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ORIGINAL ARTICLE

Outcomes with respect to disabilities of the upper limb after hand allograft transplantation: a systematic review

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Summary

The aim of this work is to compare disabilities of the upper limb before and after hand allograft transplantation (HAT), and to describe the side effects of immunosuppressive (IS) agents given to recipients of hand allografts. Clinical cases of HAT published between 1999 and 2011 in English, French, or German were reviewed systematically, with emphasis on comparing disabilities of the arm, shoulder and hand (DASH) scores before and after transplantation. Duration of ischemia, extent of amputation, and time since amputation were evaluated for their effect on intrinsic musculature function. Infectious, metabolic, and oncological complications because of IS therapy were recorded. Twenty-eight patients were reported in 56 clinical manuscripts. Among these patients, disabilities of the upper limb dropped by a mean of 27.6 (±19.04) points on the DASH score after HAT ($P = 0.005$). Lower DASH scores ($P = 0.036$) were recorded after secondary surgery on hand allografts. The presence of intrinsic muscle function was observed in 57% of the recipients. Duration of ischemia, extent of transplantation, and time since amputation were not associated statistically with the return of intrinsic musculature function. Three grafts were lost to follow-up because of noncompliance with immunosuppression, rejection, and arterial thrombosis, respectively. Fifty-two complications caused by IS agents were reported, and they were successfully managed medically or surgically. HAT recipients showed notable functional gains, but most complications resulted from the IS protocols.

Introduction

The use of immunosuppressive (IS) drugs has allowed the development of vascularized composite allograft (VCA) transplantation by several dedicated teams [1]. Hand allograft transplantation (HAT) is the most frequent VCA transplantation procedure performed nowadays; more than 50 hands have been transplanted worldwide [1–3].

To date the adoption of HAT has been restricted for two reasons: (i) putatively limited improvements in upper limb function and (ii) the requirement for the chronic administration of IS agents, which are needed to avoid rejection after transplantation, but cause complications [4,5]. Breidenbach first reported functional gains after HAT that were similar to those achieved after macroreplantations, and justified the transplant procedure by

citing reasons similar to those that are given to justify a replant procedure [6]. Their findings would seem to indicate that HAT might be adopted widely, contrary to its current limited adoption because of the belief that the procedure yields limited improvement in function [4]. However, the issue of the risks associated with the prolonged use of IS agents remains [7]. The magnitude of functional improvement following HAT has not yet been weighed against the complications that ensue from IS therapy.

Patient-reported outcome measures (PROMs) are gradually becoming the preferred method of assessing results in clinical practice, and are supported currently by the Food and Drug Administration [8,9]. The disabilities of the arm, shoulder and hand (DASH) outcome measure is a PROM that was designed in 1996 and approved by several scientific societies [10,11]. The DASH questionnaire has been assessed with respect to its validity for face, content, and convergent and divergent constructs. Its validity for the measurement of disabilities of the upper limbs (construct validity) has been confirmed, and it has been used to evaluate the disability of the upper limb as a whole [12]. In addition, the DASH has been tested for longitudinal construct validity, which confirmed that it was able to detect and differentiate small and large changes in disability over time after surgery in patients with musculoskeletal disorders of the upper extremity [13]. A decrease in DASH score of more than 15 points is the most accurate indication that a patient's condition has improved [14]. In addition to the DASH score, Chen's functional grade and the scores from the hand transplant score system (HTSS) have been used to evaluate the outcomes after replantation and transplantation procedures, respectively [15].

Our aim was to perform a systematic review of the clinical data currently available on hand allograft recipients, and to analyze their functional outcomes. The principal measures of the outcomes were (i) disabilities of the upper limb assessed using the DASH score and (ii) the extent and severity of the side effects of IS therapy.

Material and methods

We performed a systematic review of hand allograft transplants that have been reported, following a method described previously [16]. The outcomes of interest included the DASH score, the Chen functional grade, the HTSS, and complications that ensued from IS therapy. We conducted an online search of the literature on 22 April 2011 using the MedLine database and the following terms: ''composite tissue allograft'' and ''hand allograft transplant'' and ''hand transplantation''. The search identified 112 eligible papers. Only papers that described one case or more of HAT after the introduction of calcineurin inhibitors, and were published in English, French or German between 1999 and 2011, were selected for this study; reviews and experimental reports were excluded. Forty papers fulfilled the inclusion criteria and their references were checked to obtain additional primary data. Abstracts from major meetings that took place up to 2010 and that focused on transplantation were also included if they were available on the internet or had been published. In all, 82 papers (including congress papers) were retrieved from the MedLine database, by the manual retrieval of references and an internet search of congress websites. Only 56 of these references were found to provide relevant data on the course of 28 patients, and were selected for analysis. Teams that performed hand transplantation, as specified in the Hand Registry, were contacted and asked to supply missing data [17]. Those teams that supplied unpublished data were included among the authors. Unpublished data were provided by three teams, namely two different teams in Monza and one team in Innsbruck. No data were extracted from the Hand Registry nor from any of its reports. Given the heterogeneity in the data collected and reported, a meta-analysis was not possible, but numerical combinations could be studied.

During the design stage of the study, it was decided what data to extract. Demographic, surgical, IS, and functional outcome data were the main fields of investigation, and included year of transplantation, gender, age, time since amputation, duration of ischemia, extent of tissue transplanted, induction therapy, current maintenance regimen, surgical complications, pre- and post-transplantation DASH scores, pre- and post-transplantation Chen functional grades, post-transplantation HTSS results, the presence of intrinsic musculature function, infectious complications, metabolic alterations (hyperglycemia, increased serum creatinine [SCr], hypertension, and hyperlipidaemia), malignancy, graft loss and its cause, and death of the recipient if this had occurred. A database was designed in which each paper was assigned a color code on the basis of the order of publication (i.e., by date), and each input in the database was color coded. Each individual patient was followed through the various relevant publications on the basis of demographic data. If different DASH scores had been reported for any patient, the most recent available score was selected for analysis.

Statistical analysis

Quantitative variables are presented as the mean (± standard deviation), and qualitative variables as percentages. Nonparametric tests were used because of the small sample of patients. Pairwise comparisons of quantitative data were performed using the Wilcoxon signed-rank test. The

Mann–Whitney *U*-test or Kruskal–Wallis test was used to compare independent quantitative variables with qualitative variables. The differences in qualitative dependent variables were analyzed using Fisher's exact test. Statistical significance was taken as $P \leq 0.05$. The statistical analysis was performed using the SPSS statistical package, version 11.5 for Windows.

Results

Paired pre- and post-transplantation DASH scores with a minimum follow-up of 300 days were available for 10 patients, and they are shown in Table 1 [18–27]. The mean pretransplantation DASH score was 71.01 (±25.79), whereas the mean post-transplantation DASH score was 43.39 (±26.48). The mean difference in the DASH score between pre- and post-transplantation was 27.61 (±19.04). This difference was statistically significant ($P = 0.005$). Figure 1 shows the magnitude of the improvement for each patient, and the mean improvement.

The mean pretransplantation DASH score was 66.13 for unilateral amputees and 65.9 for bilateral amputees ($P = 0.93$). Recipients of unilateral allografts scored a mean of 59.4 points on the DASH post-transplantation, as compared with recipients of bilateral allografts, who scored a mean of 36 ($P = 0.14$). The magnitude of the improvement was 21.07 in recipients of unilateral allografts, as compared with 30.41 in those who received bilateral allografts ($P = 0.66$).

Differences with respect to gender were assessed postoperatively. The mean post-transplantation DASH score in males was 47.5, whereas in females it was 37 ($P = 0.63$). Regarding the magnitude of the improvement, males seemed to improve more than females (29.71 vs. 19.20), but this difference did not reach significance ($P = 0.53$). No significant differences were found between the mean amount of improvement in patients younger than 40 years and those who were 40 years or older (44.9 vs. 46.6; $P = 0.85$). Differences were found when the mean post-transplantation DASH score for patients younger than 40 years was compared with that for patients 40 years old or older, but they were not significant (35.2 vs. 16.1; $P = 0.11$).

Pre- and post-transplantation Chen functional grades were available for 17 patients. All of these patients presented with Chen grade IV before transplantation, as shown in Fig. 2. Only one recipient remained at grade IV after transplantation (5.9%). Seven (41.2%) had improved to grade III, eight (47.1%) to grade II, and one to grade I (5.9%).

The HTSS measure was available for 14 patients for the right limb and seven patients for the left allograft. The mean HTSS scores were 74.21 (±11.13) and 71.85 (±6.42) (rated as good) for the right and left allografts, respectively.

Fifteen patients (53%) underwent secondary surgery, which included tenolysis [18,28,29], removal of hardware [18,28,30,31], tendon transfers [27,31], arthrodesis of joints [27,32], removal of heterotopic ossification [18], cosmetic revision [29,31,33,34], bone shortening [26], tendon shortening, and evacuation of a hematoma/seroma [20,35]. The mean post-transplantation DASH score of those patients who did not undergo secondary surgery on their allograft was 70 (±14.73), whereas those patients who underwent such procedures presented a mean DASH score of 36.41 (±21.7). This difference was statistically significant ($P = 0.036$). With regard to the magnitude of the improvement, those patients who did not undergo secondary surgery improved less than those patients who did, with a mean improvement in DASH score of 21.5 (±10.6) vs. 29.43 (±22.56). However, this result was not statistically significant ($P = 0.77$).

Presence of intrinsic muscle function was observed in 16 recipients (57.14%). We evaluated the relation between the return of intrinsic muscle function and the following factors: time since amputation, duration of ischemia, and extent of tissue transplanted. Those patients in whom the presence of intrinsic musculature had been observed tended to have received their transplant earlier (mean 6.2 years vs. 13.7 years), but this difference was not significant ($P = 0.12$). There were no significant differences with respect to the return of intrinsic muscle function and the extent of tissue transplanted (radiocarpal *vs.* forearm and complete arm, $P = 0.086$). There was no significant association between the duration of ischemia of the allograft (more than 6 h) and the presence of intrinsic muscle function, although allografts that did not show useful intrinsic musculature tended to suffer a longer period of ischemia (8.9 h vs. 7 h, $P = 0.33$). Neither the time since amputation, the extent of tissue transplanted, nor the duration of ischemia were associated statistically with the post-transplantation DASH score or the difference in DASH score ($P = 0.9$ and $P = 0.27$, $P = 0.41$ and $P = 0.83$, $P = 0.41$ and $P = 0.41$, respectively).

A total of 52 complications derived from IS therapy were reported. Six patients (21.42%) suffered at least one episode of cytomegalovirus (CMV) infection. Other episodes of infection, such as cutaneous mycosis (four patients), herpes simplex virus (HSV; two patients), varicella-zoster virus (one patient), Epstein–Barr virus (one patient), and cutaneous human papilloma virus (one patient) were also reported. One patient suffered an episode of osteomyelitis, and an abscess in the forearm, colitis associated with *Clostridium difficile*, and an episode of pneumonia were also reported [6,21,26,27,30,31,36–41].

Table 1. Data from patients whose DASH scores were available.

Patient location (case)	Follow-up (days)	Gender	Year	Age	Time since amputation (years)	Side	Tissue transplanted	Duration of ischemia (h)	Induction therapy	Maintenance therapy	Pre-Tx DASH	Post-Tx DASH	Pre-Tx Chen	Post-Tx Chen	HTSS	Intrinsic musculature function	Secondary surgery	Side effects of IS
Brussels (1)	1129	M	2002	22	1.6	Unilateral	Hand	6	ATG + MPRED	Tac + MMF + PRED	31	10.8	IV	II	88.5	Yes	Yes	Hyperglycemia
Lyon (2)	3650	M	2000	33	4	Bilateral	Hand	9.2	ATG + MPRED	Tac + MMF + PRED	86	16	IV	II	82	Yes	Yes	Hyperglycemia
Innsbruck (1)	3102	M	2000	47	6	Bilateral	Hand	2.8	ATG + MPRED	SRL + MMF	57.5	34	IV	I		Yes	Yes	Hyperglycemia, hypertriglyceridemia
Innsbruck (2)	2044	M	2003	41	3	Bilateral	Forearm	2.6	ATG + MPRED	Eve + Tac	66.6	64	IV	III	69.5	Yes	Yes	HT, hyperglycemia, ↑SCr
Valencia (1)	1460	F	2006	47	28	Bilateral	Hand	8.9	Alemtuzumab + MPRED	SRL + MMF + PRED	29.16	17.86	IV	II	69	Yes	Yes	HT, hyperglycemia, BCC, ↑SCr
Valencia (2)	1095	M	2007	31	2	Bilateral	Forearm	7	Alemtuzumab + MPRED	SRL + MMF + PRED	70.83	36.6	IV	II	69.5	Yes	Yes	HT, hyperglycemia, fungal infection,↑SCr
Valencia (3)	730	M	2008	31	1	Bilateral	Arm	6	Alemtuzumab + MPRED	SRL + MMF + PRED	75	30.83	IV	II	79.5	No	Yes	HT, hyperglycemia, hypertriglyceridemia, ↑SCr
Wroclaw (1)	1460	M	2006	32	14	Unilateral	Forearm	10.5	Basiliximab + MPRED	Tac + MMF + PRED	100	86	IV	II	84	No	No	Hyperglycemia
Wroclaw (3)	720	M	2008	30	3	Unilateral	Hand	9	Basiliximab + MPRED	Tac + MMF + PRED	96	67	IV	–	82	Yes	No	No
Monza (4)	365	M	2010	50	3	Bilateral	Hand	4.5	Basiliximab + MPRED	Tac + MMF + PRED	98	70.9	IV	–	–	Yes	No	–

Notes: Tx, transplant; HTSS, Hand Transplant Score System; IS, immunosuppression; ATG, anti-thymocyte globulin; MPRED, methylprednisolone; Tac, tacrolimus; MMF, mycophenolate mofetil; PRED, prednisone; SRL, sirolimus; Eve, everolimus; HT, hypertension; SCr, serum creatinine; –, denotes missing data.

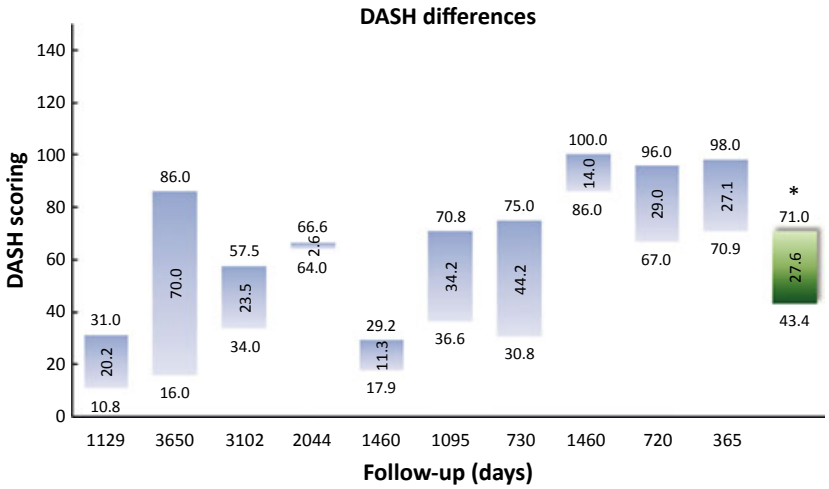

Figure 1 Gantt diagram showing the magnitude of the improvement in disabilities of the upper limb. Each bar represents a patient and the magnitude of the improvement; the maximum value of the bar represents the pretransplantation DASH score, whereas the minimum value of the bar represents the post-transplantation DASH score. The 11th bar represents the mean improvement for these 10 patients, and the asterisk denotes a statistically significant mean decrease in the DASH score ($P = 0.005$).

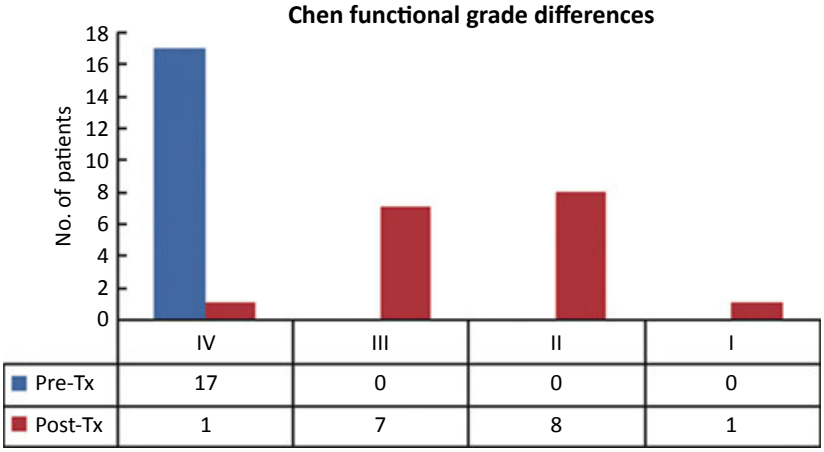

Figure 2 Before transplantation (Pre-Tx), 17 patients were graded as IV on the Chen functional scale. Only one patient remained as grade IV after transplantation (Post-Tx), whereas seven had improved to grade III, eight to grade II, and one to grade I.

The metabolic complications reported included hyperglycemia in 13 patients (46.42%), hypertension in seven patients (25%), increased SCr in five patients (17.85%), hyperlipidaemia in four patients (14.28%) [18,21, 35,39,40,42–44], and bilateral necrosis of the hip in one case [6]. All infectious and metabolic complications responded to medical or surgical treatment. No patient required dialysis as a result of renal failure.

Malignancy was diagnosed in two patients: a surgically controlled basal cell carcinoma (BCC) and a case of medically controlled post-transplant lymphoproliferative disease (PTLD) [45,46]. One graft was lost because of noncompliance with IS therapy [47], another because of vascular complications immediately after transplantation [23], and a third because of rejection [48]. One patient died 60 days after a combined face transplant and bilateral HAT [49].

Discussion

HAT has been performed for 12 years by different teams around the world, with more than 50 hands transplanted to date [1]. Most teams that perform HAT have reported the functional outcomes of their recipients using objective clinician-based outcome (CBO) measures, such as range of motion, sensitivity, strength, and cortical reintegration

[6,21,26,50]. However, CBO measures will not convey all the necessary information about what the patient is able or unable to do [8]. We used the DASH outcome to evaluate the disabilities of patients before and after HAT. In this systematic review of case reports, a statistically significant improvement of 27.6 (±19.04) points ($P = 0.005$) in the DASH score was observed in 10 patients after HAT. This finding corroborates a previous report, which found a statistically significant mean improvement in the DASH score of 29.9 (±16.9) ($P = 0.046$) in a case series of three patients after HAT [22], and underlines a previously reported notable improvement in the activities of daily living after HAT by the authors of the Hand Registry [1]. The improvement that we observed exceeded the minimum detectable change at the 95% confidence level (MDC_{95}) in the DASH score. In addition, the DASH scores of 70% of the patients improved by more than 15 points, which confirmed that the functional status of their upper limb had improved after the transplant procedure [12]. Recipients of bilateral allografts showed a greater improvement in DASH score than recipients of unilateral allografts (30.41 vs. 21.07), but the difference was not significant. However, this result highlights the possibility that bilateral amputees might gain more functionally than unilateral amputees, and thus the indication to perform unilateral hand transplants is still an open debate in Europe [2,3].

Secondary surgery has been proposed to improve the function of replanted parts, especially hand and fingers [51–55], and it was used in a similar way to improve allograft function in a number of cases that are covered in this review. Procedures for cosmetic revision were performed the most often [28,30,32,33], followed by the removal of hardware [17,27,29,30]. However, other procedures that were mainly functional were also reported [18,26, 27,29,31]. Secondary surgery is not common after solid organ transplantation, but should be available to improve hand allograft function. Those patients who underwent secondary surgery scored significantly lower on the DASH questionnaire than those who did not. This observation highlights the need to involve hand surgeons who specialize in macroreplantation in HAT procedures, a case for which they may be better suited than surgeons who specialize in the transplantation of abdominal organs.

No demographic characteristic (i.e., gender or age) could be associated statistically with better outcomes, although nonstatistical differences were found. In addition, we were not able to determine the extent to which improvement depended only on secondary surgery, because none of the authors reported the DASH scores before and after secondary surgery. It is assumed generally that the longer the follow-up period, the better the hand allograft function that is reported [6]. Thus, the passage of time might play an important role in the final DASH score. Interestingly, the function of hand allografts improves over time, in contrast to all other solid organ allografts, in which function usually worsens over time [7].

Of the 17 patients for whom the Chen functional grade was available, 16 improved at least by one grade. Although the Chen functional grade has not been validated, it is used widely to evaluate results after hand replantation. However, it was not our main outcome measure because a good correlation between the DASH score and the Chen functional grade is yet to be determined after replantation [56]. The mean HTSS values indicated the results for the allograft and patient function to be good. However, the HTSS cannot be measured before transplantation, and as a consequence the change in the functional status of the recipient after transplantation cannot be quantified on this basis. It was impractical to evaluate the function of hand allografts systematically on the basis of other instruments, mainly because these instruments were not used by all the teams, but also because other instruments have some limitations [19].

The presence of intrinsic muscle function was observed in 57% of the recipients. In contrast to sensitivity, the achievement of clinically useful intrinsic muscle function requires that reinnervation occurs within a short time after good quality neural repair. A question has arisen as to whether cortical deafferentiation would preclude reinnervation of hand allografts, especially when a long period had elapsed since amputation. In our study, there were no detectable differences with regard to time since amputation. Notably, a patient who underwent transplantation 28 years after amputation showed the return of allografted intrinsic muscles [27]. These results confirm previous findings that showed that the plasticity of the brain cortex was sufficient to allow reinnervation of hand allografts after a long period of time [57]. A duration of ischemia of more than 6 h has been determined to increase the mortality associated with graft failure after cardiac transplantation [58]. In contrast, it was not associated significantly with the presence of functional intrinsic musculature, but a tendency toward more useful function was observed in those patients who experienced shorter periods of ischemia. There were no detectable differences in the presence of intrinsic muscle function with regard to the extent of tissue transplanted. In theory, those allografts that were transplanted more distally should show better intrinsic function as a result of shorter distances between the neurorrhaphies and the target organs, but we were unable to either confirm or disconfirm this hypothesis from the data available. Whether the use of tacrolimus might be responsible for increasing the speed of growth of axons and diminishing the time required for

reinnervation has not yet been determined in the clinical setting. However, the literature is providing a growing body of empirical confirmation that this is indeed the case [59,60].

Some limiting factors deserve comment. First, we adopted a minimum follow-up time of 300 days to evaluate changes in the DASH score because, on the basis of the senior author's experience with three bilateral cases of HAT, we regarded it as a safe length of time that is sufficient to show improvement after neural recovery in most recipients. However, the difference in follow-up times is a limitation that might have clinical implications, particularly when interpreting the size of the change in DASH score to assess the effectiveness of treatment. For example, an observed change in the DASH score after 300 days might be even greater if assessed after 1500 days [21]. However, it must be noted that patients who have been followed up for short periods may show greater differences in the DASH score than patients who have been followed up for longer periods. For example, a patient who had been followed for 365 days had improved by 28 points, whereas two patients who had been followed for 2044 and 1460 days had improved by 2.6 and 11.3 points, respectively. In addition, the Hand Registry report showed that the DASH outcome of bilateral allograft recipients may worsen between the 2nd and the 9th year [1]. The second limitation is that, in the absence of a control group, it is impossible to determine the risks associated with IS therapy, which precludes the calculation of a risk-to-benefit ratio for the occurrence, prevalence or association of side effects after HAT. However, the disadvantages of not being able to calculate a risk-benefit ratio might not be as significant as might be thought, because for any risk, its management includes any corrective action that can be implemented should that risk occur. This was the case in the series reported herein, and all the patients responded to medical or surgical treatment after complications occurred. Whether any complication pertaining to metabolism (e.g., hypertension), oncology (e.g., BCC) or infection (e.g., HSV) would have occurred in the absence of IS will remain unknown, although such complications are unlikely. Only 3.5% among a cohort of 1295 showed a normal blood pressure without the administration of antihypertensive medications at 1 year after kidney transplantation [61]. New-onset diabetes after transplantation can develop in up to 50% of transplant recipients during the first year after solid organ transplantation [62]. The incidence of CMV disease in patients who are not receiving prophylaxis after liver transplantation can range between 8% and 65% [63]. The recipients who we reviewed were not free of these complications, but none of them presented with renal failure, although serious complications, which included hip necrosis and a case of PTLD, did occur. Longer follow-up periods might reveal a larger number of side effects that result from long-term IS. However, regardless of side effects, the recipients of hand allografts will enjoy the benefits of functional enhancement for years to come. At the time of writing, it is not yet possible to dispense with IS therapy for HAT. The outlook is uncertain, because tolerance of the immune system to foreign tissue has yet to be achieved in the clinical setting for other more commonly transplanted organs, such as the kidney [64].

Conclusions

In this review, the 28 recipients of hand allografts showed functional gains, but there was a cost in the form of 52 complications resulting from the current IS protocols. However, HAT is not adopted generally because of the need for chronic IS therapy after transplantation and the significant costs. Until tolerance to allografts can be achieved clinically, HAT should be offered only to selected well-informed candidates who accept the risks of the current IS therapy.

Authorship

LL: wrote the first draft and all the authors then made their own contribution to the writing of the final manuscript; they also contributed to data recovery and analysis. JB: participated in research design, data recovery, and writing the manuscript. JD: participated in data analysis and reviewing the manuscript. MN, ML, MB and SS: participated in providing unpublished data and reviewing the manuscript. TH, AL, FL, AGL, CC-S and CC-P: participated in reviewing the manuscript.

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