Title

Improvements in Disease-Specific Health-Related Quality of Life of Pediatric Liver Transplant Recipients During Immunosuppression Withdrawal

Journal

Liver Transplantation, 27(5)

ISSN

1527-6465

Authors

Mohammad, Saeed
Sundaram, Shikha S
Mason, Kristen
et al.

Publication Date

2021-05-01

DOI

10.1002/lt.25963

Peer reviewed

HHS Public Access

Author manuscript

Liver Transpl. Author manuscript; available in PMC 2022 May 01.

Published in final edited form as:

Liver Transpl. 2021 May ; 27(5): 735–746. doi:10.1002/lt.25963.

Improvements in Disease Specific Health-Related Quality of Life of Pediatric Liver Transplant Recipients During Immunosuppression Withdrawal

Saeed Mohammad, MD[1], **Shikha S. Sundaram, MD MSCI**[2], **Kristen Mason, MS**[3], **Steven Lobritto, MD**[4], **Mercedes Martinez, MD**[4], **Yumirle P. Turmelle, MD**[5], **John Bucuvalas, MD**[6], **Sandy Feng, MD PhD**[7], **Estella M. Alonso, MD**[1]

[1]Siragusa Transplantation Center, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL

[2]Division of Gastroenterology, Hepatology, and Nutrition, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, CO

[3]Rho, Inc., Durham, NC

[4]Center for Liver Diseases and Transplantation, Department of Surgery, Columbia University Irving Medical Center, New York, NY

[5]Division of Gastroenterology, Hepatology, and Nutrition, Washington University School of Medicine, St. Louis, MO

[6]Mount Sinai Kravis Children's Hospital and Recanati/Miller Transplantation Institute Mount Sinai Health System, New York, NY

[7]Division of Transplantation, Department of Surgery, University of California San Francisco, San Francisco, CA

Abstract

Long-term immunosuppression leads to systemic complications affecting health-related quality of life in pediatric liver transplant recipients. We serially assessed health-related quality of life using PedsQL™ Generic, Multidimensional Fatigue, Family Impact, and Transplant modules as part of a multicenter prospective immunosuppression withdrawal trial between 2012–2018.

Participants received a primary liver transplant ≥4 years ago, were on stable immunosuppression with normal liver tests and without rejection in the prior 2 years. Immunosuppression was withdrawn in 7 steps over 36–48 weeks. Health-related quality of life was assessed at regular intervals. The primary endpoint was change in disease-specific health-related quality of life measured by the PedsQL™ Transplant Module. Generic health related quality of life was

Corresponding Author: Saeed Mohammad MD, Northwestern University, Feinberg School of Medicine, 225 E Chicago Ave, Box 65, Chicago IL 60611, smohammad@luriechildrens.org, Telephone: (312) 227-4606, Fax: (312) 227-9645.

Conflicts of Interest Disclosure:

The authors of this manuscript have no conflicts of interest to disclose

Data Availability: "The data that support the findings of this study will be made openly available in ITN TrialShare (itntrialshare.org) and NIAID ImmPort (http://immport.niaid.nih.gov/)"

measured by the PedsQL™ Generic module and was compared to an age and gender matched multi-center cohort. Of the 88 participants, 39 were male, median age was 11 years (range 8–13years) and time since transplant was 9 years (range 6–11years). Over 36 months, disease-specific health-related quality of life improved for all participants, while generic health-related quality of life was unchanged. Neither generic nor disease-specific health-related quality of life changed for the 35 participants who developed acute rejection during immunosuppression withdrawal.

Conclusion: In the first of patient-reported outcome measures during immunosuppression withdrawal trial, we found improvements in disease-specific health-related quality of life in all participants and no lasting detrimental effects in those who experienced rejection.

Trial registration: ClinicalTrials.gov identifier: NCT01638559

Keywords

Outcomes; Side effects; Health Status; Adherence; Rejection

1. INTRODUCTION

Sustained optimal patient and allograft health are the ultimate goals after pediatric liver transplantation (LT). In the hierarchy of patient outcomes, once survival and recovery are achieved, sustainability of health and minimization of adverse consequences of maintenance therapy become the next areas of focus.[1] Long-term pediatric LT recipients report health-related quality of life (HRQOL) below that of healthy controls, even in the setting of normal graft function.[2, 3] Although some functional deficits may be due to static insults incurred prior to transplantation, the cumulative toxicities of immunosuppression (IS) including infection, nephrotoxicity, cardiovascular disease, obesity, and malignancy undoubtedly play a role.[4–7]

The multiple systemic complications associated with standard IS, mandates research to explore the potential benefit of IS minimization or elimination. Single-center reports have demonstrated that selected LT recipients tolerate reduced doses of IS.[8, 9] Prospective clinical trials have shown >40% of selected pediatric LT recipients can safely withdraw from IS [10]which is important as these patients face decades of drug exposure. Regimens that substitute standard IS for less toxic medications may hold promise, but evidence of the efficacy and toxicity of these newer approaches in children is still forthcoming.[11] Side effects of long-term IS including detrimental cognitive changes and alterations of renal function may take decades to become apparent, and possibly longer to reverse.[12, 13] The incidence of cancer increases considerably in LT recipients in their second decade of life[14], therefore medical outcomes, such as incidence and/or severity of hypertension, metabolic derangements, or infectious complications, as indicators of the benefit of immunosuppression withdrawal (ISW) are impractical trial endpoints due to the heterogenous population and duration of follow-up required.

Generic and disease-specific patient-reported outcome measures (PROMs) may provide crucial real-time information to assess potential benefits of ISW while measurable medical

benefits may take many years to emerge.[10, 15] Generic surveys of HRQOL (measuring physical, emotional, social, and cognitive function) have been applied to several chronic disease populations to determine how responses differ from those of a healthy population. While generic surveys permit comparisons among conditions, disease-specific surveys capture variables unique to a particular patient population, such as IS medication side effects in transplant recipients.

We hypothesized that prospective measurement of both generic and disease-specific HRQOL in patients who are in the process of eliminating IS would reveal significant improvements in disease-specific symptoms, regardless of the ISW outcome. Additionally, we expected to observe improvement in HRQOL for tolerant participants without sustained deterioration in the HRQOL of non-tolerant participants.

2. METHODS

2.1 Trial design and participants

We studied HRQOL as part of a multicenter, longitudinal, prospective trial of ISW, titled Immunosuppression Withdrawal for Stable Pediatric Liver Transplant Recipients (iWITH;NCT01638559). Eligible participants received primary living or deceased donor LT for non-viral, non-autoimmune liver disease at 6 years of age or younger at least 4 years prior to trial entry. Participants were required to have alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) values consistently <50 U/L on a stable dose of calcineurin inhibitor monotherapy and without rejection during the preceding 2 years. Final eligibility was determined by central assessment of a liver biopsy according to strict criteria for inflammation, fibrosis, and other histopathology.[16] The institutional review board at participating centers approved the trial and written informed consent was obtained from all parents or guardians prior to participation. Assent was obtained from children as required by individual institutions.

2.2 Trial procedures and endpoints

IS was withdrawn in 7 steps, each lasting 4 to 6 weeks (eFigure 1). Liver tests were monitored biweekly for at least 48 weeks. For-cause biopsies could be performed at any time per clinical discretion but were mandated if ALT or GGT values exceeded 100 U/L. Local histologic assessment guided clinical decision-making; central histologic assessment was utilized for data analysis. Participants who completed ISW and maintained stable liver tests without rejection were evaluated 1 year after the last dose for the primary endpoint of operational tolerance, defined as ALT and GGT values <50 U/L and liver biopsy (tolerance assessment biopsy) with no more than minimal change compared to the eligibility biopsy.[16]

2.3 HRQOL measures

Three generic and 1 disease specific HRQOL survey instruments were administered at baseline, 6, 12, 18, 24, and 36 months. These time points were chosen to capture a wide array of possible health events that may occur during trial participation. The baseline survey was performed prior to ISW, and the 6- and 12-month surveys captured health events

occurring during active ISW. The 24-month survey corresponded to the tolerance assessment biopsy, performed 1 year after complete ISW for those who did not have rejection. The last survey occurred at a time of stability, when no interventions were being undertaken. Figure 1A depicts the clinical status at each HRQOL data collection after the initiation of ISW. Figure 1B shows the 4 HRQOL surveys and their relationship to the participant.

Survey Instruments

1. PedsQL™ 4.0 Generic Core Scales (PedsQL™ 4.0): A 23-item scale that measuring child and parent perception of HRQOL through 4 subscales: physical, emotional, social, and school function.[17]
2. PedsQL™ Multidimensional Fatigue Scale (PedsQL™ MF): An 18-item scale measuring child and parent perceptions of fatigue through3 subscales: General Fatigue, Sleep/Rest Fatigue, and Cognitive Fatigue
3. PedsQL™ Family Impact Module (PedsQL™ FIM): A measure of parental HRQOL, included to provide data on the impact of a child's chronic illness on parents and family. It encompasses 6 subscales: Parental Physical Functioning, Emotional Functioning, Social Functioning, Cognitive Functioning, Communication, and Worry, as well as an additional 2 scales that measure parent-reported family functioning: Daily Activities and Family Relationships. [18]
4. PedsQL™ 3.0 Transplant Module (PedsQL™ TxM): A 46-item disease-specific scale measuring aspects of HRQOL directly impacted by LT recipients' state of health through 8 sub-scales: About My Medicines I (barriers to medical regimen adherence), About My Medicines II (medication side effects), My Transplant and Others (social relationships and transplant), Pain and Hurt (physical discomfort), Worry (worries related to health status), Treatment Anxiety (fears regarding medical procedures), How I Look (impact of transplant on appearance), and Communication (communication with medical personnel and others regarding transplant issues).[19]

The PedsQL™ 4.0 and PedsQL™ MF assess a broad array of domains related to physical, social, emotional, school, and cognitive functioning. The PedsQL™ TxM was considered the primary endpoint PROM as it is specific to the solid organ transplant population and considered to be the most sensitive to IS medication changes. The PedsQL™ FIM was chosen to measure changes to family functioning because of the child's ISW.

Except for the PedsQL™ FIM, all survey instruments include parallel child self-report and parent-proxy report that are age-specific according to the following: young child (5–7 years), child (8–12 years), and adolescent (13–18 years). Parent-proxy forms assess parents' perceptions of their child's HRQOL. Questions are formatted to ask how much of a problem each item has been during the preceding month and are scored on a 5-point Likert scale: 0= never a problem; 1= almost never a problem; 2= sometimes a problem; 3= often a problem; 4= almost always a problem. Responses were reverse-scored and linearly transformed to a 0–100 scale, with higher scores indicating better quality of life. The format, instructions,

Likert response scale, and scoring method for the PedsQL™ surveys have been previously validated[17] and are identical to ensure ease of use. Parents completed proxy versions of the HRQOL surveys while participants completed age-appropriate child self-report versions during scheduled follow-up. Trial personnel were available to answer any questions.

2.4 Statistical analysis

The sample size was determined based on power estimates for the primary endpoint of the iWITH trial, defined as the proportion of participants who attained operational tolerance. All participants completed at least 2 of the 6 surveys, with 79 (90%) of participants completing at least 5 surveys. For every time point and domain, a minimum of 72 (82%) of participants were represented (eTable 1A–D).

We used a multicenter cohort of pediatric LT recipients from the Functional Outcomes Group (FOG) study to create a matched comparison group to assess the HRQOL differences of our participants (iWITH) with a broader LT population.[3] A 1:2 matching model was used to match iWITH and FOG study participants. The iWITH sample was randomly matched to the FOG sample by age, gender, and race/ethnicity utilizing PROC SURVEYSELECT to select a simple random sample in SAS Version 8 (SAS Institute, Inc., Cary, NC, USA). The sample of healthy children was derived from the PedsQL™ literature.[20] Comparisons were made using the Student's t-test. The overall type 1 error was maintained at 0.05 by the Hochberg adjustment for multiple comparison.[21] An adjustment was made separately for each instrument and by each respondent on survey measures. All hypothesis testing was 2-sided and $p<.05$ was regarded as statistically significant.

To assess changes in HRQOL over time in relation to the outcome of ISW, each subscale was analyzed separately using a longitudinal repeated measures linear mixed model with covariates for tolerance status (tolerant or non-tolerant), time (treated as continuous and calculated as time from the initiation of IS withdrawal), and their interaction. Random intercept and slope were utilized to account for participant variation. An unstructured covariance structure was utilized to model intra-participant correlation. Slopes and their corresponding 95% confidence intervals were obtained using Restricted Maximum Likelihood.

To examine changes in HRQOL among participants who experienced rejection, a spline for time with a single knot at the time of rejection was applied to the longitudinal model described above. Thus, separate slopes were generated for change in HRQOL prior to rejection and after rejection. All available data were used in the linear mixed model; missing data were not imputed. All statistical analyses were performed using SAS Version 9.4 (SAS Institute, Inc., Cary, NC, USA).

3. RESULTS

Eighty-eight participants initiated ISW in iWITH, and 33 met the criteria for operational tolerance approximately 24 months after initiating ISW(Figure 1A). The remaining 55 participants were classified as non-tolerant based on liver histology assessed at the end point biopsy(n=16) or allograft rejection(n=39).

Baseline characteristics of all participants by tolerance status are shown in Table 1, with no significant differences between groups. Differences in generic HRQOL, as measured by the PedsQL™ 4.0 at baseline, were compared to a large, previously described multicenter cohort of pediatric LT recipients, the FOG cohort(Table 2).[3] HRQOL scores of children enrolled in iWITH compared to those in FOG did not differ significantly, and were lower than those of healthy children on psychosocial, school, and social domains by child self-reports and all domains by parent-proxy report(Table 2).

Over 36 months, all participants maintained their generic HRQOL as measured by the PedsQL™ 4.0 and PedsQL™ MF scores (eTable 1A–B). Parental HRQOL and family dynamics, as measured by the PedsQL FIM™, improved specifically in the domains of communication and daily activity, which resulted in a significant increase in PedsQL FIM™ Total Scores(eFigure 2). The generic HRQOL was unaffected by tolerance status and episodes of acute rejection.

3.1 Primary efficacy endpoint: PedsQL™ TxM scores improved during ISW

Both child self-report and parent−proxy-reported Total Scores of the PedsQL™ TxM, our primary outcome measure, improved. The largest sub-scale increase was noted in Treatment Anxiety for both child self-report and parent-proxy report (eFigure 3). Child self-report scores also improved in Communication, while parent-proxy reports improved in the About My Meds I sub-scale.

3.2 PedsQL™ TxM scores improved in tolerant participants

Figure 2 shows the Total Score (Panel A) and 3 subscale scores (About My Meds I, Treatment Anxiety, and My Transplant and Others; Panels B, C, and D, respectively) for the PedsQL™ TxM measure of tolerant(n=33) compared to non-tolerant(n=55) participants. Tolerant participants improved in Total Score, About My Meds I, and Treatment Anxiety by child self-report and My Transplant and Others by parent-proxy report. Non-tolerant participants improved in Treatment Anxiety by parent-proxy report. Tolerant participants also improved in the PedsQL™ FIM Total Score(eTable 2).

3.3 PedsQL™ TxM scores did not worsen with acute rejection

Thirty-nine trial participants were diagnosed with rejection; 4 of these were diagnosed with subclinical rejection by the tolerance assessment biopsy after the 24 month visit and so did not know they had rejection at the time of their HRQOL survey. The remaining 35 participants who experienced rejection did not show a decrement in PedsQL™ TxM scores (Figure 3). One subscale of the PedsQL™ TxM, About My Meds II, improved after the rejection episode, while generic HRQOL scores were unchanged (eTable 3).

We also compared HRQOL of these 35 participants with rejection to the 53 participants who were off IS at the time of the tolerance assessment biopsy visit at month 24 (eFigure4). Participants who were off IS at this point reported significantly higher About My Meds I, Treatment anxiety, My Transplant and Others, and Total scores by child report. Parent-proxy report of About My Meds I and My Transplant and Others also improved.

4. DISCUSSION

The iWITH clinical trial is the first to measure longitudinal changes in HRQOL during ISW for either adult or pediatric LT recipients. PROMs identified that ISW was associated with HRQOL benefits in participants over 36 months, regardless of tolerance status. These findings are novel and important as the medical benefits of ISW, will likely take many years to become apparent, particularly for healthy pediatric LT recipients. The iWITH inclusion criteria limited participants to those on monotherapy with normal liver enzymes and a strict definition of normal graft histology. These participants thereby represent the “best of the best” survivors of pediatric LT and would easily meet criteria set forth of a composite ideal LT survivor.[2]

The primary patient-reported endpoint for this trial was disease-specific HRQOL as measured by the PedsQL™ TxM. There were statistically significant improvements for the entire iWITH cohort in several domains during the first year. The Communication subscale, which speaks to the difficulties in discussing feelings with medical staff and explaining transplantation to others, also improved. We were concerned that disruptions in regular activities, (eg school), caused by more frequent interactions with the medical team and extra testing during the trial would have a detrimental impact; however, the increased interactions may have fostered a stronger relationship with the medical team, particularly in participants many years post LT.

We were also interested in understanding how trial outcomes may have impacted HRQOL. Our 33 operationally tolerant participants had improved scores in the disease-specific PedsQL™ TxM throughout the 36 months of assessments for both child self-report and parent-proxy report. Parent-proxy report scores of non-tolerant participants demonstrated improvement in the Treatment Anxiety subscale. Parents may have been reassured that the rejection, which occurred under intense monitoring, was easily reversible and did not result in graft loss. The PedsQL™ FIM improved in those who were tolerant, suggesting ISW also has a positive impact on parental wellness and family dynamics.

These data show that the process of ISW did not harm HRQOL but yielded some benefits. The improvements in disease-specific and parental HRQOL measured by PedsQL™ TxM and PedsQL™ FIM, respectively, in tolerant participants suggests that the HRQOL improvement was driven largely by tolerant participants. Although the full range of benefits of ISW, may require decades of follow-up, we have shown that during the 36-month trial period, there were tangible benefits using a disease-specific HRQOL measure.

Balancing the risks and benefits of chronic IS to achieve and maintain optimal long-term health for both the allograft and the patient is challenging. In pediatrics, this goal has even greater importance as the median age at transplant is less than 2 years, necessitating decades of exposure to IS medications during critical cognitive and physical developmental stages. Despite the known risks the families and physicians of pediatric LT recipients may be reluctant to reduce IS. Factors influencing this reluctance include parents’/caregivers’ concerns about the risk of rejection, their desire to maintain the status quo, trust in the medical team, and their anxiety regarding the lack of comprehensive safety data from

previous ISW trials. iWITH was designed to maximize patient safety. Participants underwent regimented ISW with intense clinical and laboratory monitoring to identify possible signs of rejection quickly. Although many participants experienced rejection, they responded well to IS optimization with biochemical resolution of rejection and histological stability over 4 years. Within this context, generic HRQOL was preserved and disease-specific improvements were reported. Embracing ISW in the clinical setting may not yield the same experience. Frequent monitoring to detect graft injury and maintaining a close relationship between the medical team and the family is essential to minimize detrimental effects on patient and family wellness. The use of disease specific PROMs in routine clinical practice may also provide additional data on the overall health of the patient. [22] Conversely, patients who choose ISW and fail may still have a positive view as it confirms the need for IS. Sharing results of this analysis with families as they consider participation in a withdrawal program, particularly the successful treatment of rejection without graft loss, will help frame the full spectrum of trade-offs inherent in the process.

Quality of life has been extensively studied in pediatric LT recipients. Factors influencing HRQOL include age at transplant, single parent household, diabetes, growth failure at LT, and number of days hospitalized.[5] HRQOL has been reported to be comparable to children with other chronic illnesses such as cancer.[23] Young adults who have successfully transitioned to adult care continue to demonstrate HRQOL stability, well into their fourth decade of life.[24, 25] While there are many factors associated with a successful transition of care, it remains a period of increased graft loss, medical non-adherence and death across all solid organ transplant recipients. Promoting self management strategies and improving HRQOL in adolescents may improve medication adherence, and decrease behavior and emotional difficulties, thus improving long term outcomes.[26, 27]

Our trial is the first to assess an intervention aimed at improving HRQOL longitudinally in pediatric LT. Although survival remains the benchmark in assessing LT outcomes, we expect with this publication, an increased focus on interventions seeking to improve HRQOL. Understanding that minorities are under-represented in many studies, we must improve their access to clinical trials, to ensure a representative sample which guarantees both generalizability and equity.[28]

While limited in size, this is the largest clinical trial of ISW in pediatric LT recipients and the first to use PROMs prospectively to assess changes in HRQOL. The overall lack of difference in the generic HRQOL measures may be due to our selection of healthy participants, all with excellent graft function at the outset, which limited detection of a meaningful change in these generic measures. This selection may have resulted in a ceiling effect for the generic tool, whereby it was difficult to observe variability during the trial in participants with the highest function. However, comparison to healthy controls did reveal significant differences. Thus, it would follow that any clinically relevant change in generic HRQOL would have been detectable. We did not have a direct Control group, and there are no published longitudinal HRQOL data on LT recipients using the PedsQL™ TxM or other transplant specific HRQOL instruments as these have not been in widespread use. [29]

Generic HRQOL at baseline was not significantly different from a matched cohort of LT recipients (FOG), however longitudinal follow up was unavailable. Our subjects did maintain their generic HRQOL over 36 months in the overall, tolerant and non tolerant groups.

Our findings may not be generalizable to all LT recipients particularly those with impaired graft function and multiple comorbidities, as these factors will also impact HRQOL.

We demonstrate for the first time among a highly selected cohort of pediatric LT recipients that ISW is safe and does not adversely affect HRQOL. Disease-specific HRQOL improved in all participants, with greater gains in participants who achieved operational tolerance. Our findings add a new dimension to the risk-versus-benefit assessment of IS minimization and/or discontinuation in pediatric LT recipients. These findings also reinforce the critical role of PROMs in future ISW trials and validate the need to include the patient perspective in assessing trial outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank all the iWITH investigators, research coordinators, patients, and families who agreed to participate in this trial. No compensation was received by these individuals for contributions to the trial outside of the grant funding.

Funding/Support: This research was supported by U01-AI-100807 awarded by the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Diabetes and Digestive and Kidney Diseases as well as by the Immune Tolerance Network (UM1AI109565), an international clinical research consortium headquartered at the Benaroya Research Institute and supported by NIAID. The conduct of this trial at the some of the clinical sites was supported, in part, by awards from the National Center for Advancing Translational Sciences of the National Institutes of Health, through UL1 TR000004 and UL1 TR001872 at University of California San Francisco, 5UL1TR001425-04 at Cincinnati Children's Hospital, UL1TR000003 and UL1TR001878 at Children's Hospital of Philadelphia, UL1TR000454 and UL1TR002378 at Emory University School of Medicine, and UO1AI100807 at St Louis Children's Hospital.

Abbreviations:

ALT	Alanine aminotransferase
FOG	Functional Outcomes Group
GGT	Gamma-glutamyl transferase
HRQOL	Health Related Quality of Life
IS	Immunosuppression
ISW	Immunosuppression withdrawal
LT	Liver transplant
PedsQL™ 4.0	PedsQL™ 4.0 Generic Core Scales
PedsQL™ MF	PedsQL™ Multidimensional Fatigue Scale

PedsQL™ FIM	PedsQL™ Family Impact Module
PedsQL™ TxM	PedsQL™ 3.0 Transplant Module
PROMs	Patient-Reported Outcome Measures

References

1. Porter ME, What is value in health care? N Engl J Med, 2010. 363(26): p. 2477–81. [PubMed: 21142528]
2. Ng VL, et al., Health status of children alive 10 years after pediatric liver transplantation performed in the US and Canada: report of the studies of pediatric liver transplantation experience. J Pediatr, 2012. 160(5): p. 820–6 e3. [PubMed: 22192813]
3. Alonso EM, et al., Cross-sectional analysis of health-related quality of life in pediatric liver transplant recipients. J Pediatr, 2010. 156(2): p. 270–6 e1. [PubMed: 19846110]
4. Watt KD, et al., Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. Am J Transplant, 2010. 10(6): p. 1420–7. [PubMed: 20486907]
5. Alonso EM, et al., Factors predicting health-related quality of life in pediatric liver transplant recipients in the functional outcomes group. Pediatr Transplant, 2013. 17(7): p. 605–11. [PubMed: 23902630]
6. Feldman AG, et al., Impaired physical function following pediatric LT. Liver Transpl, 2016. 22(4): p. 495–504. [PubMed: 26850789]
7. Ojo AO, et al., Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med, 2003. 349(10): p. 931–40. [PubMed: 12954741]
8. Londono MC, et al., Immunosuppression minimization vs. complete drug withdrawal in liver transplantation. J Hepatol, 2013. 59(4): p. 872–9. [PubMed: 23578883]
9. Lin HC, et al., Extended follow-up of pediatric liver transplantation patients receiving once daily calcineurin inhibitor. Pediatr Transplant, 2015. 19(7): p. 709–15. [PubMed: 26256288]
10. Feng S, et al., Complete immunosuppression withdrawal and subsequent allograft function among pediatric recipients of parental living donor liver transplants. JAMA, 2012. 307(3): p. 283–93. [PubMed: 22253395]
11. Ganschow R, et al., Everolimus and reduced calcineurin inhibitor therapy in pediatric liver transplant recipients: Results from a multicenter, prospective study. Pediatr Transplant, 2017. 21(7).
12. Pflugrad H, et al., Longterm calcineurin inhibitor therapy and brain function in patients after liver transplantation. Liver Transpl, 2018. 24(1): p. 56–66. [PubMed: 29156491]
13. Schmeding M, et al., Mycophenolate mofetil monotherapy in liver transplantation: 5-year follow-up of a prospective randomized trial. Transplantation, 2011. 92(8): p. 923–9. [PubMed: 21832958]
14. Aberg F, et al., Cancer After Liver Transplantation in Children and Young Adults: A Population-Based Study From 4 Nordic Countries. Liver Transpl, 2018. 24(9): p. 1252–1259. [PubMed: 30120902]
15. Benitez C, et al., Prospective multicenter clinical trial of immunosuppressive drug withdrawal in stable adult liver transplant recipients. Hepatology, 2013. 58(5): p. 1824–35. [PubMed: 23532679]
16. Banff Working Group on Liver Allograft, P., Importance of liver biopsy findings in immunosuppression management: biopsy monitoring and working criteria for patients with operational tolerance. Liver Transpl, 2012. 18(10): p. 1154–70. [PubMed: 22645090]
17. Varni JW, Seid M, and Kurtin PS, PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care, 2001. 39(8): p. 800–12. [PubMed: 11468499]
18. Varni JW, et al., The PedsQL Family Impact Module: preliminary reliability and validity. Health Qual Life Outcomes, 2004. 2: p. 55. [PubMed: 15450120]

19. Weissberg-Benchell J, et al., Pediatric health-related quality of life: Feasibility, reliability and validity of the PedsQL transplant module. Am J Transplant, 2010. 10(7): p. 1677–85. [PubMed: 20642689]
20. Varni JW, Burwinkle TM, and Seid M, The PedsQL 4.0 as a school population health measure: feasibility, reliability, and validity. Qual Life Res, 2006. 15(2): p. 203–15. [PubMed: 16468077]
21. Hochberg Y and Benjamini Y, More powerful procedures for multiple significance testing. Stat Med, 1990. 9(7): p. 811–8. [PubMed: 2218183]
22. Ng V, et al., Development and validation of the pediatric liver transplantation quality of life: a disease-specific quality of life measure for pediatric liver transplant recipients. J Pediatr, 2014. 165(3): p. 547–55 e7. [PubMed: 24976329]
23. Limbers CA, et al., Health-related quality of life in pediatric liver transplant recipients compared with other chronic disease groups. Pediatr Transplant, 2011. 15(3): p. 245–53. [PubMed: 21199214]
24. Mayer K, et al., Psychosocial outcome and resilience after paediatric liver transplantation in young adults. Clin Res Hepatol Gastroenterol, 2019. 43(2): p. 155–160. [PubMed: 30737022]
25. Mohammad S, et al., Health status in young adults two decades after pediatric liver transplantation. Am J Transplant, 2012. 12(6): p. 1486–95. [PubMed: 22568621]
26. Fredericks EM, et al., Adherence and health-related quality of life in adolescent liver transplant recipients. Pediatr Transplant, 2008. 12(3): p. 289–99. [PubMed: 18282211]
27. Ko D, et al., Self-management in liver transplantation. Appl Nurs Res, 2019. 45: p. 30–38. [PubMed: 30683248]
28. Aristizabal P, et al., Participation in pediatric oncology research protocols: Racial/ethnic, language and age-based disparities. Pediatr Blood Cancer, 2015. 62(8): p. 1337–44. [PubMed: 25755225]
29. Killian MO, et al., Measurement of health-related quality of life in pediatric organ transplantation recipients: a systematic review of the PedsQL transplant module. Qual Life Res, 2020. 29(5): p. 1137–1146. [PubMed: 31894507]

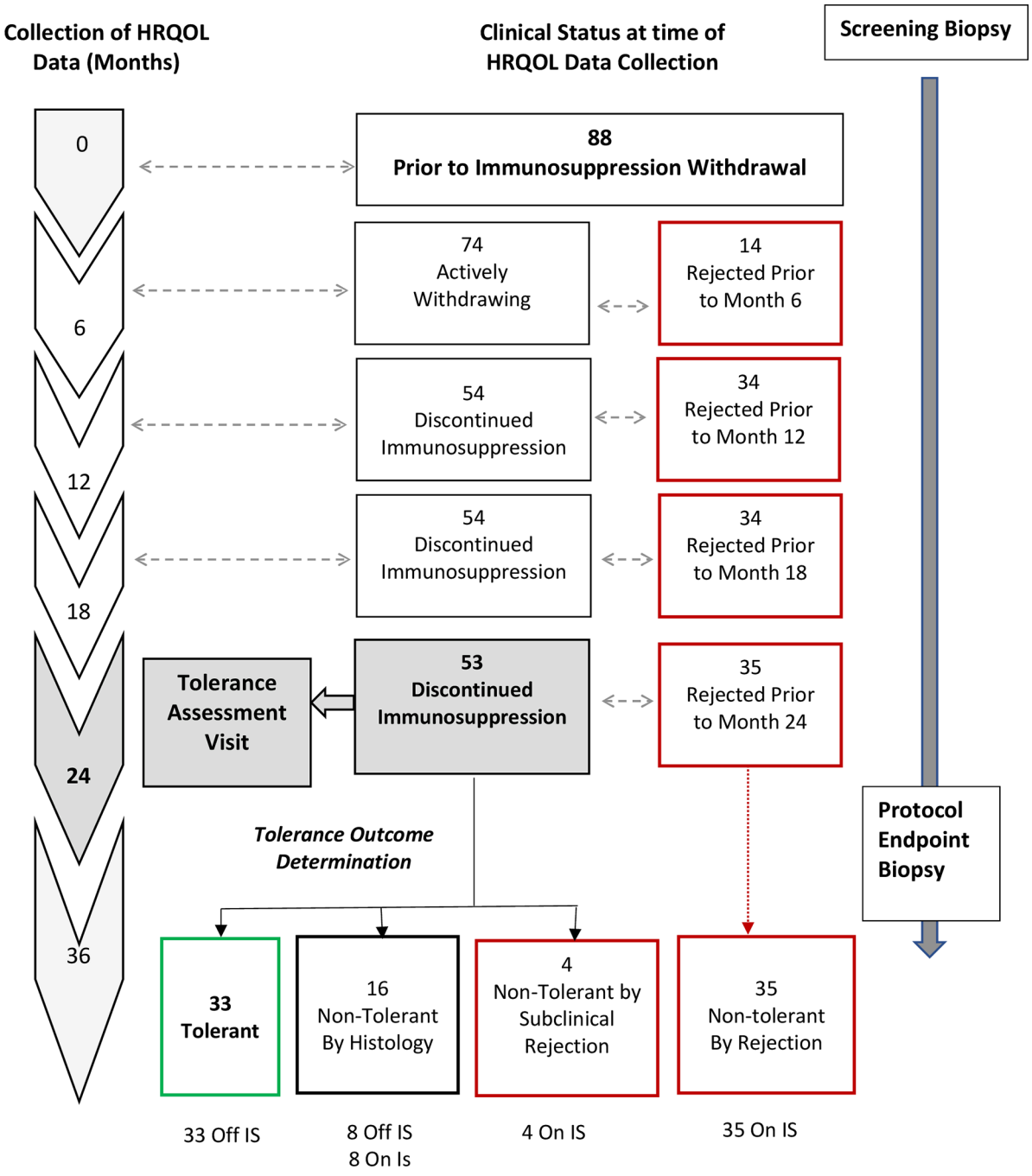

Figure 1.

Flow of 88 participants included in the trial, demonstrating the Timing of HRQOL data collection (arrows on left side) at 0,6,12,18,24 and 36 months corresponding to Immunosuppression events (in rectangles).

Tolerant participants met biochemical and histological criteria for tolerance. Non-tolerant by rejection participants had biopsy-proven rejection based on central pathology assessment according to Banff criteria or by clinical rejection, defined as elevated liver tests treated with increased or re-initiation of immunosuppression but without biopsy confirmation. Non-

tolerant by subclinical rejection participants had biopsy-proven rejection on the protocol endpoint biopsy with normal liver tests. Non-tolerant by histology participants failed secondary to histological findings although they met biochemical criteria with normal liver tests.

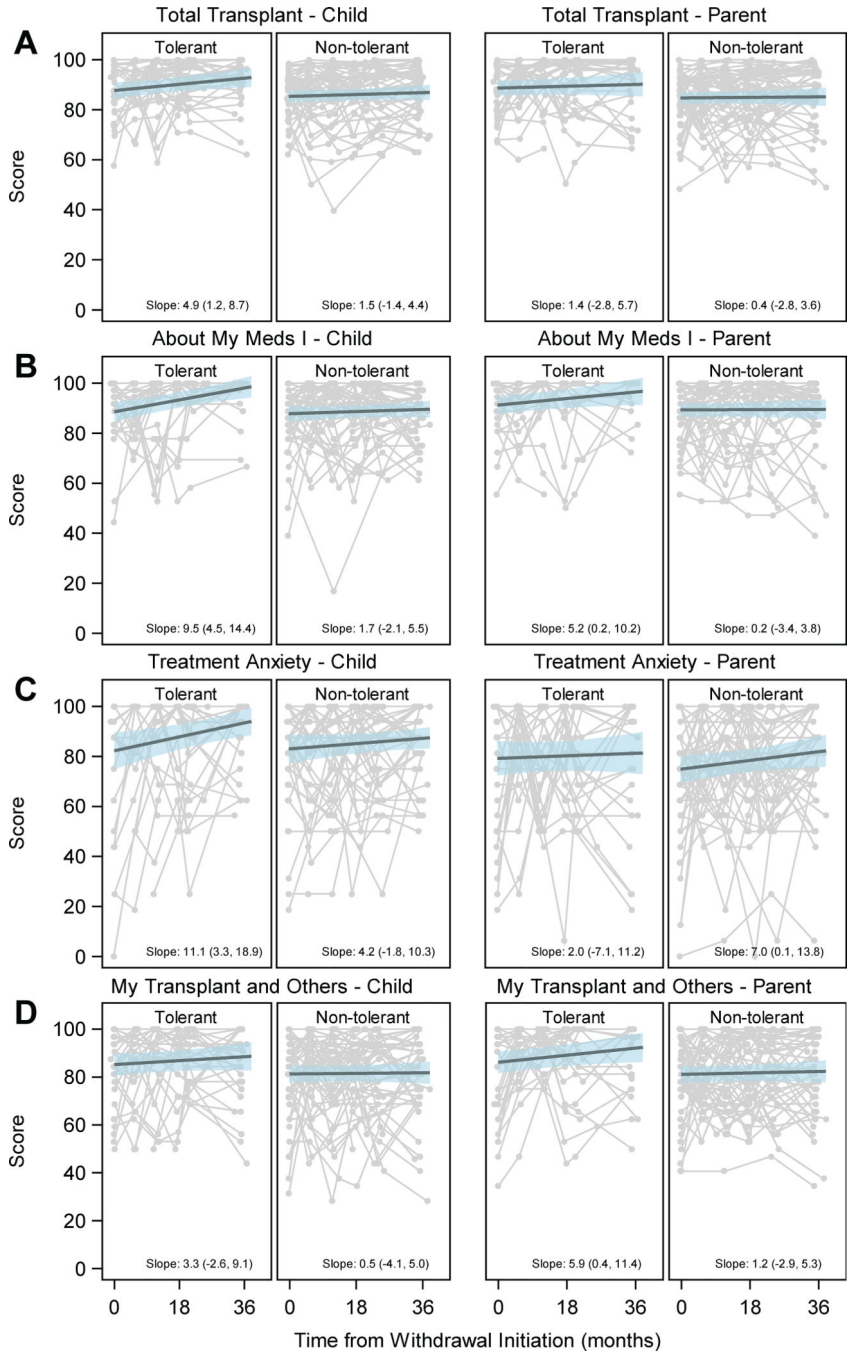

Figure 2.

PedsQL™ TxM child self-report and parent-proxy report scores from baseline to 36 months in tolerant and non-tolerant groups. PedsQL™ TxM total score (A) and 3 subscales, About My Meds I (B), Treatment Anxiety (C), and My Transplant and Others (D), in tolerant (n=33) and non-tolerant (n=55) participants are shown. The mean predicted line (solid black) and corresponding 95% confidence band (light blue) are shown for each group. Individual participant trajectories are also shown (light grey).

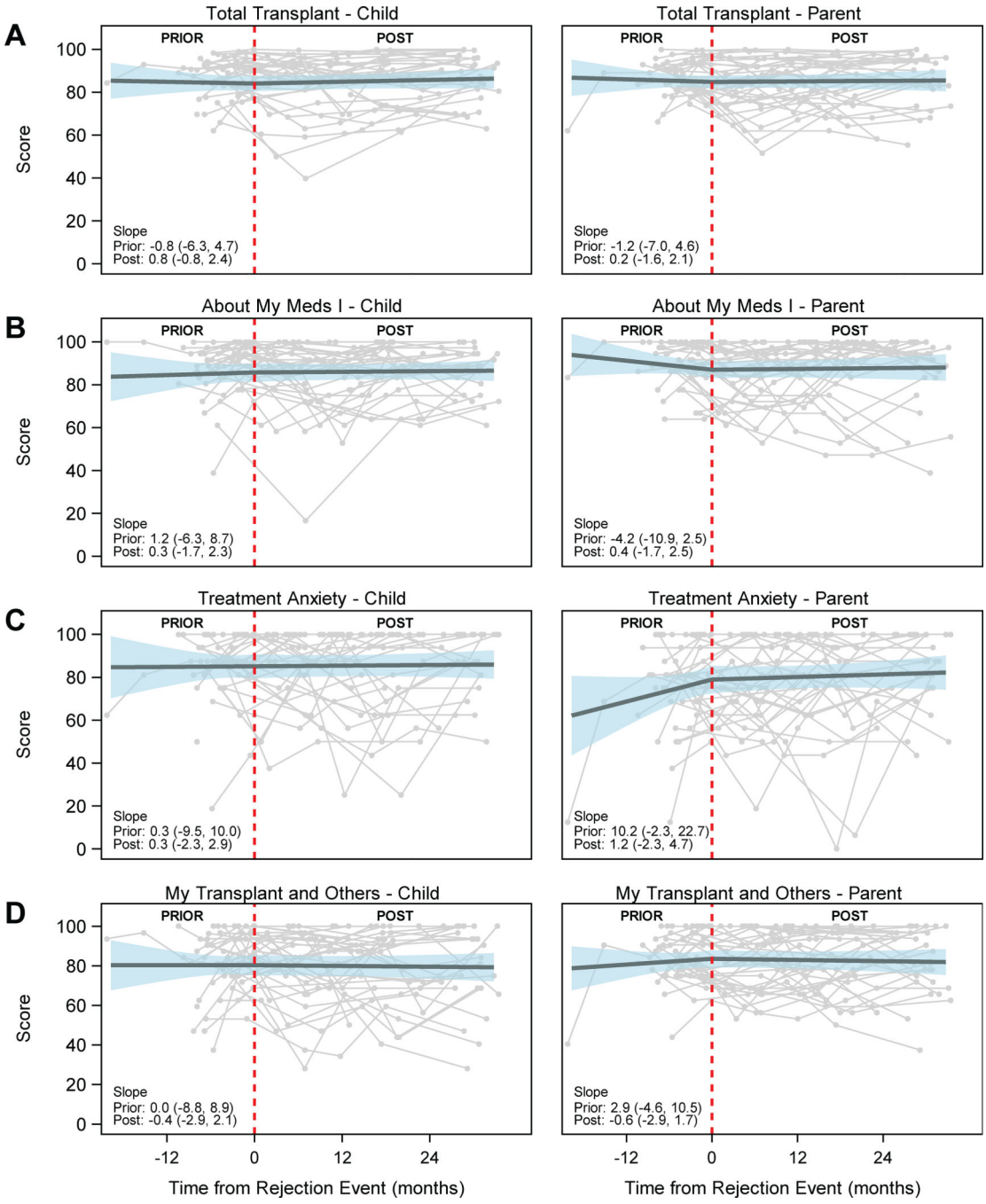

Figure 3.

PedsQL™ TxM child self-report and parent-proxy report scores in participants experiencing rejection. PedsQL™ TxM total score (A) and 3 subscales, About My Meds I (B), Treatment Anxiety (C), and My Transplant and Others (D), in participants experiencing rejection (n=35) are shown. Time (x-axis) is expressed in relation to the rejection event with a reference line (dashed red) representing the time of rejection. All PedsQL™ TM scores to the left of the reference line represent values collected prior to rejection and scores to the right represent values collected after rejection. Mean predicted line (solid black) and

corresponding 95% confidence band (light blue) are shown. Individual participant trajectories are shown (light grey). Slopes represent a 12-month change in score with separate slopes for the change prior to and post rejection.

Table 1.

Characteristics of 88 Participants Undergoing Immunosuppression Withdrawal by Tolerance Status

Characteristic[a]			**Tolerant n=33**	**Non-tolerant n=55**	**Total N=88**
Recipient	**Age at transplant** (years)		1 (1–2)	1 (1–3)	1 (1–2)
	Age (years)		11 (7–13)	11 (8–13)	11 (8–13)
	Time since transplant (years)		9 (6–10)	8 (6–11)	9 (6–11)
	Male gender		13 (39)	26 (47)	39 (44)
	Race	White	30 (91)	46 (84)	76 (86)
	Transplant indication	Acute Liver Failure	2 (6)	5 (9)	7 (8)
		Biliary Atresia	20 (61)	31 (56)	51 (58)
		Other	11	19	16 (18)
Transplant	**Whole graft**		15 (45)	26 (47)	41 (47)
	Previous rejection episode		9 (27)	23 (42)	32 (36)
	Time since last rejection prior to enrollment (years)		8 (7–9)	6 (4–8)	7 (4–9)
At study entry	**Highest educational level of adults living within the household**[b]	Some high school	1 (3)	1 (2)	2 (2)
		High school diploma or GED	2 (6)	2 (4)11	4 (5)
		Vocational school	1 (3)	1 (2)	2 (2)2
		Some college	10 (30)	11 (20)	21 (24)21
		College degree	12 (36)	24 (44)	36 (41)36
		Professional or graduate degrees	6 (18)	14 (25)	20 (23)20
	Primary caregiver's marital status[b]	Single	1 (3)	5 (9)	6 (7)
		Married	24 (73)	45 (82)	69 (78)
		Divorced	6 (18)	3 (5)	9 (10)
	School attendance[b]	Full-time	25 (76)	47 (85)	72 (82)
		Part-time	2 (6)	3 (5)	5 (6)
		Home school[c]	4 (12)	2 (4)	6 (7)
		No ongoing education[c]	0	1 (2)	1 (1)

[a]Continuous variables are summarized using median and interquartile range. Categorical variables are summarized by counts and percentages.

[b]There was no response provided for 3 subjects on education level and for 4 subjects on marital status and school attendance.

[c]Not medically indicated.

Table 2.

Generic HRQOL at Baseline Compared to Healthy and FOG Populations

Scale[a]		iWITH	FOG	p-value[b]	Healthy[c]	p-value[d]
Emotional	Child	82 79.6 ± 18.4	125 75.2 ± 18.0	0.46	400 80.9 ± 19.6	0.57
	Parent	87 75.6 ± 19.6	176 72.1 ± 19.7	0.17	718 82.6 ± 17.5	0.004
Physical	Child	82 86.1 ± 13.9	125 82.2 ± 16.4	0.41	400 84.4 ± 17.3	0.57
	Parent	87 83.6 ± 18.5	176 77.6 ± 22.0	0.09	717 89.3 ± 16.4	0.007
Psychosocial	Child	82 77.8 ± 15.7	125 76.4 ± 14.1	0.94	399 82.4 ± 15.50	0.09
	Parent	87 76.8 ± 14.9	176 72.4 ± 17.0	0.10	717 86.6 ± 12.8	<0.001
School	Child	81 71.4 ± 18.7	120 72.1 ± 17.8	0.94	386 78.6 ± 20.5	0.01
	Parent	85 71.0 ± 19.8	163 66.9 ± 20.1	0.17	611 85.5 ± 17.6	<0.001
Social	Child	82 82.2 ± 19.9	125 82.0 ± 16.3	0.94	399 87.4 ± 17.2	0.12
	Parent	87 83.2 ± 16.5	176 77.6 ± 20.6	0.09	716 91.6 ± 14.2	<0.001
Total	Child	82 80.7 ± 13.7	125 78.3 ± 13.5	0.87	401 83.0 ± 14.8	0.52
	Parent	87 79.2 ± 15.0	176 74.2 ± 17.3	0.09	717 87.6 ± 12.3	<0.001

HRQOL, health-related quality of life; FOG, Functional Outcomes Group study; iWITH, Immunosuppression Withdrawal for Stable Pediatric Liver Transplant Recipients study.

[a]Scales are summarized with n, mean ± standard deviation. Higher values equal better health-related quality of life.

[b]The Hochberg adjusted p-value represents the results of a two-sided t-test comparing of the mean score at baseline in the iWITH population vs. the FOG population.

[c]Healthy cohort comes from data collected by Varni et al.

[d]The Hochberg adjusted p-value represents the results of a two-sided t-test comparing of the mean score at baseline in the iWITH population vs. the normal population.