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Interest in Immunosuppression Withdrawal among Liver Transplant and Autoimmune Hepatitis Patients

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Abstract: Immunosuppression withdrawal (ISW) is considered in liver transplant recipients (LTRs) and autoimmune hepatitis patients (AIHPs). Immunosuppressive therapy (IST) can be burdensome both financially and due to its side effect profile, making ISW an important intervention to consider. Data on patient interest in ISW would be helpful to providers in ISW decision-making. We conducted independent single-center surveys of LTR and AIHP attitudes on IST and withdrawal interest. Of 325 LTRs screened, 120 completed the survey (50% female, mean age 58 ± 14 years, mean time since transplant 8 ± 10.5 years and 79.5% Caucasian). Of 100 AIHPs screened, 45 completed the survey (77.8% female, mean age 54 ± 2 and 82.2% Caucasian). A higher percentage of AIHPs expressed concern with their IST and were interested in ISW compared with LTRs. However, over a third of LTRs were interested in ISW, particularly those with knowledge of this potential intervention. LTRs who discussed ISW with a physician were more likely to desire withdrawal ($p = 0.02$; OR = 2.781 (95% CI = 1.125, 6.872)). As patient interest in ISW is of growing interest, investigators should continue to assess patient-reported desires and outcomes and pursue strategies to achieve immunological tolerance.

Keywords: hepatitis; autoimmune; liver transplantation; immunosuppression; patient-reported outcome measures; decision-making

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1. Introduction

In hepatology practice, liver transplant recipients (LTRs) and autoimmune hepatitis patients (AIHPs) are in a similar clinical situation, generally requiring lifelong immunosuppression therapy (IST). While lifelong IST can effectively prevent LT rejection and AIH flare-ups, it is associated with adverse events that can vary from mild to severe. Side effects can include weight gain, alopecia, diabetes, hypertension, cytopenias, gastrointestinal symptoms and osteopenia [1–4]. More severe complications from chronic IST include the risks of opportunistic infections, chronic kidney disease, metabolic disorders, cardiovascular disease and malignancy [1,3–5].

Both patient populations differ significantly in the approach to immunosuppression withdrawal (ISW). In LTRs, ISW is largely experimental and generally conducted in clinical trials. Clinical trials have studied a variety of age ranges and indications for transplants, finding varying degrees of success in highly select patients (~30–40%) [4]. On the other hand, ISW is generally part of the long-term management goals of AIHPs, with success rates between 13% and 50% [6]. Both can derive similar benefits from ISW (e.g., the avoidance of complications associated with IST). Attempting ISW does, however, risk incurring a disease flare-up in AIHPs or rejection in LTRs that may cause significant liver injury and advance liver disease [1,5]. These risks must balance the desire to decrease a patient's morbidity wing to chronic IST. Interestingly, AIH disease flare-ups and LT rejection during the course of or after ISW occur in similar percentages (50–80%) over time,

and both respond well to the resumption of IST when detected in a timely fashion. Thus, there are enough commonalities in these patient populations to assess these approaches side-by-side.

However, little has been done to assess what patients desire and value when considering ISW. Patients' attitudes toward ISW are potentially influenced by many factors outside of its risks and benefits, such as financial burden, number of medications, severity of disease before AIH presentation or liver transplantation and demographic factors, including age and gender. Despite the number of clinical studies in this area in both patient populations, there have not been efforts made to understand what motivates or influences these patients to consider this intervention and how this might play a role in provider patient selection and decision-making. Identifying a relationship between demographics, disease burden, medication burden and financial status has the potential to improve physicians' abilities to counsel these patients on the prospect of ISW. Therefore, we sought this information utilizing independent, patient-oriented surveys asking similar questions to both populations.

2. Materials and Methods

We designed a survey eliciting LTR and AIHP demographic information, medical history and attitudes toward their IST and interest in attempting ISW, with the latter being scored on a Likert-like scale. (Table S1) This survey was approved by the institutional review board. Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at Northwestern University [7,8]. REDCap is a secure, web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for importing data from external sources. Patients were chosen solely on having AIH or an LT, currently being on an immunosuppression (IS) regimen and being literate. In order to obtain an unbiased sampling across the whole patient population, patients were not excluded based on clinical variables or disease presentations. Patients that were under 18 years old, acutely ill at recruitment, had potentially confounding liver diagnoses or were pregnant or incarcerated at recruitment were excluded from the study. None of the patients had previously been involved in ISW trials at the institution.

All participants were recruited from Northwestern Memorial Hospital in Chicago, Illinois. LTRs and AIHPs who participated in person were identified ahead of time from the clinic schedule. Those who participated electronically were recruited from separate lists of LTRs and AIHPs seen in our practice. Survey participation was elicited either in person during a visit to their hepatology clinic or by phone call or e-mail survey delivery after informed consent was given. Responses to the Likert-like scale questions were dichotomized to endorsing agreement (e.g., strongly agree and agree) or not (e.g., disagree, strongly disagree and neutral). Bivariate analyses (chi-square and Fisher's exact) were conducted using SPSS statistical software to observe the association between sex, age, race or ethnicity, number of medications, number of disease complications, medication complications or side effect burden, difficulty taking the IS regimen, knowledge of expected side effects, financial burden, discussing ISW with a physician and desire to attempt ISW. Variables that were significantly associated with the desire to attempt ISW in the bivariate analyses were included in a final logistic regression model.

3. Results

Of the 325 LTRs screened, 120 LTRs completed the survey (Figure 1): 50% female, 79.5% Caucasian, mean age 58 $\pm$ 14 years, mean time since transplant 8 $\pm$ 10.5 years and 19.5% experiencing at least one rejection event. Of the 100 AIHPs screened, 45 completed the survey (Figure 1): 77.8% female, mean age 54 $\pm$ 2, 82.2% Caucasian and a mean of 2.42 $\pm$ 1.3 AIH flare-ups. As expected, the two populations were significantly different

demographically in age ($p = 0.011$), sex ($p = 0.00$), number of medications they were taking ($p = 0.038$) and number of disease complications ($p = 0.001$). The AIHPs skewed toward younger female patients taking fewer medications than the LTRs, who experienced more previous disease complications when compared with the AIHPs (Table 1). The LTRs were less likely to have discussed ISW with their providers than the AIHPs (21.7% vs. 55.5%; $p = 0.00$; Table 2). No participant said that decreased spending on medications was their primary incentive for desiring withdrawal. This corresponded to the low number of participants in either cohort who stated IST was financially burdensome (15% and 22% for LTRs and AIHPs, respectively; Table 2).

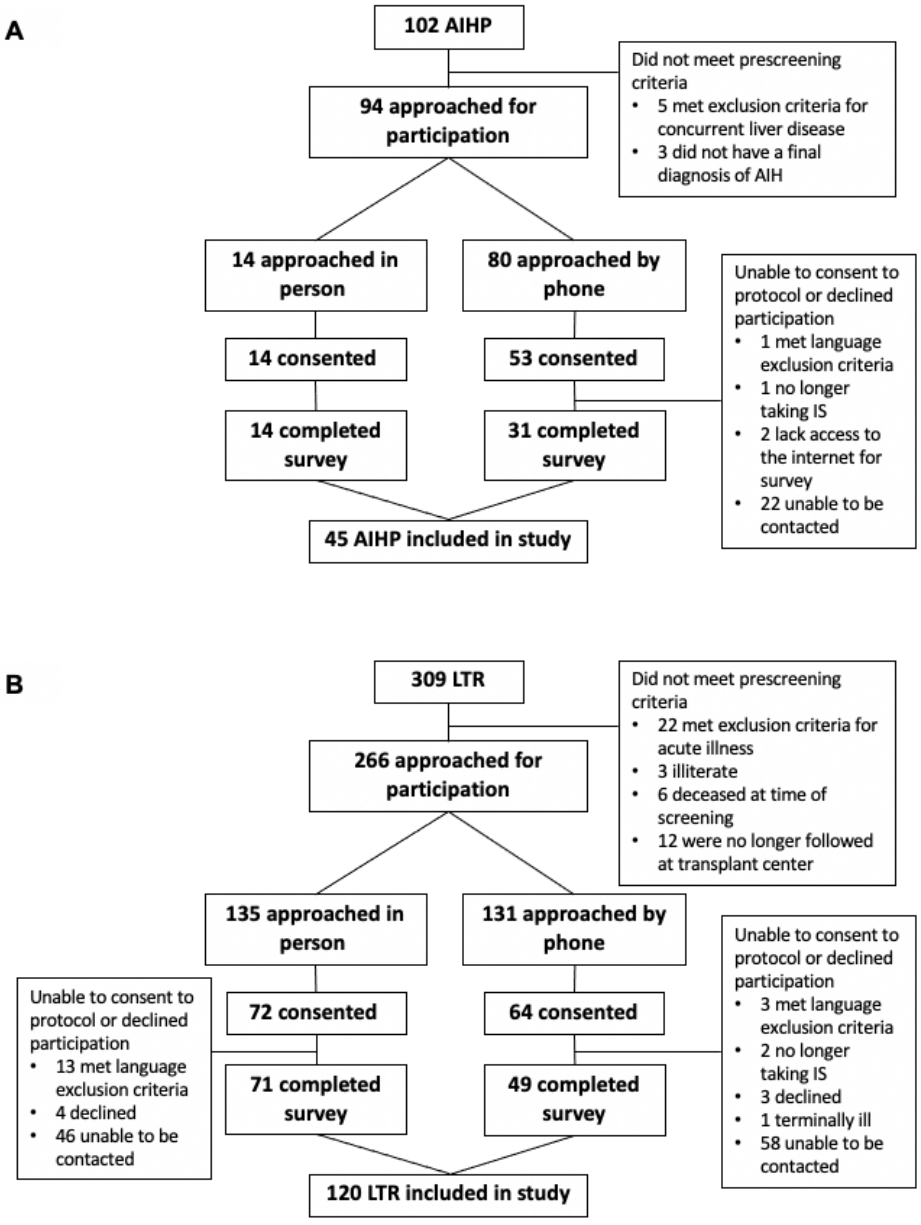

Figure 1. Recruitment and participation outline for autoimmune hepatitis patients (AIPHs) (**A**) and liver transplant recipients (LTRs) (**B**). Original patient numbers are based on the number of patients screened from a combination of patient lists and clinic encounters.

Table 1. LTR vs. AIHP cohort demographics.

	Liver Transplant (*n* = 120)	**Autoimmune Hepatitis (*n* = 45)**	***p*-Value**
Sex Male	50 (41.7)	10 (22.2)	0.00 *
Age Category <60	48 (40.0)	28 (62.2)	0.011 *
Race or Ethnicity White, non-Hispanic Other	95 (79.2) 25 (20.8)	37 (82.2) 8 (17.8)	0.662
Number of Medications >1	59 (49.2)	14 (31.1)	0.038 *
Disease Complications At Least One	104 (86.7)	28 (62.2)	0.00 *
Medication Complications At Least One	66 (55.0)	22 (48.9)	0.483

Values expressed as a number (percent), and p-values denote the results of chi-square testing conducted on each demographic category comparing LTRs and AIHPs. * denotes significant *p*-values.

Table 2. LTR vs. AIHP survey responses.

	Liver Transplant (*n* = 120)	**Autoimmune Hepatitis (*n* = 45)**	***p*-Value**
I take my immunosuppression medication(s) without difficulty or concern Agree	91 (75.8)	29 (64.4)	0.143
I know what side effects to expect from my immunosuppressive medication(s) Agree	91 (75.8)	30 (66.7)	0.236
I experience unpleasant side effects from my immunosuppressive medication(s) Agree	37 (30.8)	11 (24.4)	0.421
I feel financially burdened by the immunosuppression medication(s) I need to take Agree	17 (15.0)	10 (22.2)	0.221
My physician and I have discussed the possibility of withdrawing my immunosuppressive medication(s) Yes	26 (21.7)	25 (55.6)	0.001 *
I want to attempt withdrawal of immunosuppressive therapy Endorsed desire	45 (37.5)	20 (44.4)	0.416

Values expressed as number (percent), and *p*-values denote the results of chi-square testing conducted on each survey response comparing LTRs and AIHPs. * denotes significant *p*-values.

Among the LTRs that indicated they desired to attempt ISW (37.5%, Table 2), most patients indicated wanting to avoid the risk of major IS complications (71.1%, Figure 2) and reliance on lifelong medications (31.1%). Among those that indicated they would not attempt ISW, most indicated that they were doing well in their IST as the primary (42.1%, Figure 2) and secondary (36.8%) reasons. Of the AIHPs who endorsed a desire for ISW (44.4%, Table 2), most people stated wanting to avoid IS (65.0%, Figure 1) as their primary reason and avoiding lifelong medication use (55.0%) as their secondary reason. Among the patients indicating they did not want to attempt ISW, the most common primary reason

was to avoid the risk of an AIH flare-up (41.2%, Figure 1), and the most selected secondary reason was because they were doing well in their IST (41.2%).

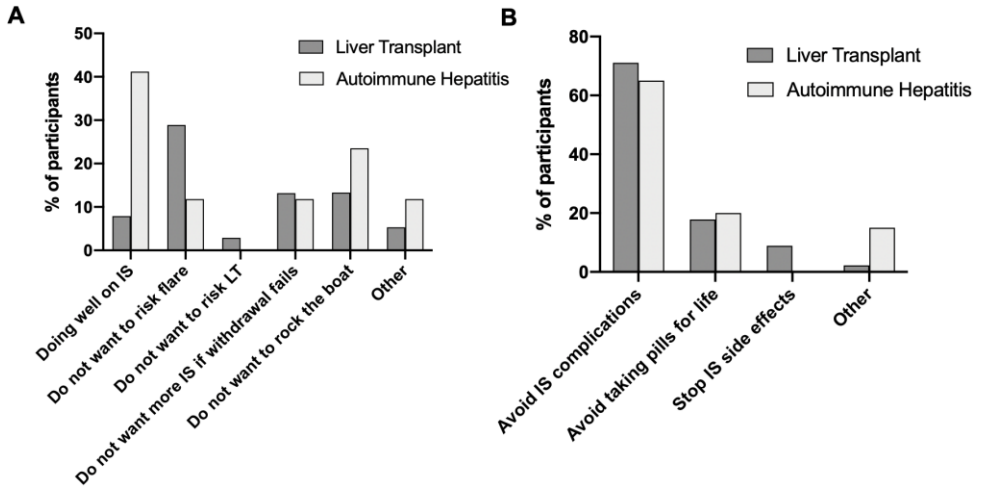

Figure 2. (**A**) Patient reasons to stay on immunosuppression (IS) if they did not desire withdrawal. If patients did not endorse withdrawal, they were asked to give their first, most-important reason why, and the results are compiled here. (**B**) Patient reasons to withdraw from IS if they endorsed a desire to withdraw. If patients endorsed withdrawal, they were asked to give their first, most-important reason why, and the results are compiled here.

Our bivariate analyses found the following initial results in the LTRs. Those who discussed ISW with a physician were more likely to desire full ISW, and female LTRs were more likely to desire ISW than male LTRs. After including the other predictive factors in the final logistic regression model, only discussion of ISW with a physician remained significantly associated with desiring ISW ($p = 0.02$; OR = 2.781 (95% CI = 1.125, 6.872)). LTR sex was not significantly associated with whether or not their physician discussed ISW with them ($p = 0.330$).

In the AIHPs, bivariate analyses found that those experiencing more medication complications were less likely to desire ISW than those experiencing fewer complications. However, this association was no longer significant when other predictive factors were accounted for in the final logistic regression model.

There were no associations between the side effect burden of medications, participants' knowledge of side effects or financial burden of IST and interest in ISW in either population.

4. Discussion

To our knowledge, this is the first study assessing patient opinions on ISW from two groups commonly seen in hepatology practice: LTRs and AIHPs. Our findings relating to interest in attempting ISW revealed differences between these patient populations. The significant association between LTRs discussing ISW with their physician and desiring to attempt ISW was not as apparent in AIHPs. That said, over half of the AIHPs had discussed ISW with their physicians, compared with 21.7% of the LTRs ($p = 0.001$, Table 2). This difference could reflect differences in the course of disease between the groups, with AIHPs more likely to be offered ISW as a normal part of management per society guidelines. Another potential explanation is that LTRs have undergone an extensive process of learning and communication with their transplant team, which may create a stronger connection between practitioner and patient and thus make this population more amenable to conversations regarding disease education and options for their care.

Although female LTRs were more likely to endorse interest in withdrawal in the bivariate chi-squared analysis ($p = 0.045$, Table 3), this association was no longer significant in the final logistic regression model ($p = 0.067$; OR = 2.057 (95% CI = 0.951, 4.450)). This suggests that variation in other predictors may confound the relationship between LTR

sex and desire to withdraw therapy, or that we would be able to identify a significant relationship with a larger sample size. We were unable to demonstrate a confounding relationship between female sex and discussing ISW with their physician in LTRs ($p = 0.330$). Further investigation would be required to properly identify the influence of LTR sex on ISW and related variables.

Table 3. Stratification of responses based on willingness to attempt ISW in the LTR and AIHP cohorts.

	Liver Transplant			**Autoimmune Hepatitis**		
	Endorses Withdrawal (*n* = 45)	**Does not Endorse Withdrawal (*n* = 75)**	***p*-Value**	**Endorses Withdrawal (*n* = 20)**	**Does not Endorse Withdrawal (*n* = 25)**	***p*-Value**
			Sex			
Male	21 (46.7)	49 (65.3)	0.045 *	6 (30.0)	4 (16.0)	0.301
			Age Category			
<60	19 (42.2)	29 (38.7)	0.700	15 (75.0)	13 (52.0)	0.135
			Race or Ethnicity			
White, non-Hispanic	37 (82.2)	58 (77.3)	0.523	15 (75.0)	22 (88.0)	0.435
Other	8 (17.8)	17 (22.7)		5 (25.0)	3 (12.0)	
			Number of medications			
>1	21 (46.7)	38 (50.7)	0.671	6 (30.0)	8 (32.0)	1.000
			Disease complications			
At least one	39 (56.7)	65 (86.7)	1.000	13 (65.0)	15 (60.0)	0.767
			Location of survey administration			
In office (in person)	27 (60.0)	45 (60.0)	0.850	4 (20.0)	10 (40.0)	0.202
			Medication complications			
At least one	29 (64.4)	37 (49.3)	0.107	6 (30.0)	16 (64.0)	0.036 *
			I take my immunosuppression medication(s) without difficulty or concern			
Agree	31 (68.9)	60 (80.0)	0.169	13 (54.0)	16 (64.0)	1.000
			I know what side effects to expect from my immunosuppressive medication(s)			
Agree	35 (77.8)	56 (74.7)	0.827	11 (55.0)	19 (76.0)	0.205
			I experience unpleasant side effects from my immunosuppressive medication(s)			
Agree	16 (35.6)	21 (28.0)	0.386	4 (20.0)	7 (28.0)	0.729
			I feel financially burdened by the immunosuppression medication(s) I need to take			
Agree	7 (15.6)	10 (13.5)	0.758	7 (35.0)	3 (12.0)	0.083
			My physician and I have discussed the possibility of withdrawing my immunosuppressive medication(s)			
Yes	15 (33.3)	11 (14.7)	0.016 *	12 (60.0)	13 (52.0)	0.764

Values expressed as number (percent), and *p*-values denote the results of chi-square testing conducted on each survey response comparing LTRs and AIHPs. * denotes significant *p*-values.

It is important to note that avoiding IST complications was the most common reason LTRs cited in explaining why they desired ISW, illustrating that the study participants were aware of and concerned about the possible deleterious effects of lifelong IST. On the other hand, LTRs that did not desire ISW most often explained that they were doing well on their IS regimen. Together, this may suggest that there are two different patient groups that value being on IST differently. This could potentially be explained by variables such as the time since a liver transplant, such that patients who have taken IST for longer may become more concerned about the effects of IST than those who have had a transplant more recently, who would be more concerned with prioritizing graft health. Future work can explore a potential temporal relationship in LTRs regarding their perception of their IST. Interestingly, physician discussion about ISW was the only predictive factor of patient interest above other potential reasons, such as side effect burden and financial implications.

This reinforces the importance of physician–patient communication in discussing the risks and benefits of IST and what patients desire long-term.

In this study, we profiled two patient cohorts, LTRs and AIHPs, as they are both involved in ISW discussions in hepatology practice but are indeed different in regard to prior transplantation. Overall, the comparison of these cohorts from our academic research center aligns with what might have been assumed from clinical experience. Not surprisingly, we found that AIHPs were more likely to be younger with a female predilection compared to LTRs, and LTRs reported higher rates of polypharmacy and disease complications. Management of IST in LTRs may be more complex than in AIHPs, and there are fewer solid guidelines that are agreed upon by practitioners and societies [3,9,10]. The main difference is that ISW is considered a standard of care option in AIHPs, while it is generally only an option in LTRs in clinical research studies unless clinically warranted in rare circumstances (e.g., severe opportunistic infections, post-transplant lymphoproliferative disorder and metastatic cancer).

There are important limitations to acknowledge for our findings. Data was collected at a single high-volume academic center that conducts ISW trials specifically in LTRs. We would expect similar studies at centers not engaging in such trials to report smaller percentages of participants desiring ISW or having had a discussion about it with their physicians. Our findings are also vulnerable to response and recall bias by nature of data collection by surveying participants. Additionally, the limited racial diversity might underrepresent the disease complications, since multiple studies have shown that non-caucasian patients with AIH present with more severe liver disease and symptoms [11,12]. Lastly, AIH is a rarer disease with less formal institutional organization than LT, which contributed to a lower number of participants and analytical power.

5. Conclusions

We have conducted the first study on patient opinions from two groups in hepatology practice considered for ISW: LTRs and AIHPs. We have demonstrated evidence of sufficient patient interest in ISW, confirming that it is not only the providers but also patients who are interested. Therefore, patients need to be informed of this intervention and properly counseled on current knowledge and practices to enhance patient-reported outcomes and quality of life.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/gastroent12020013/s1, Table S1: survey-LTAIH. This survey was provided to participants through REDCap. Once patients chose whether they were LTR or AIHPs, the survey would branch to allow for appropriate questions regarding rejection or flare ups accordingly, as well as transplant date. Both branches of the survey are included.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Northwestern University (ID STU00207617, approved 10/3/19).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

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