The Efficacy of Intensive Monitoring of Serum Tacrolimus Level Post Itraconazole Cessation in Preventing Rejection after Heart Transplant

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Introduction

Itraconazole is routinely used for prophylaxis against invasive fungal infections amongst heart transplant (HTx) recipients in our institution. Prior research in our institution has demonstrated that cessation of itraconazole prophylaxis in the HTx population results in marked individual variations of serum tacrolimus levels despite pre-emptive dose escalation, leaving a proportion of individuals at increased risk of acute rejection due to subtherapeutic serum tacrolimus levels[1]. Subsequently, we have noted an anecdotal increase in the frequency of clinically significant acute rejection following itraconazole cessation. This prompted the introduction of an intensive monitoring regimen of tacrolimus levels post itraconazole cessation to facilitate timely dose adjustments to maintain therapeutic tacrolimus levels. Here, we report the efficacy of intensive monitoring of tacrolimus levels post itraconazole cessation in preventing acute rejection.

Method

This retrospective, single centre analysis included all patients undergoing HTx at our institution from January 2017 to March 2018 who underwent itraconazole cessation at 3 to 8 months post-transplant whilst receiving a stable regimen of tacrolimus-based immunosuppression. Exclusion criteria are outlined in *Figure 1.* Patients were classified as intensive monitoring group if tacrolimus levels and dose titration were performed at least once a week in the outpatient setting for 6 weeks post cessation of itraconazole unless hospitalised for clinically significant infection or rejection; or the control group, where tacrolimus levels measurements and dose titration were performed less frequently on clinic follow-ups only (up to monthly). Outpatient dose titration were achieved through at least weekly phone calls to patients, which was introduced for the patients who underwent itraconazole cessation from February 2018. The primary outcome included clinically significant rejection defined as biopsy proven ISHLT grade 2R rejection or left ventricular dysfunction proven on echocardiography requiring glucocorticoid pulsing, and infections requiring hospitalisation, up to 8 weeks post itraconazole cessation. Secondary outcome includes the number of tacrolimus dose adjustments made within 4 weeks of itraconazole cessation. Statistical calculations were performed using Fisher's exact test and Mann-Whitney's U test.

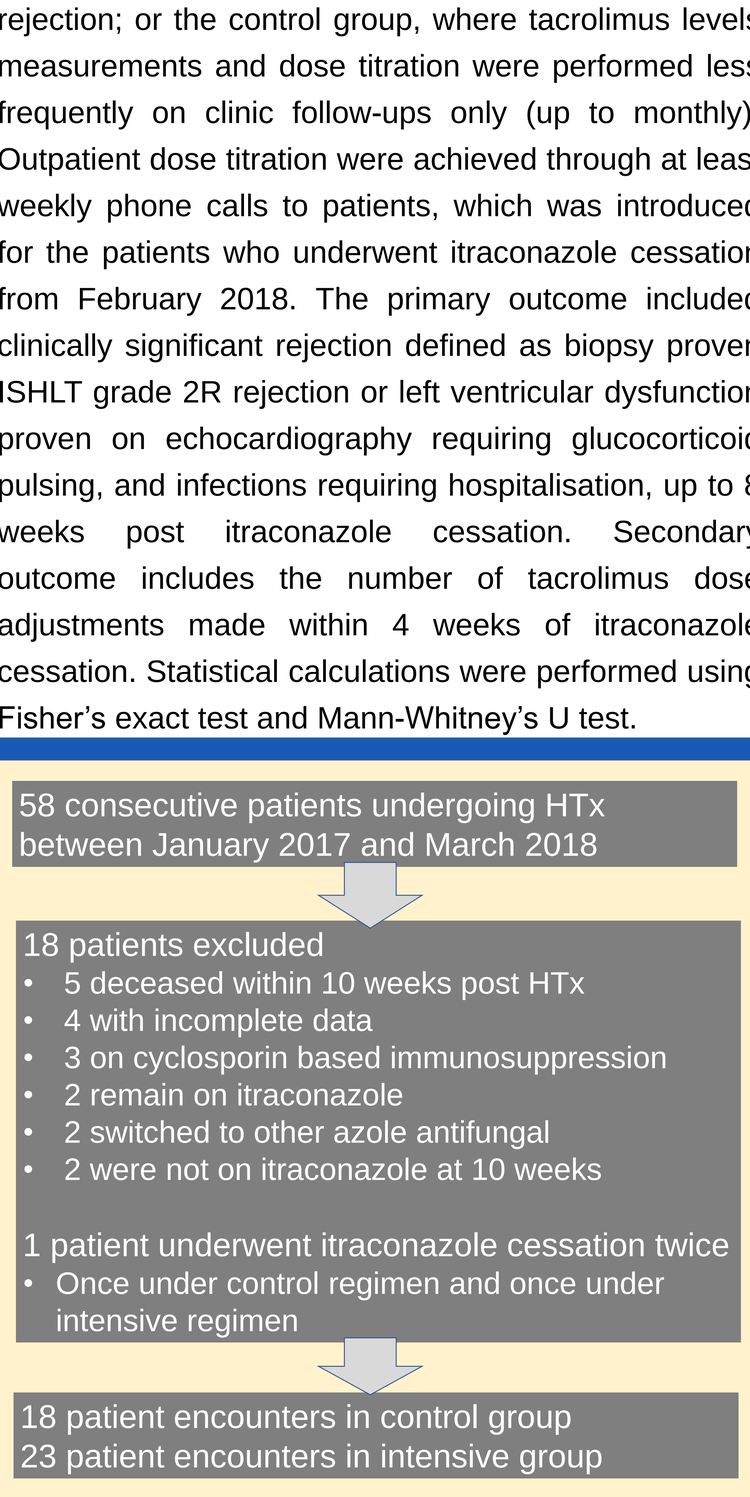

Figure 1. Patient inclusion and exclusion criteria

Results

A total of 40 patients were included in this study, with 18 patients in the control group and 23 patients in the intensive group (one patient underwent itraconazole cessation twice, totalling 41 patient encounters). Baseline characteristics are presented in *Table 1*. Within 2 months of itraconazole cessation, 7 patients in the control group and 2 patients in the intensive group had clinically significant rejection (P = 0.028). In the same timeframe, 0 patients in the control group and 5 patients in the intensive group developed bacterial infections that required hospitalisation (P = 0.056), as represented by *Figure 2*. Four out of the 5 hospitalised patients were found to have invasive nocardia species infections despite trimethoprim/sulfamethoxazole prophylaxis, requiring prolonged intravenous antibiotics, with one patient having concurrent cytomegalovirus reactivation, and 0 of them had supratherapeutic tacrolimus levels. No fungal infection had been observed in any patient post itraconazole cessation within the 2 month follow up period designated to this study.

During the first 4 weeks since itraconazole cessation, 20 out of the 23 patients in the intensive group had documented dose titrations, with 3 patients having poor quality data. The mean number of dose adjustments made during the first 4 weeks was 4.850 ± 1.424. Ten patients (50%) continued to require further dose adjustments until 6 weeks post itraconazole cessation.

Table 1. Group	Control	Intensive	P Value
Number of patient encounters (n)	18	23	-
Female (%)	5 (28%)	7 (30%)	1.000
Age (years)	54.6 ± 12.9	51.3 ± 16.6	0.624
Days post HTx at time of itraconazole cessation	143 ± 47.2	171 ± 30.2	0.060
Baseline creatinine (µmol/l)	114 ± 45.9	107 ± 52.3	0.230
Tacrolimus dose at cessation (mg/day)	1.47 ± 1.23	1.08 ± 0.73	0.596
Pre-emptive tacrolimus dose increase (%)	70.4 ± 111	76.7 ± 50.7	0.294
Itraconazole level at cessation (µg/l)	773 ± 496	838 ± 392	0.276
Tacrolimus level at cessation (µg/l)	11.9 ± 4.9	10.1 ± 3.5	0.019

Table 1. Baseline characteristics of HTx patients undergoing itraconazole cessation

Discussion

Despite the small sample size, the finding that an intensive monitoring regimen reduced clinically significant rejection is an important finding given the high morbidity associated with acute cellular rejection in HTx patients. The non-significant trend towards increased infection requiring hospitalisation appeared to be due to an outbreak of nocardia infections among the intensive monitoring group, but was unlikely associated with supratherapeutic tacrolimus levels as the frequent dose adjustments would have prevented prolonged excessive immunosuppression.

Our study has several limitations. Aside from the aforementioned small sample size, the intensive regimen of tacrolimus dose titration post itraconazole cessation is a labour intensive process and geographically isolated patients found it difficult to access a pathology centre capable of processing tacrolimus levels on a weekly basis. Patient compliance with complex tacrolimus dosing regimens and blood collection for trough levels may have impacted on our results, as several dose adjustments were found to be inappropriate retrospectively upon clinic visits, where a more comprehensive history was obtained. In patients with confirmed infections, lower tacrolimus levels were intended, thus deviating from the usual practice of dose adjustments. Nevertheless, patients required between 4 to 5 dose adjustments over the first 4 weeks, and only half reached therapeutic steady state at 4 weeks.

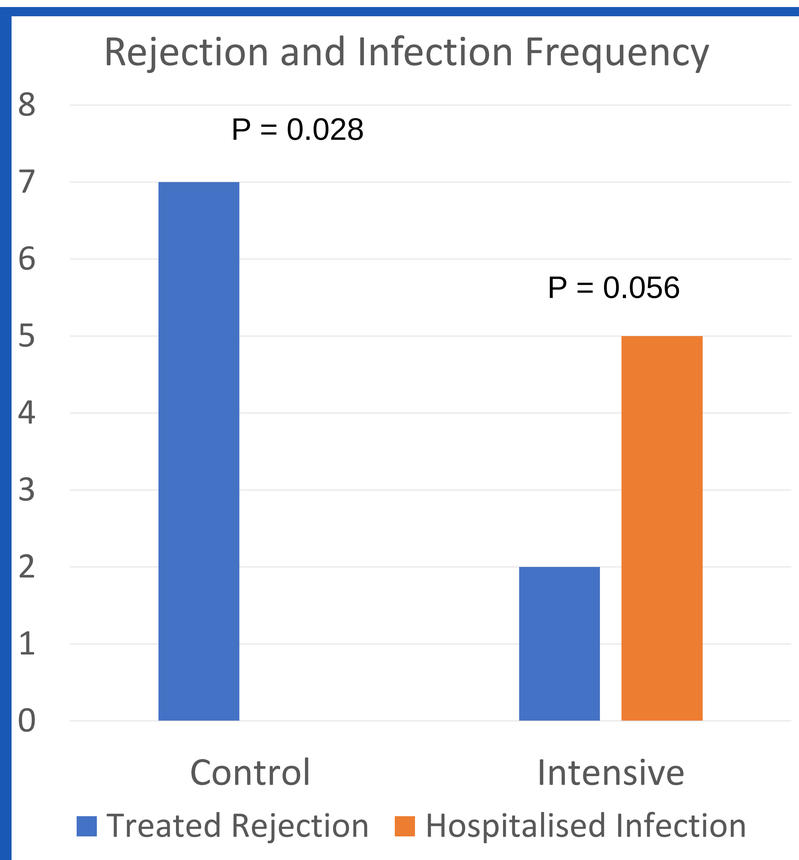

Figure 2. Rejection and Infection Frequency

Conclusion

Intensive monitoring of tacrolimus levels at least weekly post cessation of itraconazole is effective in preventing clinically significant rejection, although there is a non-significant trend towards an increased risk of non-fungal infections.

References

1. F Burrows et al. Effect of Itraconazole Prophylaxis on the Incidence of Rejection in Heart Transplant Recipients. Poster presented at 38th ISHLT Annual Meeting, 2018. Nice, France.