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Effect of co-treatment with diltiazem on ciclosporin dosage in renal transplant patients

Key Messages

1. We have demonstrated the cost-effectiveness of using diltiazem co-treatment with ciclosporin in the management of renal transplant patients.
2. We observed no excess of serious adverse outcomes or complications (deaths, rejection episodes, infections, renal functional impairment, hospital in-patient days and hospital out-patient visits) in patients receiving diltiazem.

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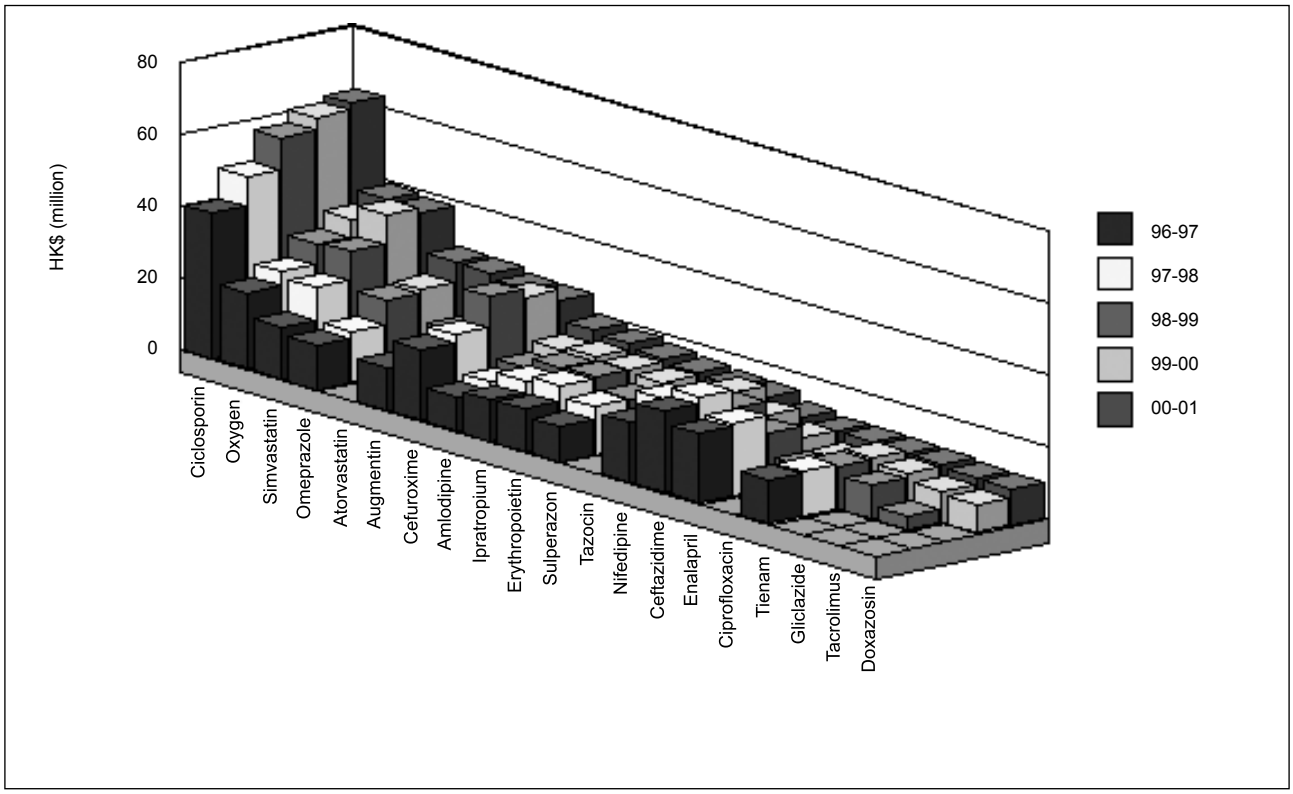
Introduction

Use of ciclosporin, the largest single item of Hospital Authority (HA) expenditure on pharmaceuticals in the 1990s (Fig), continues to increase. Such usage is largely due to the increasing numbers of surviving renal transplant patients who are prescribed this drug orally as long-term anti-rejection therapy. Diltiazem, a popular antihypertensive agent for such patients, interferes with the extraction of orally administered ciclosporin by the gut and liver and therefore serves to conserve the latter drug's dosage. This possibility has not been studied in our population, or with Neoral (Novartis International AG, Basel, Switzerland)—the newer ciclosporin formulation now in use. Therefore, a multi-centre, randomised, placebo-controlled, double-blind clinical trial was undertaken at Queen Mary (QM), Princess Margaret (PM), and Queen Elizabeth (QE) hospitals to determine whether diltiazem co-treatment in our setting results in a clinically and statistically significant reduction in Neoral dosage and improved overall cost-effectiveness for managing renal transplant patients.

Methods

This study recruited patients during the period December 1997 to March 2000. Renal transplant patients being cared for at QM, PM, or QE hospitals and treated with ciclosporin were recruited. Exclusion criteria and reasons for withdrawal from the study were: (1) persistently low blood pressure, (2) any overriding reason to continue or start taking diltiazem (or certain other drugs interfering with ciclosporin metabolism), (3) known hypersensitivity to diltiazem, and (4) at the discretion of that patient's physician (whatever the reason). All patients were closely monitored with respect to (a) ciclosporin dosage, (b) blood ciclosporin 12-hour trough concentrations, (c) clinical and laboratory evidence of rejection, (d) overall mortality and morbidity, (e) quality-of-life indices, including days spent in hospital, and (f) total amounts of all drug usage (and expenditure) and other health care costs (for in-patients and out-patients). All recruits gave written informed consent and the relevant ethics committees approved the entire study. Patients were stratified into three categories: (i) those transplanted at their respective hospital ≤6 months earlier, (ii) those transplanted elsewhere (mainly China) ≤3 months earlier, and (iii) the remaining group (transplanted at their respective hospital >6 months earlier or elsewhere >3 months earlier). Active treatment consisted of diltiazem tablets 30 or 60 mg twice daily for patients weighing <60 kg or ≥60 kg, respectively. All patients were followed up for at least 6 months. The mean difference in the cost of graft survival in the sixth month was the primary outcome; secondary and ancillary outcomes targeted changing ciclosporin dosages and blood levels, and untoward outcomes.

The cost-effectiveness analysis included logging/recording resources used for each patient in terms of (a) drugs, (b) monitoring blood ciclosporin levels, and (c) preventing and treating rejection episodes, infections and other complications, whether by means of in-patient care and/or out-patient follow-up. Locally relevant costs were applied to the identified use of drugs in both treatment arms, using a range of statistical methods to evaluate variations between the two groups. In areas of uncertainty or potential bias, sensitivity analyses were also performed to test the robustness of any of the assumptions underlying the analysis.



Courtesy: Hospital Authority Chief Pharmacist's Office

Fig. Hospital Authority (HA) top 20 drug expenditures (1996-2001)

Since 1997 (and earlier) ciclosporin has continued to be the HA's largest single item of expenditure on pharmaceuticals and this has been increasing in successive years, though the increases in 2000 and 2001 were less marked than before. Nevertheless, expenditure on ciclosporin is more than 50% greater than on the second ranked item (oxygen). Missing blocks, particularly in years 96-97 and 97-98 are a consequence of the respective items not appearing in the top 20 lists in those years

All results were analysed on an intention-to-treat basis.

Results

After giving their informed consent, 114 eligible patients (54% transplanted in mainland China) were recruited and randomised to receive diltiazem or a placebo. Four patients were excluded from the analysis as they were no longer taking ciclosporin or were unavailable for assessment. Table 1 contains a summary of patients randomised for the trial. Respective mean costs for all medications, investigative tests, hospitalisation, and out-patient care during weeks 23 to 26 on trial medication are summarised in Table 2. Mean ± standard deviation ciclosporin dosages/day for the diltiazem and placebo groups were significantly different (183±52 and 220±79 mg, respectively). During the sixth month treatment with diltiazem yielded an average net saving on drug costs per patient of HK$12 to 13 (P=0.011) per day. Untoward outcomes (adverse events/complications, hospital in-patient days or out-patient visits, inferior quality of life) were no greater in the group receiving diltiazem treatment.

Discussion

In stable renal transplant patients receiving Neoral ciclosporin, diltiazem co-treatment (according to our dosage scheme) conserved substantial resources for the community. The daily average ciclosporin requirement was reduced by about 25 mg or 1 tablet. This resulted in a 15% average net decrease in overall drug expenditure (mainly on Neoral). Although considerably smaller than the 30 to 50% figure reported by others using the older ciclosporin formulation, these savings were nevertheless clinically and statistically significant. Presumably, since substantially more ciclosporin from the newer oral formulation Neoral normally gets into the body, diltiazem co-treatment has much less scope for yielding greater amounts being absorbed unscathed. Furthermore, these savings were achieved with no apparent excess in untoward events or compromise in quality of life (hospitalisations, out-patient visits, quality-of-life scores). Based on current costs, our diltiazem co-treatment regimen, if applied to the 1800 or so surviving renal transplant patients managed by HA hospitals, has the potential to save HK$7.9 to 8.5 million annually. Moreover, even if the costs of this type of ciclosporin formulation were to decrease by up to 50% due to the advent of generic formulations, our regimen could still achieve annual savings of about HK$4 million.

Acknowledgements

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Table 1. Summary of patients randomised to trial medication

(a) Patients omitted from analysis

Age (years)/ gender	Event/reason	Timing (weeks)	Treatment
57/F	Graft kidney removed	2	Placebo
45/M	Withdrew from trial (business in China)	2	Diltiazem
49/F	Withdrew (alleging side-effects)	1	Placebo
50/M	Rejection, tacrolimus subsituted for ciclosporin	15	Diltiazem

(b) Patients included in analysis*

No. of patients by hospital and category†	Diltiazem	Placebo
Queen Mary		
EI	12	11
EE	3	3
RG	21	21
Princess Margaret		
EI	2	2
EE	9	8
RG	6	8
Queen Elizabeth		
EI	0	0
EE	1	1
RG	1	1
Total	55	55
Males/females	39/16	39/16
Age (years)		
Mean±SD (range)	42.2±10.6 (14-72)	41.8±9.6 (21-67)
Body weight (kg)		
Mean±SD (range)	59.5±9.6 (42-89.2)	61.5±13.2 (40-102)
<60/≥60	33/22	28/27
Creatinine (μM/L)		
Mean±SD (range)	132.2±34.2 (81-244)	136.4±35.3 (80-294)
Urea (μM/L)		
Mean±SD (range)	10.6±3.7 (4.8-23.6)	10.5±5.1 (4.6-35.5)
No. of patients with prior disease		
Diabetes mellitus‡	10	1
Hypertension	41	40
Cardiovascular disease	8	10
Tuberculosis	4	3

* Among the 110 patients at the three hospitals whose outcome was analysed, 24/71, 31/35, and 4/4 respectively were transplanted in mainland China. Prior to being recruited, 7 and 8 patients randomised to diltiazem and placebo were hepatitis B surface antigen positive, and 36 and 32 respectively had positive cytomegalovirus titres

† EI denotes early indigenous (transplanted at that hospital ≤6 months earlier), 12 within 3 months and 2 between 3-6 months on diltiazem, and 10 and 3 respectively on placebo; EE early elsewhere (transplanted elsewhere, usually mainland China ≤3 months earlier); RG remaining group (transplanted at that hospital >6 months earlier [14 and 10 on diltiazem and placebo respectively] or elsewhere >3 months earlier [14 and 20 on diltiazem and placebo respectively])

‡ P=0.01 (Fisher's Exact test)

Table 2. Drug costs, use of in-patient and out-patient services, and recourse to relevant clinical investigations per patient during weeks 23 to 26 (6th month) on trial medication

	Diltiazem, n=55 Mean (SD)	Placebo, n=55 Mean (SD)	P value
Drug costs (HK$)			
Immunosuppresants			
Ciclosporin orally	2905 (826)	3431 (1263)	0.011
Others	456 (656)	560 (840)	NS
Anti-hypertensives			
Diltiazem	33 (17)	0	
Others	53 (78)	69 (131)	NS
Antimicrobials	17 (86)	31 (150)	NS
Anti-diabetic drugs	13 (38)	4 (29)	NS
Statins	38 (111)	27 (64)	NS
Others	47 (18)	48 (160)	NS
Total drug cost	3562 (1180)	4171 (1559)	0.023
No. of investigations			
Ciclosporin levels	1.53 (0.81)	1.36 (0.55)	NS
Renal function levels	1.53 (0.81)	1.36 (0.56)	NS
Blood count	1.06 (0.78)	1.07 (0.74)	NS
X-rays, CTs, US*	0.07 (0.26)	0.18 (0.55)	NS
In-patient days	0	0.35 (2.17)	-
Out-patient visits	1.42 (0.78)	1.27 (0.53)	NS

* CT denotes computed tomography, and US ultrasound

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