Author's response to reviews

Title: Budd-Chiari Syndrome: Long term success via hepatic decompression using transjugular intrahepatic porto-systemic shunt

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Author's response to reviews: see over
Cover Letter

Dear Editor Dr. Zauner,

thank you very much for the comments of the reviewer which were extremely helpful to improve our manuscript.

In the following we are giving a point-by-point response to the comments of the reviewer Martin Rössle.

Major Revisions:

1. This is correct the reduction in survival in the TIPS group is 7.7% and not 25%. We modified and corrected the Kaplan-Meier analysis as you can see in figure 1. In each group (non-intervention, TIPS and OLT) one patient died. The probability of survival in the whole collective was 72.6%. This was corrected in the manuscript.

2. We agree with the comments of the Reviewer. After submission of our manuscript actually the first prospective study on Budd-Chiari syndrome has been published (Darwish Murad S, et al. Etiology, management, and outcome of Budd-Chiari Syndrome. Ann Intern Med. 2009 Aug 4; 151(3): 167-75). Therefore, we dropped the paragraph, as suggested and inserted a new paragraph referring to the above mentioned study (see Major Compulsory Revision 1. of Reviewer Juan Gonzalez-Abraldes): “Recommendations and guidelines for the management of BCS have been derived from retrospective studies. So far, only one prospective study on BCS has been published”.

3. We removed this mistakable formulation. We added the time of presentation to Table 1, as suggested. As you can see from Table 1, two patients were transplanted after TIPS had been introduced as a treatment option of BCS. Both patients had cirrhosis with signs of chronic liver failure in terms of hepatic encephalopathy and high bilirubin levels so that liver transplantation was considered the best option.

4. We unfortunately made a mistake and did not mention that we have used covered Viatorr stents. In Heidelberg, the first covered stent for the treatment of BCS was applied in 2002. We completed the Patients and Methods Section (third paragraph): “All TIPS were created using standard techniques by insertion of Palmaz stents
(Johnson and Johnson Interventional Systems, Warren, New Jersey), Wallstents (Schneider, Minneapolis, Minnesota) or covered Viatorr stents (GORE, Flagstaff, AZ).” A pressure gradient between 10 and 12 mmHg was tried to achieve. We corrected this in the manuscript.

5. We added a chapter to the Methods Section giving a definition of disease severity (acute, subacute or chronic): “Disease severity was defined as acute, subacute or chronic. In contrast to the acute disease, the subacute and chronic forms were assumed to be present for several weeks to more than six months prior to clinical presentation.”. Disease severity at presentation did not influence the outcome. In the OLT group chronic disease was proportionately higher than in the TIPS group.

6. In our study, one patient died in the course of the underlying hematologic disease. This is already mentioned in the Results Section. We added this fact to the Abstract and the Discussion.

7. We agree, the comparison of the gender distribution may not be enough to draw such a general conclusion. Therefore, as suggested by the Reviewer, we compared our cohort to that of Darwish Murad et al (see Ref 18) which is one of the largest cohorts in the literature and changed the text as follows: “Although, our collective of 20 patients is limited in number, it is however comparable to collectives in other studies, with respect to the demographic data of the patients included. As example, in accordance with the collective of Darwish Murad et al. 80% of our patients are women who presented with symptoms in the third or fourth decade.”

8. According to the suggestion of the Reviewer we replaced the last part of the second paragraph of the Discussion Section.

9. The Reviewer asked if we have applied treatments in a stepwise manner. In part, we applied treatment in a stepwise manner. In our collective there are still 2 patients which have not had an intervention, yet and which are still without clinical symptoms under anticoagulation therapy. Furthermore, as you can see from table 1 in 5 of 13 patients in the TIPS group the time between primary diagnosis and intervention was at least 1 month. In the meantime these 5 patients received symptomatic therapy including diuretics and anticoagulation. As they did not improve, TIPS insertion was performed. To our knowledge, a recommendation concerning an adequate duration of medical treatment before intervention is not given in the present Baveno consensus, neither a clear definition of treatment failure. Percutaneous angioplasty and stenting which is recommended before TIPS in the present Baveno consensus was not
considered feasible in any of our patients. This approach seems to be justified, particularly as the AASLD guideline 2009 recommends to consider TIPS in patients without ongoing improvement on anticoagulation therapy with or without angioplasty (De Leve LD et al. Hepatology 2009 May; 49(5): 1729-64). On the basis of radiological imaging and the severity of clinical presentation in 8 of 13 patients in the TIPS group an intervention was performed shortly after the primary diagnosis. This decision was reached by an experienced interdisciplinary team. Liver transplantation was performed in patients with cirrhosis and contraindications for TIPS. We added this approach to the Methods Section: “Different from the last Baveno consensus treatment was only partly applied in a stepwise manner. On the basis of radiological imaging and the severity of clinical presentation a decision by an experienced interdisciplinary team concerning adequate treatment was reached. This could either be a medical treatment or a prompt intervention. If patients did not improve on medical therapy TIPS insertion was performed.”.

10. In the literature the use of covered stents in patients with BCS has been associated with a lower rate of dysfunction. However, TIPS revisions in patients with covered stents have been necessary, in our collective, too. Patients who needed TIPS revision and who initially received an uncovered stent, were treated by angioplasty alone or by placement of an additional stent using covered stents after 2002. We added the following to the Discussion: “Since, covered stents have a considerable advantage over bare stents for the treatment of BCS patients, with a lower dysfunction rate covered stents should be preferred.”

11. We revised the sentence as follows: “None of our patients in the TIPS group had to undergo OLT, subsequently.”

12. 1. Two patients were transplanted before TIPS was introduced as a treatment option in BCS patients. As already mentioned above (see 3.) the other two patients had signs of cirrhosis in terms of hepatic encephalopathy and high bilirubin levels so that TIPS insertion was counterindicated.

2. The patients in the OLT group did not have a number of additional diseases. One had a sarcoidosis and one an osteoporosis, the other two were otherwise healthy. On average patients in the OLT group were younger than in the TIPS group and after a resurvey of the patients characteristics no additional risk factors could be found.

3. Anticoagulation was started 4 hours after transplantation with heparin in a prophylactic dosage. After 24 hours heparin was applied in a therapeutic dosage. HIT
was not diagnosed in any of the transplanted patients. In the long run all patients received coumarin derivatives.

4. In our centre approximately 100 liver transplantations and 70 TIPS procedures are performed per year. Given the rarity of BCS, we believe that our centre is skilled in the required procedures, even in patients with BCS.

In the following we are giving a point-by-point response to the comments of the reviewer Juan Gonzalez-Abraldes.

**Major Compulsory Revisions:**

1. The recently published study of Darwish Murad S, et al is now cited in the Introduction Section (see paragraph 2: “So far, only one prospective study on BCS has been published”). The results of the study are discussed in the Discussion Section (see paragraph 2): “Surprisingly, in the recently published first prospective study nearly 50 % of the patients were managed conservatively, too. But there may be limitations of this study, on the one hand the study was not restricted to patients with severe disease and on the other hand the median follow-up was only 17 months.”

2. As we mentioned above (see Major Revisions 4. of reviewer Martin Rössle), we have used covered stents. We unfortunately made a mistake and did not mention that we have used covered Viatorr stents. In Heidelberg, the first covered stent for the treatment of BCS was applied in 2002. We completed the Patients and Methods Section (third paragraph): “All TIPS were created using standard techniques by insertion of Palmaz stents (Johnson and Johnson Interventional Systems, Warren, New Jersey), Wallstents (Schneider, Minneapolis, Minnesota) or covered Viatorr stents (GORE, Flagstaff, AZ).”

3. The 3 patients who did not have TIPS or OLT have been added to Table 1.

**Minor Essential Revisions:**

4. Some patients previously considered of unknown etiology can currently be diagnosed of MPD by the analysis of the JAK2V617F mutation. Therefore, we added the following sentence “As our study begun in 1988, not all of our patients were screened
for the JAK2V617F mutation." to the Patients and Methods Section and the following sentence “As not all of our patients were screened for the JAK2V617F mutation latent MPD may have been missed in several patients. ” to the Results Section.

Yours sincerely, Alexandra Zahn and Peter Sauer.