs)
Presence of a pacemaker or an automated implantable cardioverter defibrillator (AICD) device (if not removed 2 days or more before randomization). This is not an exclusion criterion, if all of the following conditions are fulfilled: pacemaker or AICD was implanted at least 6 months prior, and
catheter-related infection, skin and soft tissue infection or surgical wound infection is present and no clinical signs of infective endocarditis, and infective endocarditis unlikely by

echocardiography (preferably TEE), and pocket infection unlikely (no clinical or imaging signs)
• Failure to remove any intravascular catheter which is present when first positive blood culture was drawn within 4 days of the first positive blood culture.
• Severe liver disease. This is not an exclusion criterion, if the following condition is fulfilled: catheter-related infection, skin and soft tissue infection or surgical wound infection is present.
End-stage renal disease. This is not an exclusion criterion, if all of the following conditions are fulfilled: catheter-related infection, skin and soft tissue infection or surgical wound infection is present and no clinical signs of infective endocarditis, and infective endocarditis unlikely by echocardiography (preferably TEE), and in patients with a hemodialysis shunt with a non-removable foreign body (e.g. synthetic PTFE loop): no clinical signs of a shunt infection
Severe immunodeficiency (e.g. neutropenia, high dose steroid therapy, immonusuppresive combination therapy, biological (last year), hematopoietic stem cell transplant, solid organ transplant)
Life expectancy < 3 months
Inability to take oral drugs
Expected low compliance with drug regimen
Participation in other interventional trials
Pregnancy/nursing
For included women: Failure to use highly-effective contraceptive methods

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-01-2016
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Cefazolin
Registration:	Yes - NL intended use
Product type:	Medicine
Generic name:	Flucloxacillin
Registration:	Yes - NL intended use
Product type:	Medicine
Generic name:	Vancomycin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cubicin
Generic name:	Daptomycin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Zyvoxid
Generic name:	Linezolid
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	02-10-2014
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	06-05-2015
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	17-06-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	22-06-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-08-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-01-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-09-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-02-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-11-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-11-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-12-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-01-2018
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2013-000577-77-NL
ClinicalTrials.gov	NCT01792804
CCMO	NL48081.041.14

Study results

Date completed:	31-03-2020
Results posted:	14-03-2022
Actual enrolment:	60

Summary results
Trial is onging in other countries

First publication
14-06-2021