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Research article

Current state of clinical trials regarding liver transplant rejection

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ABSTRACT

Background: Liver transplant (LT) is the second most common transplant intervention. The rate of acute cellular rejection (ACR) is 15–25% after LT, while being higher in chronic rejection (CR). Clinical trials had a major role in getting more potent and selective immunosuppressive medications. Our study plays an important role by evaluating and tracking clinical trials related to liver transplant rejection, focusing on interventional therapeutic trials.

Methods: On October 28, we searched Clinicaltrials.gov for interventional clinical trials related to liver transplant rejection. A total of 27 clinical trials included in this study. Characteristics on each trial were collected, and availability of linked publications was searched using Medline/PubMed and Embase/Scopus. Content of publications was reviewed and main findings were summarized.

Results: Majority of trials were completed (15 out of 27). Eleven trials had between 11 and 50 participants, and 10 had above 100. The study duration was between 1 and 4 years for the majority of trials (16 trials), with an average of 3.77 years. Most of the trials were done in Europe/UK/Russia ($n = 12$). The results were provided in 9 trials but published in 4, showing the possible tolerogenic efficacy of MSC in liver transplantation, increased success of immunosuppression (IS) withdrawal after sirolimus addition, efficacy of Alemtuzumab, normal graft function and stability within 1 year of immunosuppression withdrawal.

Conclusion: This study revealed a low number of trials, lack of variety in location and low publishing rates. The focus of trials was mainly towards side effects and safety of immunosuppressants, and their withdrawal. These trials reached results that must be built on to reach definitive guidelines and treatment strategies. This highlights the need for better management of human and financial resources, in order to reach new and more effective therapeutic strategies, leading to the decrease in rate of LTR.

1. Introduction

Liver transplantation (LT), which restores normal health and expands lifespan, is a lifesaving intervention for patients with acute and chronic end-stage liver disease [1]. Fulminant hepatic failure, a life-threatening systemic complication of liver disease, liver-based metabolic defect, and more commonly, cirrhosis with complications such as hepatic encephalopathy, ascites, hepatocellular carcinoma, hepatorenal syndrome, or bleeding caused by portal hypertension are the main indications for liver transplant [2].

LT is the second most common transplant intervention, after the kidney transplant. In 2018, 7887 adult patients underwent liver transplantation and the waiting list had 12,820 adult patients. 83,925 liver transplant recipients were living with a functioning liver graft till June 30 [3].

This surgery was first attempted in 1963, after which there was continuous advances and major improvements on different aspects, as the surgical technique, the type of organ donation, the organ donation pool, and the quality of life of both the recipients and donors [4]. Therefore, the incidence of acute and chronic rejection has decreased,

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especially with development of better immunosuppressive drugs used in liver transplant recipients decreasing the rate of acute cellular rejection (ACR) to 15–25% after LT [5,6]. Usually, ACR responds well to treatment, while chronic rejection (CR) remains a difficult scenario, with a significant number of patients not responding to increased immunosuppression doses [7,8]. This is associated with high graft failure and mortality rates, especially if no re-transplantation was made [9].

LT have overcome many difficulties, reaching lower proportions of rejection and failure every day. More research is necessary to overcome remaining obstacles [10]. Clinical trials had a major role in reaching this success, by getting more potent and selective immunosuppressive medications, with better effects and less toxicity. For this reason, our study plays an important role by evaluating and tracking clinical trials related to liver transplant rejection, focusing on interventional therapeutic trials.

2. Methods

2.1. Search strategy and selection criteria

Clinicaltrials.gov is a database of clinical studies conducted all around the world, with weekly update. It is a resource provided by the U. S Library of Medicine [11].

On October 28, we searched Clinicaltrials.gov for all clinical trials related to liver transplant rejection without applying any limitation. Forty-five clinical trials were collected. Afterwards, 17 non-interventional trials and 1 diagnostic study were excluded, leading to a total of 27 clinical trials included in this study (Fig. 1).

2.2. Data collection

Phase (I, I/II, II, II/III, III), status (completed, active, recruiting, not recruiting, suspended, terminated, etc.), donor type (dead, living, relative), lobe (right, left), primary endpoints, selection criteria, sample size, study design, experimental interventions, duration, location, results, and publication were assessed for each trial using the website mentioned

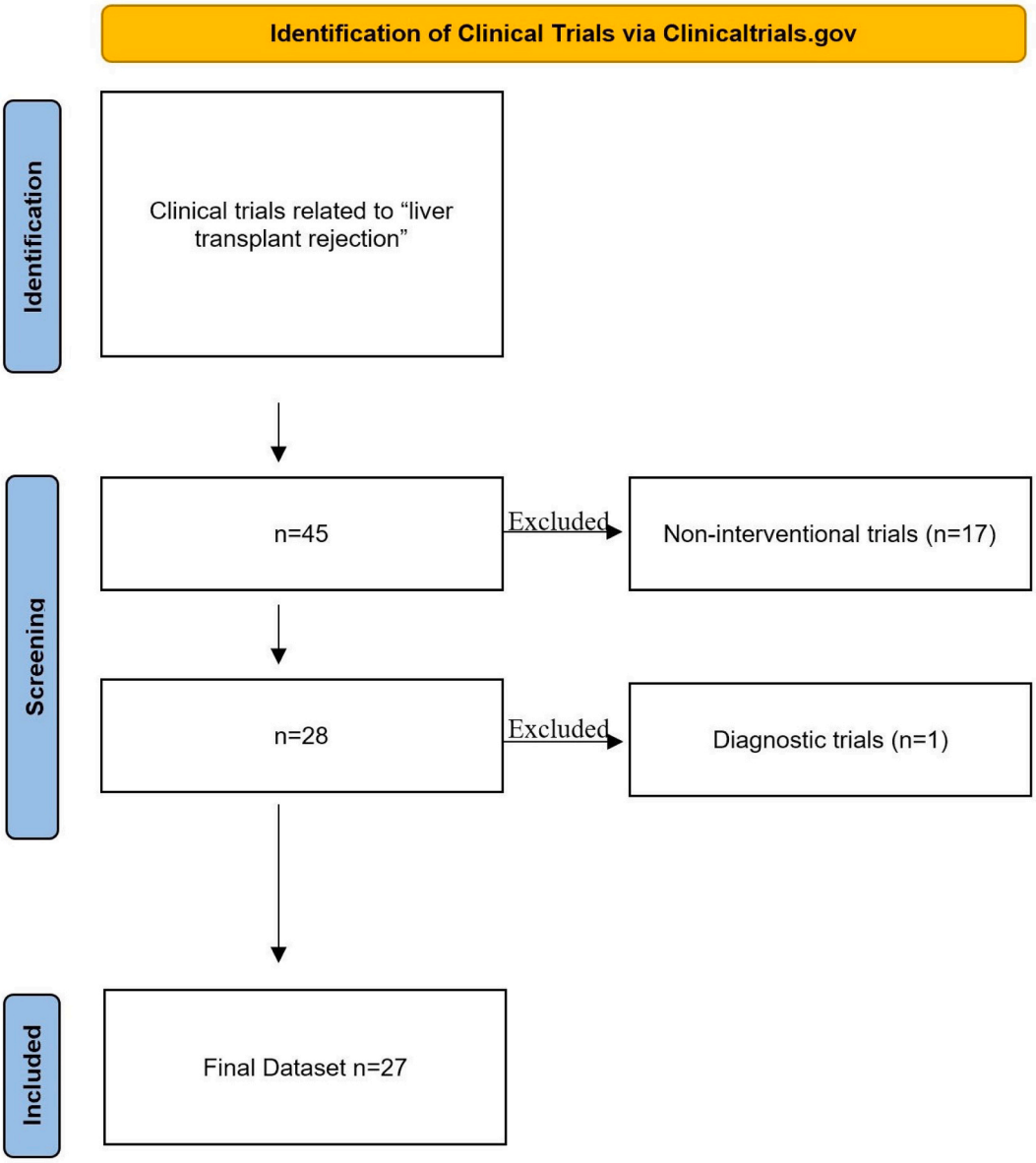

Fig. 1. Clinical trial selection process.

above.

2.3. Retrieving publications

Using NTCID number (registry number), we searched two databases (PubMed/Medline and Embase/Scopus) for any corresponding published work, where the number will be mentioned in published articles. Content of publications was reviewed, and main findings were summarized. Two investigators applied the search to exclude any chance for mistake.

3. Results

3.1. Trial characteristics

Twenty-seven clinical trials met the criteria mentioned above. Table 1 shows the distribution of trials based on specific criteria (phase, trial status, estimated enrollment, origin of the donor, lobe of liver used, results provided, transplant program location, and linked publications). Majority of trials were completed (15 out of 27), and none were active not recruiting or enrolling with invitation. Eleven trials had between 11 and 50 participants, 10 had above 100. Only 2 trials had below 10 participants. Mainly, no specific characteristics concerning donor type were specified (16 out of 27 trials), followed by brain-dead donors (8 out of 27 trials). In 25 out of 27 studies, the type of retrieved lobe was not specified. The study duration was between 1 and 4 years for the majority of trials (16 trials), and in only 1 trial, it was above than 10 years with an average of 3.77 years. The results were provided in 9 trials but published in 4. The majority of trials were done in Europe/UK/Russia ($n = 12$) while 10 were conducted in USA/Canada. Only 1 trial was intercontinental.

30% of trials were in phase IV, while 11% were in phase I (Fig. 2A). A total of 2492 participants were enrolled in these trails, distributed on different phases (Fig. 2B) with the majority being in phase IV (44%).

Table 1
Clinical trials in liver transplant rejection as found in ClinicalTrials.gov as of October 28, 2021 ($n = 27$).

Phases	I	II	III	IV	N/A	Total
Number of trials	3	6	3	8	7	27
Trial Status						
Completed	1	5	2	5	2	15
Active, not recruiting	0	0	0	0	0	0
Recruiting	1	1	0	1	2	5
Not yet recruiting	0	0	0	1	2	3
Enrolling by invitation	0	0	0	0	0	0
Terminated	0	0	1	0	1	2
Withdrawn	0	0	0	1	0	1
Unknown status	1	0	0	0	0	1
Estimated enrollment						
0–10	1	0	0	1	0	2
11–50	2	4	1	1	3	11
51–100	0	1	0	2	1	4
>100	0	1	2	4	3	10
Donor						
Living Related	2	0	0	0	0	2
Living Unrelated	0	0	0	0	0	0
Brain-dead	0	2	2	3	1	8
Brain-dead or related	0	0	0	1	0	1
Not specified	1	4	1	4	6	16
Lobe						
Right	0	1	0	0	0	1
Left	0	0	0	0	0	0
Total	0	0	0	1	0	1
Not specified	3	5	3	7	7	25
Results provided						
Yes	1	2	1	4	1	9
No	2	4	2	4	6	18
Location						
North America (US/Canada)	1	3	0	4	2	10
Europe/UK/Russia	1	2	3	3	3	12
Asia/Australia	1	0	0	0	0	1
Intercontinental	0	1	0	0	0	1
Africa	0	0	0	0	1	1
N/A	0	0	0	1	1	2
Linked Publication						
Yes	2	1	0	0	1	4
No	1	5	3	8	6	23
Study duration						
1–4 years	2	4	1	7	5	19
5–9 years	0	2	1	1	2	6
>10 years	1	0	0	0	0	1
Not provided	0	0	1	0	0	1
Average Duration (in years)	4.67	4.5	4	3.5	3	3.77

Abbreviations: N/A = not available.

3.2. Main results provided by trials

- Budesonide had no relevant effect on acute cellular rejection after transplantation.
- Glycemic control had a slight effect on rejection: slightly higher number of rejection when blood glucose was 180 mg/dl, compared to blood glucose of 140 mg/dl.
- Sirolimus besides a CellCept (mycophenolate mofetil) made higher change in GFR than that using a calcineurin inhibitor (tacrolimus, cyclosporin) with a CellCept.
- No difference between adjusted and fixed doses as long CellCept is given with tacrolimus and a corticosteroid.
- No difference in renal function between using an immunosuppressing regimen consisting of tacrolimus, mycophenolate mofetil and a corticosteroid, and an immunosuppressant consisting of reduced tacrolimus, everolimus and a corticosteroid.
- Alemtuzumab use in pediatric intestinal transplantation for patients undergone liver transplant showed a high incidence of post-transplant lymphoproliferative disorder.
- In pediatric liver transplant recipients, a high proportion of participants successfully withdrawn from Immunosuppression was reached after remaining free of immunosuppressant for 1 year.
- No difference in terms of liver transplant rejection between complete withdrawal and decreased dose of calcineurin inhibitor when received with Mycophenolate Mofetil.
- Reduction of immunosuppression by calcineurin inhibitor leads to improved native kidney function.

3.3. Publications linked to clinical trails

3.3.1. Quantitative analysis

Out of the 27 clinical trials, only 4 were linked to publications (Table 2). They were published before 2015, and 2 of them were in phase I. The number of enrolled participants ranged between 20 and 25. Inclusion criteria, primary outcome, and result were different among these studies.

3.3.2. Qualitative analysis and future targets

The 4 studies that were published are Casiraghi F, et al. (2014), Levitsky J, et al. (2014), Sindhi R, et al. (2010), Feng S, et al. (2006). Respectively, these studies showed the possible tolerogenic efficacy of MSC in liver transplantation, increased success of immunosuppression (IS) withdrawal after sirolimus addition, efficacy of Alemtuzumab in pediatric liver transplant receivers needing intestinal transplantation, and normal graft function and stable allograft histology within 1 year of immunosuppression withdrawal.

The study done by Casiraghi F, et al. showed mild positive changes in immunoregulatory T and NK cells in the peripheral blood, when 20 liver transplant patients have received a single pretransplant intravenous

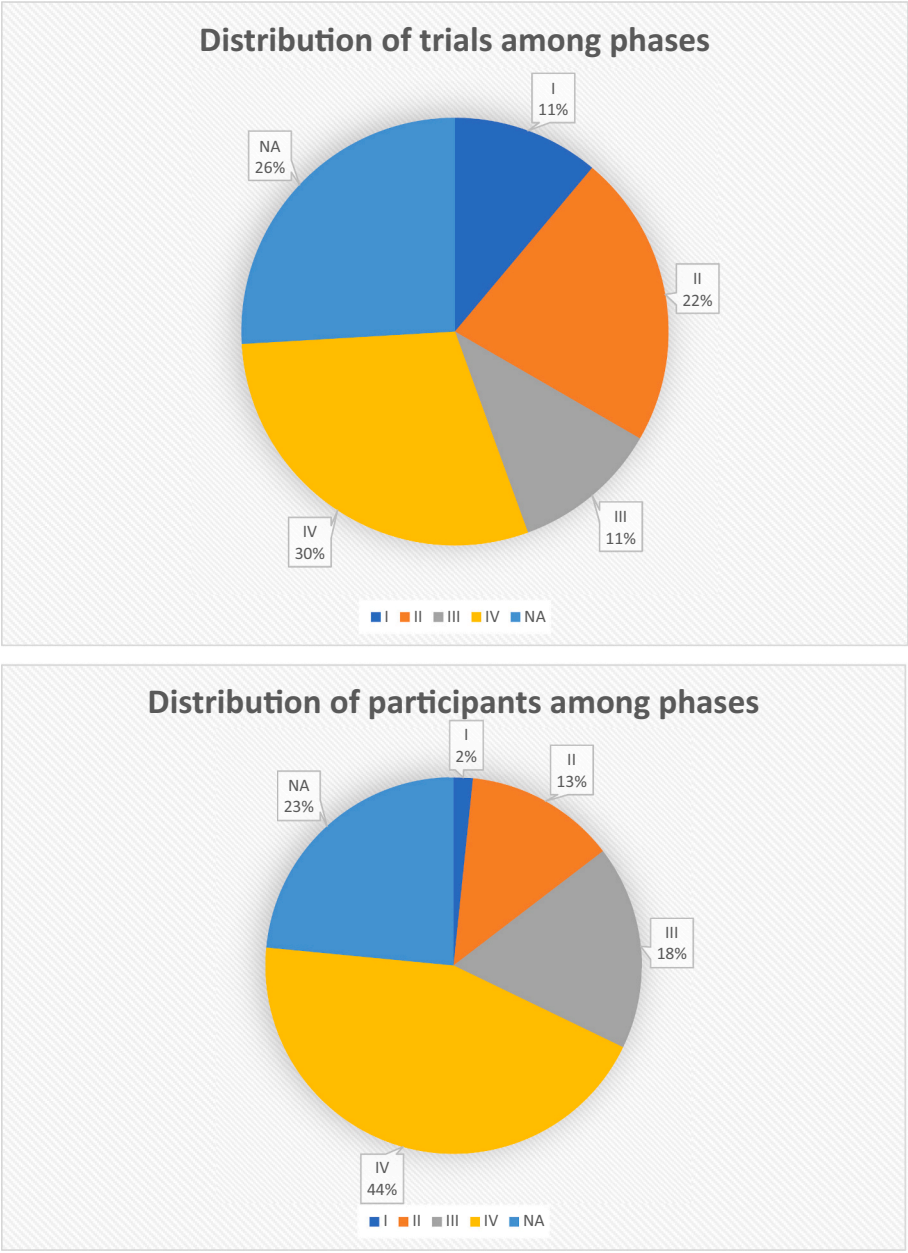

Fig. 2. Distribution of trials (A) and patients (B) among phases.

infusion of third-party bone marrow derived MSC or standard of care alone [12].This opened the door for a trial on possible tolerogenic efficacy of MSC in liver transplantation.

The study done by Levitsky J, et al. evaluated immunosuppression withdrawal directly from mTOR-I therapy (sirolimus) in liver transplant recipients and achieved >50% operational tolerance [13]. New studies can be beneficial in assessing backgrounds that permit withdrawal of immunosuppressors without resulting to transplant rejection.

The study done by Sindhi R, et al. proved that Alemtuzumab induction at the time of transplant may reduce the rate of early acute cellular rejection compared to historical controls, but may increase rate of alternate post-transplant complications, such as Post Transplant Lymphoproliferative Disorder (PTLD). It also showed that induction of Alemtuzumab at time of transplant may increase the likelihood of weaning off steroids sooner after transplant than patients who did not receive Alemtuzumab as induction immunosuppression medication [14]. Further studies are needed to approve the above theory.

The study done by Feng S, et al. showed normal graft function and stable allograft histology, in addition to absence of increased inflammation or progressive fibrosis in 60% of pediatric recipients of parental living donor liver transplants that remained off immunosuppression therapy for at least 1 year [15]. This paves the way for future studies assessing the minimum suppression possible for recipients facing transplant rejection.

3.4. Phase I trials

Only 3 trials were phase I: 1 completed, 1 recruiting, and 1 unknown. All included less than 50 participants. Two trials enrolled living donors with unspecified used liver lobe. Only one trial provided results, yet two were published: 1 from USA/Canada, 1 from Europe/UK/Russia had 1 trial, and 1 done in Asia/Australia. The average duration for phase I trials was 4.67 years.

Table 2
Clinical findings of published trials in liver transplant rejection, as of October 28, 2021 ($n = 4$).

Authors	Year	Trial	NCTID	Phase	Number Enrolled	Inclusion criteria	Primary Outcome	Results
Casiraghi F, et al.	2014	MSC Therapy in Liver Transplantation	NCT02260375	1	20	First liver transplant	Number of adverse events	N/A
Levitsky J, et al.	2014	SRL (Sirolimus) Withdrawal (SRL)	NCT02062944	NA	25	Underwent primary living or deceased donor liver transplantation ≥3 years and on ≥3 months of stable SRL monotherapy	Proportion of patients off SRL therapy with normal liver biochemistry and graft histology	Statistically increased blood tolerogenic dendritic cells and cell phenotypes correlating with chronic antigen presentation in the TOL versus non-TOL groups
Sindhi R, et al.	2010	Safety and Efficacy of Alemtuzumab in Pediatric Intestinal Transplantation	NCT01208337	2	23	Intestine transplantation in the setting of a previous or simultaneous liver transplantation	Incidence of Post-Transplant Lymphoproliferative Disorder (PTLD)	Time-to-rejection-risk resolution measured with CD154 + TcM portends 50% reduction in sample sizes in a simulated trial of alemtuzumab vs. rATG
Feng S, et al.	2006	Withdrawal of Immunosuppression in Pediatric Liver Transplant Recipients	NCT00320606	1	20	Liver from living donor, and transplant at least 4 years prior to study entry	Proportion of Participants Successfully Withdrawn from Immunosuppression	Operationally tolerant pediatric liver transplant recipients maintain generally stable allograft histology, and the absence of increased inflammation or progressive fibrosis suggests that a subset of liver allografts seem resistant to the chronic injury.

Abbreviation: NCTID = National Clinical Trial Identification; MSC = Mesenchymal Stem Cell; N/A = Not available.

3.5. Phase II trials

Six trials were phase II, of which 5 were completed and 1 is recruiting. The majority had between 11 and 50 participants, with no specific requirements regarding the type of donor and lobe. Three were from North America (US/Canada), 2 from Europe/UK/Russia, and 1 was intercontinental. Two out of the 6 phase II trials had results provided, while another 1 had a linked publication. The average duration for phase II trials was 4.5 years.

Going more into details regarding phase II trials, 5 had parallel assignment as the interventional model, making around 83% of the total. Concerning the treatment allocation, 66.7% were randomized (4 trials), while 1 was non-randomized, and 1 unspecified (16.7% each). All studies were open label. Three trials (50%), had efficacy and safety as their primary endpoint, wile the remaining 3 had pharmacokinetics, prevention and enhancement of liver generation (each forming 16.7%). (Table 3)

Table 3
Primary outcomes of Phase II clinical trials ($n = 6$).

	Number	Percentage
Interventional Model		
Single Group Assignment	1	16.67
Parallel Assignment	5	83.33
Not Specified	0	0.00
Treatment Allocation		
Non-randomized	1	16.67
Randomized	4	66.67
Not Specified	1	16.67
Masking		
Open Label	6	100.00
Not Specified	0	0.00
Primary Endpoint		
Pharmacokinetics	1	16.67
Prevention	1	16.67
Efficacy and safety	3	50.00
Enhancement of liver generation	1	16.67

3.6. Phase III trials

Only 3 trials were phase I: 2 completed and 1 terminated. Two trials included more than 100 participants. Two trials comprised brain-dead donors, and all 3 had nonspecific requirement concerning the transplanted liver lobe. All 3 trials were from Europe/UK/Russia. None of the trials were published, and only 1 had results provided. The average duration for phase III trials was 4 years.

3.7. Phase IV trials

Eight trials were phase IV, of which 5 were completed, 1 recruiting, 1 non recruiting, and 1 withdrawn. The majority enrolled more than 100 participants. Brain-dead donors were used in 3 trials while the donor type was not specified in the other 5. In 7 trials, no specific requirement concerning the lobe was noted, while in only 1, the total liver was used. In 4 out of 8 trials, the results were provided, but not published. Four trials were from North America (US/Canada), 3 from Europe/UK/Russia, and 1 unspecified. The average duration for phase IV trials was 3.5 years.

3.8. Unknown phase trials

Seven tropical trials had unknown phase. These varied widely in terms of status. The majority had between 11 and 50 or above 100 participants. No specificity regarding the used lobes was mentioned in any of the trials, and only in 1 trial brain-dead donor was used. The results were provided in 1 study and published in another 1. This phase included 1 trial from Africa (phase IV), 3 from Europe/UK/Russia, 2 from North America (US/Canada), and 1 was unspecified. The average duration for unspecified phase trials was 3 years.

4. Discussion

The current state of clinical trials related to LT is summarized in our study. Improvement of survival rates and the clinical benefits are related to the introduction of new treatment protocols which require bigger

number of clinical trials with better design.

4.1. The low number of trials

Only 27 trials regarding our topic have been established as therapeutic and interventional as of October 28, 2021. In comparison, we found 2609 interventional trials concerning liver cancer in clinicaltrials.gov. The low number of clinical trials discussing rejection in LT can be ascribed to numerous factors. First, we can link this dearth in clinical trials to the high success rates of LT, which may reach as high as 90% [16], leading to a seemingly small number of patients who have faced liver rejection for the trials. In addition, our results show that liver transplant rejection clinical trial activity in many continents has been scarce. African countries do not have any clinical trials related to LT rejection. We can relate this shortage to the small number of regional liver transplant procedures. For example, in 2019 only 12 liver transplants were performed in Africa [17]. There is no doubt that the weakness in this field is caused by the fragility of the medical sector and the modest economic situation in these countries, especially sub-Saharan Africa [18,19]. In Eastern Mediterranean, we counted only 651 liver transplants in 2019 which is low compared with the number counted in the Americas, 13,070 in the same year. However, despite the high number of liver transplants in the Americas, the number of clinical trials remained relatively low.

4.2. Accrual issues

We noted the clear discrepancy in the number of clinical trials between regions. This may be explained by the high expenses and bureaucracy playing a major hindering role in the clinical trial initiation [20]. We also mention that many clinical trials have terminated, and the grounds may be due to strict eligibility criteria, trial location, and insufficient marketing to reach participants. Recruitment methods can be one of the most important factors controlling the number of participants. Reliance to traditional methods may have a negative impact on the pool of participants [21]. In addition, many studies have shown that the doctor's recommendations clearly contribute to increasing the percentage of patients' participation in trials [22], and therefore physicians should be more involved in enhancing recruitment methods. As the methods of recruitment are improved and supported by innovative and advanced strategies, the number of participants increases, thus attracting more companies to conduct more clinical trials.

4.3. Absence of geographic diversity

Our results show that regions with highest liver-related mortality and morbidity rates presented the lowest LT rejection clinical trial activity. The vast majority (81%) of clinical trials were conducted in North America (US/Canada) and Europe/UK/Russia regions, while Asia/Australia and Africa regions were poor contributors to the total number of clinical trials (3.7% each), despite having liver disease as a significant regional burden [23,24]. For example, we mention the high liver cirrhosis mortality in Central Asia [25] and the elevated viral hepatitis burden in Africa and Asia regions [26]. This fluctuation can be partly caused by the difference in availability of infrastructure and resources [27].

4.4. Trial duration and low published results

Out of the 27 clinical trials, 19 (70%) took between one and 4 years in duration. The average duration of the clinical trials was 3.77 years, which may be further decreased with improving trials' design and removing inefficiencies. One possible solution is to apply a Master Protocol which [28], for example, will screen patients for various biomarkers and different sources of morbidity and mortality that affect LTR, in order to better assign them to adequate clinical trials [29,30].

Only 9 (one third) of clinical trials provided results regarding their primary outcomes. Moreover, only 4 trials had published work. Some trials will never reach publication for numerous reasons [31], for example, obtaining negative results and/or lack of interest by the authors themselves, and the low compliance to reporting requirements [32]. This gap in providing results creates an obstacle not only for the investigators, but also for the patients who seek to know the latest updates about their disease [33].

4.5. Therapeutic benefit

Several trials reported positive outcomes. Levitsky J, et al. [13] highlighted the effect of Sirolimus (SRL) withdrawal on transplant rejection. Dendritic cells manipulation plays an important role in transplant tolerance [34], and SRL withdrawal showed an increased blood tolerogenic dendritic cells which correlates with chronic antigen presentation in groups who achieved operational tolerance (TOL). Sindhi R, et al. [14] studied the safety and efficacy of Alemtuzumab in pediatric intestinal transplantation, which included intestine transplantation in the setting of a previous or simultaneous liver transplantation. They emphasized the 50% sample size reduction in time-to-rejection-risk resolution measured with CD154+ T-cytotoxic memory cells (TcM). Finally, Feng S, et al. [15]studied the withdrawal of immunosuppression in pediatric liver transplant recipients. In this pilot study, 60% of participants remained off immunosuppressants at least 1 year while showing normal graft function and histology, suggesting that a subset of liver allografts seem resistant to the chronic injury.

4.6. Quality of trials

Focus of trials was not towards prevention of rejection, as much as side effects and safety. Many clinical trials related to liver transplant rejection focused on the effects of immunosuppressive drugs on kidney function, some of which have shown positive results for improving kidney function while minimizing the use of some of these drugs. Furthermore, it is noted that several clinical trials targeted the idea of increasing tolerance with decreasing immunosuppression, so mainly targeting 'withdrawal". Some of them have achieved various results that can be built upon in this regard. For example, Alemtuzumab that was used in the clinical trial of Sindhi R, et al. has the potential to revolutionize the field of liver transplantation by showing that with its use, steroids can be discontinued sooner after transplantation [14].

Overall, we cannot deny the quality of some clinical trials and the impressive results reached, yet this field still needs more progressive trials that cover increasing tolerance and reducing the use of immunosuppressive drugs.

4.7. Limitations

The main limitation of our study is that data may be limited by the use of ClinicalTrials.gov. Some trials may be registered incorrectly, including missing and/or not up-to-date data, as described by Cihoric et al. [34]. Furthermore, this study targets interventional trials only, lacking track to other types, as observational trials.

5. Conclusion

This study sheds the light on the current state of clinical trials regarding liver transplant rejection. The emergence of new research projects and clinical trials is necessary to overcome rejection obstacles. This study shows the low number of trials, lack of variety in location and low publishing rates. In addition, it showed that the focus of trials was mainly towards side effects and safety of immunosuppressants, and their withdrawal. These trials reached results that must be built on to reach definitive guidelines and treatment strategies. This highlights the need for better management for human and financial resources, aiming to

new and more effective therapeutic strategies, leading to the decrease in rate of LTR.

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Declaration of competing interest

Authors declare no conflict of interest.

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