Vorlagenummer: 4033936
Meldungsnummer: B20A30
Prüfplancode: PATRON_07
EudraCT: 2007-003561-40

1) Name of Sponsor/Company
Free State of Bavaria
represented by Regensburg University
represented by Regensburg University Hospital
represented by theDepartment of Surgery

2) Name of Finished Product
Rapamune

3.) Name of Active Substance
Sirolimus

4) **Individual Study Table: Referring to Part of the Dossier (Volume, Page)**
not applicable

5) Title of Study
A Pilot Study to Determine the Safety and Efficacy of Induction-Therapy, De Novo MPA and Delayed mTOR-Inhibition in Liver Transplant Recipients with Impaired Renal Function: PATRON-Study

Protocolnumber: Patron_07, Version 3, including amendment 2, 30Oct2008

6) Investigators
Principal Investigator of the study: Prof. Dr. Hans J. Schlitt
Coordinating Investigator: PD Dr. Andreas A. Schnitzbauer
Investigator: Dr. Lucia Baier, Prof. Dr. Marcus Scherer
Statistics Development: Justine Rochon

7) Study centre(s)
Regensburg University Hospital, Department of Surgery

8) Publication (reference)
Study Protocol:
Schnitzbauer AA, Scherer MN, Rochon J, Sothmann J, Farkas SA, Loss M, Geissler EK, Obed A, Schlitt HJ. Study protocol: a pilot study to determine the safety and efficacy of induction-therapy, de novo MPA and delayed mTOR-inhibition in liver transplant recipients with impaired renal function. PATRON-study. BMC Nephrol. 2010 Sep 14;11:24. doi: 10.1186/1471-2369-11-24. PubMed PMID: 20840760; PubMed Central PMCID: PMC2945344.

Final data publication currently in progress.

9) Studied period (years):
date of first enrolment: Dec. 28th2008
date of last completed: May 31st 2012

10) Phase of development:
III

11) Objectives
The primary objective of the study was to evaluate a de novo calcineurin-inhibitor-free immunosuppressive regimen based on induction therapy with anti-CD25 monoclonal anti- body, mycophenolate mofetil (MMF/MPA), and mTOR-inhibition with sirolimus to determine its safety and to investigate the preliminary efficacy in patients with impaired renal function at the time-point of liver transplantation with regards to the incidence of steroid resistant acute rejection within the first 30 days after liver transplantation.

Secondary endpoints for the underlying study were:

1. Incidence of acute rejections within 30 days and 3, 6 and 12 months after LT
2. Number of acute rejections per patient
3. Time-point of acute rejection(s) after LT
4. Improvement and deterioration of renal function at 1, 3, 6 and 12 months in comparison to pre-transplant renal function
5. Number of patients requiring renal replacement therapy
6. Duration of renal replacement therapy
7. Liver allograft function
8. Infectious complications
9. Treatment failure, defined as reintroduction of CNI
10. Hemato-lymphatic side effects
11. Incidence of hepatic artery stenoses
12. Wound-healing disturbances
13. Mortality

12) Methodology
prospective, open-label, sigle-arm, two-stage study.

13) Number of patients (planned and analysed)
Maximum of 29, included 27, analyzed 27.

14) Diagnosis and main criteria for inclusion
1. Patients undergoing primary liver transplantation.
2. Patients older than 18 years.
3. Patients with a hepatorenal syndrome
4. Female patients of childbearing potential willing to perform a highly effective contraception during the study and 12 weeks after conclusion of study participation
5. eGFR < 50 ml/min at the time point of transplantation
6. Serum creatinine levels > 1.5 mg/dL at the time-point of transplantation

15) Test product, dose and mode of administration, batch number
Sirolimus was used in 1 and 2mg oral tablets in this investigator initiated trial. Commercially available drug was prescribed. Patients were advised to oral intake as prescribed in the leaflet of the drug. Regular trough-level measurements and laboratory controls (as standard procedure after liver transplantation at our center

including the study specific procedures (visits) were performed to monitor compliance of the patients. C0-trough-levels aimed at 4 to 8 ng/ml.

16) Duration of treatment
Permanent post transplant immunosuppressive therapy with Sirolimus not starting before day 10 after transplantation.

17) Reference therapy, dose and mode of administration, batch number
no reference therapy applied

18) Criteria for evaluation: Efficacy, Safety
The objective of the study is to evaluate a de novo calcineurin-inhibitor-free immunosuppressive regimen based on induction therapy with anti-CD25 monoclonal anti- body, mycophenolate mofetil (MMF/MPA), and mTOR-inhibition with sirolimus to determine its safety. The primary endpoint was the incidence of steroid resistant acute rejection within the first 30 days after liver transplantation. Based on Cochrane database and Medline database data including a total of 2.200 patients, the incidence of steroid resistant rejection within the first year after transplantation with the commonly used CNI-based and CNI-reduced protocols is 12.5% of all patients undergoing LT. This means that 87.5% of patients are without steroid resistant rejection (i.e., the response proportion is 87.5%). The primary endpoint was chosen because steroid resistant acute rejections reflect the most relevant allograft threatening situation in a liver transplant setting and therefore are a good parameter to control efficacy of the underlying treatment.

Renal function was measured by Serum-creatinine values and the eGFR (MDRD) using the formula: Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D, for the Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 1999;130:461-470. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002;39(suppl 1):S76-S110. **Estimated GFR (mL/min/1.73 ^{2}) = 170 x (SCr)$^{-0.999}$ x (Age)$^{-0.176}$ x (BUN)$^{-0.170}$ x (Alb)$^{+0.318}$ x (0.762 if female) x (1.180 if African-American).** In case a patient was on dialysis the creatinine value was logged as 4 mg/dL and the eGFR value was logged as 20ml/min.
Hepatic artery thromboses were evaluated by Doppler-ultrasound in the US-center of Regensburg University. Liver allograft function, hematolymphatic side-effects were determined from basic laboratory work-up.

AEs were evaluated from patient charts during clinical stay and with a specific checklist in the outpatient care setting. Events brought to the attention of the investigators by the patient or by patient documents from other medical treatment independent from checklists were documented accordingly. For every AE, an evaluation with regards to start and stop date, seriousness, unexpectedness, relation to study drug and the requirement for a specific treatment was made by the investigators and documented by the study nurse/ study assistant. All criteria had to be confirmed by one of the investigators. Follow-up of AEs were performed during study visits, and whenever new information came to the attention of the investigators or study nurse.

19) Statistical methods

This was a prospective, open-label, two-stage study. The primary endpoint was the incidence of steroid resistant acute rejection within the first 30 days after liver transplantation (LT). Based on Cochrane database and Medline database data including a total of 2.200 patients, the incidence of steroid resistant rejection within the first year after transplantation with the commonly used CNI-based and CNI-reduced protocols is 12.5% of all patients undergoing LT. This means that 87.5% of patients are without steroid resistant rejection (i.e., the response proportion is 87.5%). Based on this estimation an optimal two-stage design [28] was applied to test the following statistical hypotheses:

H_0: The true response probability p is less than the uninteresting level p_0 ($p \leq p_0$). versus

H_1: The true response probability p is at least the target level p_1 ($p \geq p_1$).

In this study, the uninteresting level was defined as $p_0 = 0.80$, which means that 20% of our examined cohort would experience a steroid resistant early acute rejection within the first 30 days after LT. The target level was defined as $p_1 = 0.95$, which means that 5% of our collective would experience a steroid resistant early rejection within the first 30 days. Under these assumptions, 9 patients have been enrolled in the first stage. After testing the immunosuppressive regimen on 9 patients in the first stage, the trial would be terminated if 7 or fewer responded to the therapy. Thereafter the trial went on to the second stage with the following assaumptions: an additional 20 patients will be enrolled. With a total of 29 patients, the following decisions were made: If 26 or fewer responders are observed, then do not reject H_0. In this case, the immunosuppressive therapy is not promising with a high probability and is not worth to be tested in a greater trial in this indication. If 27 or more responders are observed, then reject H_0. In this case, the immunosuppressive regimen was considered promising. If the therapy was actually not promising, there is a 0.049 probability of concluding that it was (the target significance level was set to 5%). If the therapy was actually promising, there was a 0.198 probability of concluding that it was not (the target for this value was set to 20%). The confirmatory analysis was performed for the intent-to-treat population.

20) Summary – Conclusions: Efficacy Results, Safety Results, Conclusion

The primary endpoint of steroid resistant biopsy proven acute rejection was reached after inclusion of 27 patients in the study. In the ITT analysis no event occurred. We therefore can conclude that bottom-up immunosuppressive therapy is efficient in patients undergoing liver transplantation with preexisting renal impairment as stated in our primary hypothesis. Notably, none of the transplanted organs was lost due to an acute rejection or due to a repeated acute rejection. Renal function, as the most interesting secondary outcome measure improved by 20ml/min in GFR for all patients in median until 1 year after transplantation. This is a promising result but must be seen individually for each patient. First, some patients were permanently on dialysis (n=4) until the end of the study or until they died (n=2). In case renal function did not improve in the early phase between day 30 or month 3, renal function was likely to be stable or even deteriorate until 12 months after transplantation progressively. Side effects - especially black box warnings - like excessive mortality under sirolimus treatment (n=2, 7%) and occurrence of hepatic artery thrombosis were very low (n=1, 3,5%). Otherwise, typically described side effects like a slightly increased prevalence of infections, hemato-poetic disorders, or edema were present

but not exaggeratingly high and comparable to data published and reported in earlier prospective clinical trials. Nonetheless, it is not clear whether bottom-up immunosuppressive therapy is absolutely necessary using an mTOR-inhibitor. Our data indicate that drug holiday (mTOR or CNI) in patients with renal impairment prior and after liver transplantation is both resulting in similar and comparable renal functions by month 12 after liver transplantation (PP 12 month, renal function).
Concerning the primary endpoint there have been no observations of steroid resistant biopsy proven acute rejections throughout the study period indicating feasibility and safety of bottom-up immunosuppression with mTOR-inhibition in the early phase after transplantation (up to day 30). Thereafter, calcineurin-inhibitor treatment should be considered in case an acute rejection occurs in order to avoid repeated acute rejection episodes. These findings are known from other trials in a liver transplant setting with sirolimus and do thus not change the overall benefit-risk assessment for the drug. Notably, there were 3 retransplantations in 2 patients, none due to lack of efficacy and 2 non-immunosuppressive related deaths. A total of 20 patients (74%) showed mild to moderate improvement of renal function by 1 year after transplantation, 4 were on dialysis (including the 2 death cases at the time point of death) and 3 had equal or worse renal function 1 year after transplantation. The study did not reveal important risks that were not yet known under sirolimus treatment. Calcineurin inhibitor free bottom-up immunosuppression with and even without sirolimus is feasible. Calcineurin inhibitor treatment in case of biopsy proven acute rejections and in general beyond day 30 after transplantation should be considered. Side effects (SAEs and SADRS) occurring under sirolimus treatment are those expected. The prevalence is acceptable. There was no excessive mortality under sirolimus treatment.

Conclusions:
The primary endpoint of steroid resistant biopsy proven acute rejection was reached after inclusion of 27 patients in the study. In the ITT analysis no event occurred. We therefore can conclude that bottom-up immunosuppressive therapy is efficient in patients undergoing liver transplantation with preexisting renal impairment as stated in our primary hypothesis. Notably, none of the transplanted organs was lost due to an acute rejection or due to a repeated acute rejection. Renal function, as the most interesting secondary outcome measure improved by 20ml/min in GFR for all patients in median until 1 year after transplantation. This is a promising result but must be seen individually for each patient. First, some patients were permanently on dialysis (n=4) until the end of the study or until they died (n=2). In case renal function did not improve in the early phase between day 30 or month 3, renal function was likely to be stable or even deteriorate until 12 months after transplantation progressively. Side effects, especially black box warnings like excessive mortality under sirolimus treatment (n=2, 7%) and occurrence of hepatic artery thrombosis were very low (n=1, 3,5%) were very low. Otherwise, typically described side effects like a slightly increased prevalence of infections, hemato-poetic disorders, or edema were present but not exaggeratingly high and comparable to data published and reported in earlier prospective clinical trials. Nonetheless, it is not clear whether bottom-up immunosuppressive therapy is absolutely necessary using an mTOR-inhibitor. Our data indicate that drug holiday (mTOR or CNI) in patients with renal impairment prior and after liver transplantation is both resulting in similar and comparable renal functions by month 12 after liver transplantation (PP 12 month, renal function). Notably, there were 3 retransplantations in 2 patients, none due to lack of efficacy and 2 non-immunosuppressive related deaths. A total of 20 patients

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21) Date of report.
February 20th 2014