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Comparison of Sandimmun with a new cyclosporin derivative (IMM 125) in renal transplant patients with stable renal function

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Abstract A double-blind switch-over study was carried out on 70 renal transplant patients to assess the value of a new cyclosporin derivative, IMM 125. Preclinical in vitro and in vivo studies indicated that IMM 125 was as equally immunosuppressive as Sandimmun, but that its therapeutic index should be superior. The duration of the treatment was 24 weeks. The assumption that the dosage of IMM 125 could be 2.5 times lower than Sandimmun proved to be false; three patients suffered acute rejection episodes, probably as a consequence of the low dosage, and dosage adjustments had to be made for all patients receiving IMM 125 after only a few weeks. Although IMM 125 is an effective immunosuppressive agent, it does not appear to offer advantages over Sandimmun with regard to renal function. In addition, IMM 125 causes some disturbances in liver function.

Key words Cyclosporin IMM 125 · Immunosuppression

Introduction

With cyclosporin A, the initial and long-term survival rates in virtually all forms of transplantation have improved considerably [5]. In addition, its use is accompanied by a reduced rejection incidence and less morbidity [6, 7]. Nevertheless, the nephrotoxicity of this drug remains a major drawback, particularly in renal transplantation. When renal function deteriorates, it is often very hard to differentiate between an acute rejection and cyclosporin nephrotoxicity. Attempts to circumvent this side effect include the production of a new cyclosporin derivative with the same or stronger immunosuppressive potency, but without the nephrotoxic side effects. IMM 125 is such a derivative of the cyclosporin family with powerful immunosuppressive properties in vitro. IMM 125 is made from D-serine-8-cyclosporin followed by chemical modification [1]. It is neither cytostatic nor cytotoxic. In preclinical in vitro and in vivo studies it has been shown to be equally as immunosuppressive as Sandimmun [3, 4].

Based on biochemical and histological studies, IMM 125 has a toxicological profile qualitatively similar to Sandimmun. However, quantitative comparison suggests that the therapeutic index for IMM 125 should be superior to that of Sandimmun in clinical use [2]. In human volunteers, single doses of IMM 125 up to 800 mg were only followed by a transient increase in transaminases. The pharmacokinetics of IMM 125 have already been described [4].

In this study, IMM 125 is compared with Sandimmun in renal transplant patients with stable renal function to evaluate its immunosuppressive properties and side effects. Because in animals the toxicity of IMM 125 is lower than that of Sandimmun, reduction of side effects, especially an improvement in renal function, is expected after conversion from Sandimmun to IMM 125.

Patients and methods

In this double-blind switch-over study, patients either remained on Sandimmun or were switched to IMM 125, while the blood level of IMM 125 was kept the same as the blood level of Sandimmun before switching. Important end-points were side effects, especially renal dysfunction, the incidence of acute rejections and the frequency of graft loss in both groups.

Table 1 Reasons for discontinuation of the study

IMM 125 group ($n = 8$)
Acute rejection ($n = 3$)
Elevated liver enzymes ($n = 2$)
Poor compliance
Persistent increase in serum creatinine
Medication error (Sandimmun instead of IMM 125) causing creatinine increase
Sandimmun ($n = 3$)
Acute pancreatitis
Inclusion criteria violation ($n = 2$)

Included in this study were only adult recipients of a cadaveric renal allograft, who were 7–24 months after transplantation, and received a stable immunosuppressive regimen with Sandimmun and steroids for 2 months prior to entry. The Sandimmun dose should not be lower than 4 mg/kg per day and renal function had to be stable (serum creatinine between 150 μmol/l and 300 μmol/l, irrespective of gender) for 2 months prior to entry. Excluded from this study were patients with a third or subsequent renal transplantation, with diabetes, with proteinuria of more than 3 g/24 h, with a bilirubin level of more than 1.5 times the upper limit of normal, or with transaminases more than 2 times the upper limit of normal. Also excluded were patients taking any drugs potentiating nephrotoxicity of Sandimmun in the 2 weeks before entry or drugs interfering with Sandimmun pharmacokinetics in the 2 months before entry. Finally, treatment with ATG, OKT3 or azathioprine during 2 months prior to entry was also prohibited.

Patients were randomly assigned to either continuation of Sandimmun at the same maintenance dose or to switch-over to IMM 125. The starting number of capsules of IMM 125 was the same as the number of Sandimmun capsules taken the day before switching therapy. Dosages were taken in two separate and equal (if possible) doses, 12 h apart and, preferably, before meals. The duration of the treatment of 24 weeks. Sandimmun capsules contained 25 or 100 mg and IMM 125 capsules were of 10 or 40 mg according to the assumption (based on previous studies) that the bioavailability of IMM 125 capsules (versus Sandimmun capsules) was 2.5 times higher. Dose adjustments based on whole blood trough levels were made in steps of 50 or 100 mg for Sandimmun and in equivalent doses for IMM 125, again equally divided between morning and evening. Blood levels were determined at one central place (Dr. Holt, London), and only the value of the blood level was passed to the centre.

Results and discussion

The study population consisted of 58 males and 12 females in seven centres. The mean age of the participants was 46.5 years (range 18–65 years). Thirty-four continued with Sandimmun and 36 were switched to IMM 125. Eleven patients prematurely discontinued the study medication for reasons shown in Table 1. None of the patients who were withdrawn from the study suffered from serious problems for a prolonged time. In three cases, IMM 125 medication was discontinued because of an acute rejection episode. These rejection episodes occurred between weeks 10 and 12 after the switch and were all reversible by treatment with i.v. steroids. Up to the time of rejection, the blood level of IMM 125 was consistently lower than the baseline Sandimmun level, despite dosage increments. After the initial three acute rejections in the IMM 125 group, probably caused by undertreatment, dosage adjustments in the case of low blood levels were more vigorously carried out (Table 2). Since the remaining 28 patients had no immunological problems one can state that, with trough levels in the therapeutic range, IMM 125 is an effective anti-rejection immunosuppressive agent. Adverse events are shown in Table 3. All except 11 adverse events were mild to moderate in severity according to predefined criteria. The 11 adverse events that were classified as severe were hypertension, acute pancreati-

Table 2 Percentage changes in creatinine, dose, blood level and alanine aminotransferase *(ALAT)* relative to baseline in both the IMM 125 and Sandimmun groups (means ± SD)

Period of study	Sandimmun				IMM 125			
	Creatinine (% diff)	Dose (% diff)	Blood level[a] (% diff)	ALAT (% diff)	Creatinine (% diff)	Dose (% diff)	Blood level[a] (% diff)	ALAT (% diff)
Baseline	0	0	0	0	0	0	0	0
Week 1	2 ± 12**	0 ± 0	8 ± 23	−4 ± 33**	−5 ± 11*,**	0 ± 0	7 ± 29	41 ± 74*,**
Week 2	2 ± 12**	−1 ± 6**	6 ± 30**	−10 ± 29**	−8 ± 9*,**	52 ± 47*,**	−59 ± 24*,**	79 ± 109*,**
Week 3	2 ± 11**	−3 ± 7**	17 ± 41*,**	−1 ± 26**	−8 ± 14*,**	62 ± 52*,**	−29 ± 41*,**	94 ± 137*,**
Week 4	2 ± 12**	−3 ± 10**	8 ± 32**	1 ± 39**	−7 ± 14*,**	71 ± 47*,**	−30 ± 39*,**	113 ± 140*,**
Week 6	2 ± 13**	−4 ± 10**	9 ± 40**	2 ± 40**	−7 ± 12*,**	81 ± 50*,**	−20 ± 40*,**	99 ± 140*,**
Week 8	2 ± 13	−3 ± 11**	2 ± 35**	5 ± 39**	−5 ± 10*	85 ± 50*,**	−19 ± 41*,**	92 ± 144*,**
Week 10	3 ± 13**	−3 ± 13**	8 ± 36**	3 ± 44**	−5 ± 12*,**	94 ± 58*,**	−19 ± 33*,**	158 ± 254*,**
Week 12	0 ± 11	−3 ± 13**	12 ± 51**	−2 ± 37**	−7 ± 14*	93 ± 54*,**	−4 ± 57**	178 ± 462*,**
Week 16	2 ± 10**	−3 ± 13**	10 ± 41	3 ± 37**	−9 ± 11*,**	94 ± 53*,**	−14 ± 33*	163 ± 269*,**
Week 20	1 ± 13**	−3 ± 13**	4 ± 37**	3 ± 36**	−6 ± 14*,**	102 ± 47*,**	−17 ± 31*,**	215 ± 350*,**
Week 24	1 ± 16	−5 ± 14**	3 ± 36**	4 ± 32**	−7 ± 15*	107 ± 41*,**	−18 ± 28*,**	191 ± 323*,**

* $P < 0.05$ versus baseline; ** $P < 0.05$ versus other group during same observation week

[a] Trough blood level of cyclosporin and IMM 125, respectively

Table 3 Adverse events

	IMM 125	Sandimmun
Total number of patients	36	34
Patients with adverse events	23	16
Total number of events	52	28
Gastrointestinal Dry mouth, gastritis, diarrhoea, retrosternal pain, acute pancreatitis, flatulence, increased liver enzymes, gingival hyperplasia, cholelithiasis, gastric reflux	11	5
Central nervous system Tremor, dizziness, tiredness, headache, burning feeling in hands, sleepiness, anorexia, paraesthesia, vision decrease	8	2
Locomotor Gout, backache, pain in thumb, chest plus shoulder pain, leg trauma, hyperuricaemia, hydrops left knee, bone pain, pain right leg	10	3
Cardiovascular System Heart failure, flushing, hypotension, ankle oedema	5	10
Skin Acne rash, skin tenderness, hair loss, itch	5	
Renal Increase serum creatinine, rejection	4	1
General Weight gain, thirst, fever, fatigue, apathy, sensation of heat	5	5
Other Psychosis, paradontosis, anaemia, thyroid hypertrophy, hypercholesterolaemia	4	2

tis, diarrhoea, creatinine increase and psychosis in the Sandimmun group, and rejection (3×), anaemia, liver enzyme increase and gout in the IMM 125 group.

In the Sandimmun control group, serum creatinine values were stable over time, with fluctuations from visit to visit in the range of 0 % to 3 % versus baseline (Table 2). No significant changes could be detected. In the group switched from Sandimmun to IMM 125, serum creatinine dropped significantly by 5 % at week 1. Till week 24 the creatinine levels remained significantly lower at each visit as compared with baseline values. This is obviously caused by persistent lower blood levels, despite the fact that IMM 125 dosages were increased (Table 2). After 1 week of treatment with IMM 125, the levels were still unchanged, but thereafter blood levels decreased significantly, ranging from 59 % to 4 % in comparison with baseline values. In the Sandimmun control group the blood levels hardly changed and were significantly higher than the levels in the IMM 125-treated patients in the corresponding week. Also, the dose in the Sandimmun control group remained the same during the investigation (decrease from 1 % to 5 %).

The assumption that the dosage of IMM 125 could be 2.5 times lower than the dosage of Sandimmun proved to be false. From the data of this trial one can conclude that the dosage of IMM 125 should be equal to that of Sandimmun to achieve similar trough levels. Due to this fact it is clear that the double blindness of this trial was hampered; after a few weeks the clinicians could guess what medication was given on the basis of the need for dose adjustments.

No substantial changes were observed with respect to alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT) and alkaline phosphatase in the Sandimmun control group. In contrast, a rise in ALAT was readily detected after therapy was switched from Sandimmun to IMM 125 (Table 2). The rise in ALAT was detected as soon as the first visit after switching. On average, the increase was maximal at week 20 when the mean levels more than tripled the baseline value. Ten out of 26 patients had at that time point ALAT levels above normal. This may be explained by the progressive increase in the dose of IMM 125. The rise in ASAT was much milder, reaching 60 % at week 20. No signs of cholestasis were observed and the alkaline phosphatase level was unchanged, even in the patients who had the largest increase in ALAT. The liver intolerance constituted a new adverse event in comparison with Sandimmun. The rise in ALAT was dose-dependent, of quick onset (a few days), stable on a given dose of IMM 125, and reversible in a few days after therapy was stopped. Because of the liver intolerance, the ceiling dose of IMM 125 is currently limited to 350 mg/day. This means that IMM 125 can only be used as maintenance therapy, since the induction therapy after transplantation generally involves dosages above 350 mg/day.

With respect to blood pressure, no major changes were found after switch-over from Sandimmun to IMM 125 (data not shown).

In conclusion, one can state that IMM 125 is an effective immunosuppressive agent. As compared to Sandimmun, IMM 125 does not appear to offer important advantages with regard to renal function, while IMM 125 causes more liver function disturbances.

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