Impact of NOD2 genotype-guided antibiotic prevention on survival in patients with liver cirrhosis and ascites

INCA

Patients with advanced liver scarring (cirrhosis) are at high risk for infections. A common and dangerous complication is the infection of the abdominal fluid (ascites), which is also known as Spontaneous Bacterial Peritonitis (SBP). Our recently performed genetic study has indicated that genetic factors determine SBP risk. Three risk variants of the gene NOD2 are linked to an increased SBP rate and shorter survival of affected patients. Patients who have already suffered from SBP benefit from subsequent prophylaxis with antibiotics. The drug norfloxacin has been demonstrated to be effective in this scenario and has been used for many years for patients with cirrhosis to avoid the recurrence of SBP. A general prophylactic treatment of all patients with cirrhosis to avoid a first SBP episode has not been shown yet to provide clinical benefit.

This clinical trial will examine whether or not patients who carry a NOD2 risk variant and hence an increased risk to develop SBP benefit from antibiotic prophylaxis with norfloxacin. In principle, all patients with cirrhosis of the liver who have already developed ascites but not SBP, are eligible for the trial. Particularly, SBP has to be excluded and ascitic protein content has to be determined by a clinically indicated index paracentesis (maximally 10 days prior to baseline visit). Patients who cannot undergo paracentesis because of small amounts of ascites can only be included in the trial if SBP is unlikely taking into account clinical and blood test indicators. All patients must be checked for the three NOD2 risk variants. A randomized allocation of the study participants in one of the two treatment arms (ratio 1:1) will be performed. The remaining measures in both treatment arms are identical so that neither the patient nor the investigator know which arm the patient is assigned to (double-blind). One half of the patients will then receive a daily dose of norfloxacin (capsule of 400 mg) over a time period of 12 months, while the other half in the control-arm receive an identical-looking capsule with an inactive ingredient (placebo) over 12 months. The clinical trial tests whether the prophylaxis with norfloxacin improves the survival of patients with cirrhosis and ascites. In addition, the clinical trial investigates whether the frequencies of SBP and other serious infections decrease in the arm receiving norfloxacin, and if this results in a reduction of hospital stays.

Chronic liver diseases can ultimately result in liver cirrhosis. The alcoholic and
non-alcoholic fatty liver diseases as well as the chronic virus hepatitis are the most important causes of cirrhosis. Patients with cirrhosis display a tenfold risk for bacterial infections. Spontaneous bacterial peritonitis (SBP) and urinary tract infections are most common. Moreover, the occurrence of infections represents a negative prognostic factor. In the setting of bacterial infections, the mortality risk quadruples to a median mortality of 63% within one year. Since currently up to 50% of the patients on the waiting list for liver transplantation die of infectious complications, prevention of infection should optimize patient care. After successfully treated SBP, patients have a high recurrence risk, hence antibiotic long-term secondary prophylaxis has become the standard of care for this group of patients. The best evidence exists for fluoroquinolones, in particular norfloxacin. On the contrary, a broad use of antibiotics to prevent SBP (primary prophylaxis) cannot be recommended based on current data. Recently NOD2 gene variants were found to be associated with SBP and mortality in patients with decompensated cirrhosis. Current research should thus aim to implement this information into individualized algorithms to optimize patient care. The INCA trial will test whether antibiotic primary prophylaxis for patients at highest genetic risk of SBP can improve their survival rate. This high risk group will be defined based on the presence of NOD2 risk variants. In general, patients with cirrhosis who have already developed ascites will be verified to carry at least one of the common NOD2 risk variants p.N289S, p.R702W, p.G908R, c.3020insC or rs72796367. The most important exclusion criteria are current or previous SBP. The clinical trial will be performed in a double-blind and placebo-controlled design with two parallel treatment arms (Arm A: norfloxacin 400 mg once daily; Arm B: placebo once daily) and an intervention phase of 12 months. Norfloxacin, with predominant activity against gram-negative bacteria, is an evidence-based intervention for secondary prophylaxis of SBP. Overall, 186 patients are planned to be allocated to the treatment arms using central randomization (1:1 ratio), stratified for the protein content of the ascites (<15 vs. ≥15 g/l). The primary endpoint of the study is survival after 12 months. The secondary endpoints aim to evaluate whether the frequencies of SBP and other clinically relevant infections (urinary tract infection, pneumonia, sepsis, bacteremia) as well as the total duration of unplanned hospitalization due to cirrhosis differ in both study arms.
Health condition or Problem studied

- ICD10: K74 - Fibrosis and cirrhosis of liver
- ICD10: R18 - Ascites

Interventions/Observational Groups

- Arm 1: Norfloxacin (Norfloxacina ABC), 400mg/d p.o. (capsule), for 12 months
- Arm 2: Placebo, once daily p.o. (capsule), for 12 months

Characteristics

- Study Type: Interventional
- Study Type Non-Interventional: [---]*
- Allocation: Randomized controlled trial
- Blinding: [---]*
- Who is blinded: patient/subject, investigator/therapist
- Control: Placebo
- Purpose: Prevention
- Assignment: Parallel
- Phase: III
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): Yes

Primary Outcome

Overall survival after 12 months

Secondary Outcome

1. Spontaneous bacterial peritonitis (SBP) within 12 months
2. Other clinically significant infections (urinary tract infections, pneumonia, sepsis, bacteraemia) requiring antimicrobial treatment within 12 months
3. Duration of unscheduled cirrhosis-associated hospitalisation within 12 months

Countries of recruitment

- DE Germany

Locations of Recruitment
University Medical Center Klinik für Innere Medizin II, Homburg/Saar

University Medical Center Medizinische Klinik 1, Bonn

University Medical Center Klinik für Gastroenterologie und Hepatologie, Essen

University Medical Center Medizinische Klinik 1, Frankfurt a.M.

University Medical Center I. Medizinische Klinik, Hamburg

University Medical Center Klinik für Innere Medizin IV, Jena

Medical Center Klinik für Innere Medizin 3, Kaiserslautern

University Medical Center Klinik für Gastroenterologie, Leipzig

University Medical Center I. Medizinische Klinik, Mainz

University Medical Center Klinik für Innere Medizin I, Halle Saale

University Medical Center Klinik für Innere Medizin II, Mannheim

University Medical Center Klinik für Innere Medizin III, Aachen

University Medical Center Medizinische Klinik und Poliklinik II, Würzburg

University Medical Center Klinik für Gastroenterologie und Hepatologie, Köln

University Medical Center Klinik für Innere Medizin II, Freiburg im Breisgau

University Medical Center Klinik für Gastroenterologie, Hepatologie und Endokrinologie, Hannover

University Medical Center Abteilung Gastroenterologie und Endokrinologie, Rostock

Recruitment

Planned/Actual: Actual

(Anticipated or Actual) Date of First Enrollment: 2014/03/04

Target Sample Size: 186

Monocenter/Multicenter trial: Multicenter trial

National/International: National

Inclusion Criteria

Gender: Both, male and female

Minimum Age: 18 Years

Maximum Age: no maximum age

Additional Inclusion Criteria

Age ≥ 18 years.

Written informed consent to participate in the clinical trial and written informed consent for genetic testing.
Patients have to be able to understand and follow instructions and be willing to attend all study visits (compliance).

Presence or history of ascites in case of advanced liver disease compatible with cirrhosis (liver biopsy not required).

Diagnostic paracentesis to exclude a spontaneous bacterial peritonitis within 10 days before the baseline visit. Patients who cannot undergo paracentesis because of small amounts of ascites can only be included in the trial if SBP is unlikely taking into account clinical and blood test indicators.


Pregnancy is to be excluded by a pregnancy test (beta-HCG blood test or urine test) in females at child-bearing age who have not undergone surgical contraceptive methods or hysterectomy. These patients have to use effective contraceptive methods.

**Exclusion criteria**

*Age <18 years.*

*Absent written informed consent to participate in the clinical trial or for genetic testing.*

*Patients unable to understand or follow instructions, or not willing to attend all study visits.*

*Simultaneous participation in another clinical trial (study medication has to be stopped for almost 30 days before the baseline visit).*

*Persistent drug abuse (alcohol abuse may be tolerated in the setting of adequate compliance).*

*Pregnancy, planned pregnancy, or breastfeeding patients.*

*Spontaneous bacterial peritonitis diagnosed by the index paracentesis within 10 days before baseline.*

*Previous history of spontaneous bacterial peritonitis (when this is uncertain, absence of an antibiotic secondary prophylaxis may be used as an alternative criterion to exclude SBP).*

*Patients without history of ascites.*

*Antibiotic long-term prophylaxis irrespective of the indication. Long-term treatment is to be completed at least 28 days before randomisation.*

*Contraindications against norfloxacin,*
*e.g. intolerance to norfloxacin, to substances with related chemical structure or to other components of norfloxacin or placebo;*  
e.g. patients with acquired Long-QT syndrome, or other not modifiable risk-factors causing a persisting QTc prolongation (corrected according to Bazett's formula: $>470$ms for males and $>480$ms for females);  
e.g. patients with galactose intolerance, lactamase deficiency, or glucose/galactose-malabsorption;  
e.g. patients with myasthenia gravis;
e.g. patients with tendinitis or tendon rupture linked to fluorochinolone intake.

Patients with a life expectancy of less than 12 months due to hepatocellular cancer, other malignant diseases, or another severe comorbidity.

HIV infected patients with a CDC-classification clinical stage C or laboratory stage 3.

Addresses

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Status

- Recruitment Status: Recruiting ongoing
- Study Closing (LPLV): [---]*

Trial Publications, Results and other documents

* This entry means the parameter is not applicable or has not been set.

*** This entry means that data is not displayed due to insufficient data privacy clearing.