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ORIGINAL RESEARCH

Heart rate reduction for 36 months with ivabradine reduces left ventricular mass in cardiac allograft recipients: a long-term follow-up study

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Background: Due to graft denervation, sinus tachycardia is a common problem after heart transplantation, underlining the importance of heart rate control without peripheral effects. However, long-term data regarding the effects of ivabradine, a novel I_f channel antagonist, are limited in patients after heart transplantation.

Methods: In this follow-up analysis, the resting heart rate, left ventricular mass indexed to body surface area (LVMI), tolerability, and safety of ivabradine therapy were evaluated at baseline and after 36 months in 30 heart transplant recipients with symptomatic sinus tachycardia versus a matched control group.

Results: During the study period, ivabradine medication was stopped in three patients (10% of total). Further analysis was based on 27 patients with 36 months of drug intake. The mean patient age was 53.3±11.3 years and mean time after heart transplantation was 5.0±4.8 years. After 36 months, the mean ivabradine dose was 12.0±3.4 mg/day. Resting heart rate was reduced from 91.0±10.7 beats per minute before initiation of ivabradine therapy (ie, baseline) to 81.2±9.8 beats per minute at follow-up (P=0.0006). After 36 months of ivabradine therapy, a statistically significant reduction of LVMI was observed (104.3±22.7 g at baseline versus 93.4±18.4 g at follow-up, P=0.002). Hematologic, renal, and liver function parameters remained stable during ivabradine therapy. Except for a lower mycophenolate mofetil dose at follow-up (P=0.02), no statistically significant changes in immunosuppressive drug dosage or blood levels were detected. No phosphenes were observed during 36 months of ivabradine intake despite active inquiry.

Conclusion: In line with previously published 12-month data, heart rate reduction with ivabradine remained effective and safe in chronic stable patients after heart transplantation, and also during 36-month long-term follow-up. Further, a significant reduction of LVMI was observed only during ivabradine therapy. Therefore, ivabradine may have a sustained long-term beneficial effect with regard to left ventricular remodeling in heart transplant patients.

Keywords: heart transplantation, heart rate control, ivabradine, left ventricular mass

Introduction

An inverse correlation between resting heart rate and life expectancy has been demonstrated in healthy humans.[1–6] Due to allograft denervation, sinus tachycardia is a common problem in heart transplant recipients. As described previously, ivabradine, an I_f channel antagonist, regulates pacemaker activity in the sinoatrial node, without the systemic side effects of beta-blocker therapy.[7–9] However, long-term study data examining the association between heart rate and left ventricular mass in heart transplant recipients are insufficient.[7,8,10,11] The current follow-up study examines the long-term tolerability, efficacy, safety, and echocardiographically determined effects on left ventricular mass after 36 months of ivabradine therapy in stable patients after

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heart transplantation presenting with symptomatic sinus tachycardia compared with a matched control group.

Patients and methods

Patients

Patients participating in this study were stable, chronic heart transplant recipients experiencing symptomatic sinus tachycardia. All patients were in sinus rhythm.[7,8] As previously reported, at baseline all patients were more than 6 months post-heart transplant, and no rejection episode (mean interval since preceding biopsy without signs of rejection: 4.0±2.7 months) or acute infection was present.[7,8] Additionally, all patients received steady immunosuppressive doses, and left ventricular ejection fraction was at least 60% at study inclusion. This was a long-term follow-up analysis after 36 months of ivabradine intake. Written informed consent was obtained from all patients prior to study entry.

Methods

The main target parameters were resting heart rate, left ventricular mass, left ventricular mass indexed to body surface area (LVMI, as assessed by echocardiography), tolerability, and safety after 36 months of ivabradine therapy in 30 patients after heart transplant versus a matched control cohort of heart transplant patients without medication affecting heart rate. Matching criteria were age, sex, time post-transplant, diagnosis leading to heart transplant, and immunosuppressive therapy.[7,8,12,13] At baseline and after 36 months, standard resting heart rates (assessed by electrocardiography) were determined. In ivabradine patients, baseline examination was defined as the routine assessment one day prior to the first dose of ivabradine. In matched control patients, baseline was defined as the routine examination at the beginning of the 36-month follow-up period. Ivabradine therapy was initiated and carefully escalated as described previously.[7,8] In line with previously published studies, further increase of ivabradine dosage was individually stopped for reasons of safety after at least three episodes of minimal heart rates of less than 60 beats per minute, or drops in systolic blood pressure at rest below 90 mmHg.[7,8] According to local clinical practice, all patients performed blood pressure and heart rate self-measurement on a daily basis. Commercially available ivabradine was used (Procoralan®; Servier Deutschland GmbH, Munich, Germany).

Transthoracic echocardiography

Transthoracic echocardiography was performed as described previously.[7,14] LVMI was calculated by Devereux's formula.[12] Body surface area (BSA) was calculated according to the following equation:[13] BSA =0.007184 × height (cm)$^{0.725}$ × weight (kg)$^{0.425}$.

Statistical analysis

The Statistical Package for Social Sciences version 14.0 (SPSS Inc, Chicago, IL, USA) was used for the statistical analysis. The χ^2 test, Mann–Whitney *U* test, and Wilcoxon signed-rank test were applied for comparisons between groups (nonparametric testing was used due to the limited sample size and an absence of normal distribution). Spearman correlation analysis was used for correlation testing. The level of statistical significance was set at $P \leq 0.05$.[7] All parameters are given as the mean ± standard deviation.

Results

Baseline characteristics

As described previously, patients in this follow-up study were in New York Heart Association class I and left ventricular ejection fraction at study entry was above 60%.[7] Detailed patient characteristics and laboratory values are given

Table 1A Patient demographic and clinical parameters at baseline

Parameter	Baseline ivabradine group	Baseline control group	Level of significance
Sex	n	n	
Male	23	21	NS
Female	4	6	NS
Mean age (years)	53.3	47.5	*P*=0.09 (NS)
Range	23.0–71.0	18.0–66.0	
Standard deviation	11.3	11.8	
Mean time post-transplant (years)	5.0	5.4	NS
Range	0.5–19.6	1.0–18.8	
Standard deviation	4.8	4.9	
Initial diagnosis	**n, % of total**	**n, % of total**	**Level of significance**
CAD	5, 18.5	4, 14.8	NS
DCM	19, 70.4	19, 70.4	NS
Other	3, 11.1	4, 14.8	NS
Comorbidity			
Diabetes mellitus	9, 33.3	10, 37.0	NS
Angiographic vasculopathy score			
No vasculopathy	22, 81.5	24, 88.9	NS
<25% stenosis	4, 14.8	2, 7.4	NS
≥25% stenosis or intervention	1, 3.7	1, 3.7	NS
Comedication			
ACE inhibitor therapy (n, % of total)	22, 81.5	23, 85.2	NS
Statin therapy (n, % of total)	25, 92.6	25, 92.6	NS

Abbreviations: ACE, angiotensin-converting enzyme; CAD, coronary artery disease; DCM, dilated cardiomyopathy; NS, not statistically significant.

Table 1B Patient laboratory parameters at baseline

Laboratory parameter	Ivabradine group at baseline	Control group at baseline	Significance level
	Mean ± SD	Mean ± SD	
Creatinine (mg/dL)	1.7±1.5	1.8±2.0	NS
Urea (mg/dL)	58.2±24.6	60.9±32.4	NS
GOT/AST (U/L)	25.6±13.0	27.1±14.3	NS
GPT/ALT (U/L)	27.1±12.1	28.4±17.1	NS
GGT (U/L)	50.5±71.8	52.2±44.1	NS
Hemoglobin (g/dL)	12.9±1.9	13.5±2.3	NS
Leukocyte count (10^9/L)	7.0±2.9	6.7±3.2	NS
Thrombocyte count (10^9/L)	248.1±60.9	242.2±79.5	NS
Serum cholesterol (mg/dL)	192.8±58.6	183.0±38.5	NS
Serum HDL (mg/dL)	44.0±12.9	54.3±19.7	NS
Serum LDL (mg/dL)	104.2±39.6	100.7±29.0	NS
Systolic BP (mmHg)	124.0±20.8	121.9±12.1	NS
Systolic BP range (mmHg)	100–180	90–140	
Diastolic BP (mmHg)	77.0±14.6	76.7±8.9	NS
Diastolic BP range (mmHg)	60–120	55–90	

Abbreviations: BP, blood pressure; GGT, gamma-glutamyl transferase; GOT/AST, glutamate-oxaloacetate transaminase/aspartate transaminase; GPT/ALT, glutamate-pyruvate transaminase/alanine transaminase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NS, not statistically significant; SD, standard deviation.

in Tables 1 and 2. A mean of 1.5 rejections ≥2R ISHLT (revised classification of the International Society for Heart and Lung Transplantation) or rejection episodes requiring specific antirejection therapy had been diagnosed per patient prior to study inclusion. Accordingly, before study entry all patients were on stable doses of immunosuppressives, with a combination of mycophenolate mofetil and a calcineurin inhibitor (cyclosporine A or tacrolimus) being the most common (Table 2).[7] Twenty-seven heart transplant patients without medication affecting heart rate served as the control group (see Patients and methods section).[7]

Table 2 Immunosuppressive therapy in ivabradine group at baseline

Immunosuppressive drugs	Patients, n (%)
Mycophenolate mofetil	16 (59.3)
Mycophenolate sodium	6 (22.2)
Cyclosporine A	11 (40.7)
Tacrolimus	8 (29.6)
Azathioprine	2 (7.4)
Sirolimus	2 (7.4)
Everolimus	9 (33.3)
Immunosuppressive regimens	
Cyclosporine A/mycophenolate mofetil	8 (29.6)
Cyclosporine A/everolimus	2 (7.4)
Mycophenolate sodium/everolimus	6 (22.2)
Mycophenolate mofetil/sirolimus	2 (7.4)
Tacrolimus/everolimus	1 (3.7)
Tacrolimus/azathioprine	1 (3.7)
Tacrolimus/mycophenolate mofetil	6 (22.2)
Cyclosporine A/azathioprine	1 (3.7)

Study completion

Thirty patients initially entered the current study. After 36 months, 27 patients were available for statistical analysis due to discontinuation of ivabradine in three patients (10%). No discontinuations occurred after 1 year of treatment with ivabradine (Table 3).[7] After 36 months of ivabradine therapy, 14 (51.9%) of the remaining 27 patients were on the intended ivabradine target dose (15.0 mg/day), with a mean daily dose of 12.0±3.4 mg. Among the reasons for dose reduction not necessitating discontinuation of ivabradine, asymptomatic bradycardia (12 patients) during self-measurement was most common, and nausea was observed in one patient. As described previously, symptoms resolved after reduction of the ivabradine dose to the preceding level.[7]

Heart rate

After 36 months of ivabradine therapy, resting heart rate decreased from 91.0±10.7 (median 91.0) beats per minute at baseline to 81.2±9.8 (median 81.0) beats per minute (P=0.0006). In contrast, the level of statistical significance regarding reduction in heart rate was not reached in control patients, ie, 87.3±8.0 (median 87.0) beats per minute at baseline versus 83.0±13.6 (median 79.0) beats per minute after 36 months (P=0.06 versus baseline, Table 4). During ivabradine therapy, a decrease in resting heart rate of more than 10% was observed in 48.1% of patients. In line with previously published data, clinically relevant episodes of bradycardia were not seen during 36 months of follow-up.[7,8] Again, during ivabradine therapy, a significant association was found between baseline resting heart rate and relative heart rate reduction ($P<0.0001$), and no statistically significant association was seen between heart rate reduction during ivabradine therapy and sex, time post-transplantation, age, body weight, prior diagnosis of rejection episodes requiring therapy, or transplant vasculopathy.[7,8]

Left ventricular mass

After 36 months of ivabradine therapy, left ventricular mass and LVMI decreased significantly (left ventricular mass

Table 3 Adverse events requiring drug discontinuation

n (% of total)	
Ivabradine	
1 (3.3)	Patient preference
2 (6.7)	Nausea
3 (10.0)	Total

Table 4 Efficacy results

Parameter	Ivabradine group at baseline (mean ± SD)	Ivabradine group at month 36 (mean ± SD)	Significance level (ivabradine group)	Control group at baseline (mean ± SD)	Control group at month 36 (mean ± SD)	Significance level (control group)
LV mass (g)	202.3±46.3	181.1±37.7	*P*=0.002	191.9±48.1	187.1±43.3	*P*=0.20
LVMI (g)	104.3±22.7	93.4±18.4	*P*=0.002	100.4±21.2	97.2±21.1	*P*=0.19
Resting heart rate (bpm)	91.0±10.7	81.2±9.8	*P*=0.0006	87.3±8.0	83.0±13.6	*P*=0.06
LVEDD (mm)	48.2±4.1	45.1±5.5	*P*=0.004	43.8±3.8	45.1±3.7	*P*=0.08

Abbreviations: bpm, beats per minute; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVMI, left ventricular mass index; SD, standard deviation.

202.3±46.3 g at study entry compared with 181.1±37.7 g after 36 months, *P*=0.002; LVMI 104.3±22.7 g at study entry compared with 93.4±18.4 g after 36 months, *P*=0.002), whereas in the matched control group the level of statistical significance was not met (left ventricular mass 191.9±48.1 g at study entry compared with 187.1±43.3 g after 36 months, *P*=0.20; LVMI 100.4±21.2 g at baseline versus 97.2±21.1 g at follow-up, *P*=0.19, Table 4).[7,8] However, no statistically significant association regarding the correlation between decrease in left ventricular mass or LVMI and heart rate was seen in either group (neither absolute or relative heart rate reduction was statistically significant). Left ventricular end-diastolic diameter during ivabradine therapy was reduced from 48.2±4.1 mm at baseline to 45.1±5.5 mm (*P*=0.004) at follow-up. In control patients, no statistically significant difference in left ventricular end-diastolic diameter was observed (43.8±3.8 mm at baseline compared with 45.1±3.7 mm at follow-up, *P*=0.08, Table 4).

Blood pressure

Ivabradine therapy had no statistically significant influence on systolic or diastolic blood pressure (systolic 124.0±20.8 mmHg at baseline versus 124.6±17.8 mmHg after 36 months of ivabradine therapy; diastolic 77.0±14.6 mmHg at baseline versus 79.1±14.5 mmHg after 36 months of ivabradine therapy). Likewise, in the matched control group, no statistically significant alterations in systolic or diastolic blood pressure were seen (systolic 121.9±12.1 mmHg at baseline versus 118.3±11.4 mmHg after 36 months; diastolic 76.7±8.9 mmHg at baseline versus 74.2±8.4 mmHg after 36 months).

Side effects/adverse events

Mild adverse effects not requiring discontinuation of ivabradine therapy were seen in 14.8% of ivabradine patients (nausea in one patient, mild dizziness in two patients, and tremor in one patient, in addition to the symptoms stopping a further dose increase; see earlier section on Study completion). As in our 12-month analysis, adverse events did not correlate with the amount of heart rate reduction. Further, after 36 months of ivabradine therapy, phosphenes were not seen despite active inquiry. Immunosuppressive therapy containing a calcineurin inhibitor had no statistically significant effect on reduction in heart rate, either absolute or relative.

Laboratory and clinical parameters

No statistically significant differences in immunosuppressive drug dosage or blood levels were observed during the study (only the mycophenolate mofetil dose was significantly lower at follow-up, being 2,218.8±769.9 mg at study entry versus 1,763.4±545.7 mg at follow-up, *P*=0.007). No significant differences regarding renal, liver function tests, and hematologic parameters were found during the study period.

Discussion

Despite the common occurrence of sinus tachycardia in heart transplant recipients, data regarding heart rate control in this distinct patient cohort are extremely limited.[7,8,10,11] Ivabradine is a comparatively new therapeutic agent offering selective reduction of heart rate without the systemic side effects of beta-blockade. Currently, only short-term data and limited long-term data on the effects of heart rate reduction with ivabradine in heart transplant patients are published.[7,8,10,11] The present follow-up study in heart transplant patients examines the effects of 36 months of ivabradine intake in comparison with a matched control cohort. In line with previously published data, we observed a sustained effect on heart rate reduction and a significant decrease in left ventricular mass and LVMI after 36 months of ivabradine.[7,10,11]

Heart rate

Consistent with the data reported earlier, analysis of 27 patients after heart transplant showed a sustained and statistically significant decrease in mean heart rate at rest during ivabradine treatment.[7] No dropouts were observed after 1 year of ivabradine treatment, indicating excellent long-term tolerability.

Additionally, in accordance with the mechanism of action of ivabradine, systolic and diastolic blood pressure were not affected.[7,8] A reduction in mean heart rate at rest was also observed in the control group after 36 months, but this did not reach statistical significance, which might possibly be attributable to reinnervation processes. It would be interesting to know whether this might allow a reduction or cessation of ivabradine therapy in the late phase post-heart transplant, and this should be addressed by future studies.

Comparable with our earlier report, the target dose was not reached most commonly because of asymptomatic bradycardia during self-measurement (see Patients and methods section).[7] Nevertheless, a mean ivabradine daily dose of 12.0 mg after 36 months is acceptable, and might be attributed to excellent patient compliance and tolerability.

The long-term safety of ivabradine therapy was supported by the lack of pharmacokinetic interaction (due to potential cytochrome P450 3A4 inhibition) between ivabradine and calcineurin inhibitors, given that no excessive additional effect on heart rate reduction was found in patients on calcineurin inhibitor therapy (versus immunosuppressive regimens not including a calcineurin inhibitor).

Left ventricular mass

In accordance with previously published short-term and medium-term findings, a marked and sustained reduction of left ventricular mass and LVMI was observed only in the ivabradine group, which might eventually be attributed to the positive effects on left ventricular remodeling by selective reduction of heart rate, indicating the need for future multicenter studies addressing the prognostic relevance of these findings.[7,8,11]

Conclusion

Given that sinus tachycardia is a common problem in heart transplant recipients, there is an urgent need for a therapeutic agent lacking the unwanted systemic effects of beta-blocker therapy. The current open-label, single-center, long-term, follow-up study in stable chronic heart transplant recipients analyzes the effects of 36 months of ivabradine therapy. It was very important to show the feasibility, safety, tolerability, and effectiveness of long-term heart rate reduction via I_f channel antagonists in a clinical routine setting. Most importantly, due to the multitude of comedications given to patients after heart transplantation, an increased reduction of heart rate caused by cytochrome P450 3A4 interaction was not observed, in line with the previously reported short-term and medium-term data.[7,8] Similar to the earlier reports, the present long-term, follow-up study shows a significant decrease in left ventricular hypertrophy without effects on blood pressure during ivabradine treatment in heart transplant recipients with sinus tachycardia.[7,8,11] This will be addressed by future multicenter studies, currently in preparation, to define cutoff heart rates for ivabradine use. However, we must point out that use of ivabradine in heart transplant recipients with sinus tachycardia is still off-label. Certainly, from the currently available data, a general recommendation for ivabradine treatment in heart transplant patients cannot be given. However, given the distinct patient population, beta-blocker intolerance is a common problem, making ivabradine an excellent therapeutic option.[7,8] Further multicenter studies appear warranted to address the potentially beneficial effects on survival after heart transplantation by heart rate reduction with ivabradine.

Disclosure

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