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Analysis of 100 pregnancy outcomes in women treated systemically with tacrolimus

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Abstract The aim of this paper is to provide a summary of clinical findings regarding the safety of tacrolimus in pregnancy. From 1992 to 1998 data were collected on 100 pregnancies from 84 mothers who received tacrolimus systemically; 83 cases of solid organ transplantation, and 1 case of Behçet's disease. Maternal mean age at conception was 28 years and pregnancy outcome was live birth in 68%, spontaneous abortion in 12%, induced abortion in 12%, stillbirth/perinatal death in 3%, ongoing pregnancy in 2%, and lost to follow up in 3%. Fifty-nine percent of the neonates were delivered prematurely (< 37 weeks of gestation). Birth weight was appropriate for the gestational age in 90% of the cases. Malformations occurred in 4 neonates: case 1, meningocele and urogenital defects; case 2, alcoholic embryopathy; case 3, ear defect, cleft palate and hypospadia; case 4, multicystic dysplastic kidney. There was no consistent pattern of malformations and 2 mothers subsequently delivered a healthy neonate while on tacrolimus therapy. Nearly 70% of pregnancies following systemic tacrolimus administration resulted in a favourable outcome without any significant effect on intrauterine growth. The incidence of malformations was similar to that reported with other immunosuppressants in transplant recipients.

Key words Tacrolimus · Transplantation · Pregnancy · Outcome

Introduction

Tacrolimus (Prograf), a macrolide, is a widely used primary immunosuppressant in solid organ transplantation. By mid 1998, the total cumulative number of patients worldwide exposed to systemic treatment with tacrolimus was estimated by Fujisawa to be about 70000. The increasing use of tacrolimus has resulted in a growing number of pregnancies in mothers receiving tacrolimus systemically. The first published reports of a child born to a transplant patient who was receiving tacrolimus-based immunosuppression were in 1993 from the University of Pittsburgh, USA [1] and Hanover, Germany [2]. This was followed by a number of additional reports, notably from Jain et al. [3] and Armenti et al. [4] who presented data on cohorts of 27 pregnancies in 21 liver recipients and 22 pregnancies in 19 kidney, liver, heart and lung recipients. The present report is believed to represent the largest published experience of pregnancies in women treated with systemic tacrolimus to date. A summary of clinical findings regarding the safety of tacrolimus in 100 pregnancies is presented.

Materials and methods

From 1992 to July 1998, data were collected on the Fujisawa global database of 100 pregnancies in 84 mothers who received tacrolimus systemically. Information sources included clinical studies, spontaneous reporting by health care professionals, routine surveys performed by transplant registries and published literature. For cases where a successful outcome or abortion was reported, the completeness of data was accepted as provided by the reporting source, for example, physician or transplant registry. The results are presented using descriptive statistics only.

Table 1 Tacrolimus dosing information prior to and during pregnancy

Time interval	Number of pregnancies	Tacrolimus dose (mg/day) in treated mothers		
		Mean	Median	Range
Preconception	26	11.7	10.0	4.0–48.0
First trimester	45	12.2	10.0	1.0–64.0
Second trimester	43	12.1	10.0	1.0–64.0
Third trimester	39	12.8	10.0	4.0–64.0

Table 2 Intrauterine growth based on gestational age and birth weight

Intrauterine growth retardation	Number of neonates	
	(n)	(%)
Small for gestational age	3	5
Appropriate for gestational age	51	90
Large for gestational age	3	5
Total	57	100

Results

The mean age of 84 mothers at date of conception was 28 years (range 18–43). The indication for treatment with tacrolimus was solid organ transplantation in 83 mothers and autoimmune disease (Behçets) in 1 mother. In most cases the transplanted organ was liver (55/83, 66%) or kidney (22/83, 27%). The dosing of tacrolimus prior to and during pregnancy is represented in Table 1.

Between the first and third trimesters the dose of tacrolimus was increased in 18%, decreased in 13%, and remained unchanged in 69% mothers ($n = 39$). The outcome of pregnancies was live births in 68%, spontaneous abortion in 12%, induced abortion in 12%, still birth/perinatal death in 3%, ongoing pregnancy in 2% and lost to follow up in 3%. Table 2 provides details of the intrauterine growth from 57 neonates and shows that the birth weight was appropriate for the gestational age in 90% of cases. A premature birth (< 37 weeks gestation) occurred with 59% neonates ($n = 63$).

Malformations were reported in 4 out of 68 neonates (live births): case 1, meningocele, urogenital defects and umbilical hernia; case 2, alcoholic embryopathy; case 3, ear defect, cleft palate and hypospadia; case 4, multicystic dysplastic kidney and dimple without areola. All neonates were born alive and there was no consistent pattern of malformation. In cases 1 and 4, subsequent pregnancies resulted in the delivery of a healthy neonate during the continued administration of tacrolimus.

Discussion

This short report represents the largest published experience to date on pregnancy outcomes in women treated systemically with tacrolimus. A favourable outcome occurred in 68% of these cases. Importantly, there was little evidence of intrauterine growth retardation as the birth weight of nearly all neonates was appropriate for the gestational age. The dose of tacrolimus was unchanged during the majority of pregnancies; the mean tacrolimus dose and maternal blood levels remained fairly stable in a manner similar to an earlier published experience [3].

Pregnancy in the transplanted patient may carry an increased risk of malformation. There is an approximate background incidence of malformations of 3% in non-transplant individuals. In the transplant recipient, this incidence has been reported to be 4% with corticosteroids and 7% with azathioprine therapy [4]. In the present series, the incidence of malformations (5.9%, 4/68 live births) is similar to that reported by Jain et al. [3] (4%, 1/25 live births) and no higher than previously reported with other immunosuppressants in transplant recipients. Of note, the malformations described do not follow a consistent pattern. In the present analysis, the possibility of underreporting of pregnancies with a successful outcome can also not be excluded. It is concluded that the majority of pregnancies under tacrolimus-based therapy result in a successful outcome.

References

1. Jain A, Venkataramanan R, Lever J, Warty V, Fung J, Todo S, Starzl T (1993) FK506 and pregnancy in liver transplant patients. Transplantation 56: 751
2. Winkler ME, Niesert S, Ringe B, Pichlmayr R (1993) Successful pregnancy in a patient after liver transplantation maintained on FK506 Transplantation 56: 751–753
3. Jain A, Venkataramanan R, Fung JJ, Carlton Gartner J, Lever J, Balan V, Warty V, Starzl TE (1997) Pregnancy after liver transplantation under tacrolimus. Transplantation 64: 559–565
4. Armenti VT, Moritz MJ, Davidson JM (1998) Drug safety issues in pregnancy following transplantation and immunosuppression. Drug Safety 19: 219–232