Cyclosporine and Pregnancy in the Heart Transplant Recipients: A Review

M **VURAL, Y MAINGOURD, F KOCHERT, FM CARON, E BOURGES-PETIT**

Unite de Recherche en Physiologie et Physiopathologie-Cardiorespiratoires Pediatiques-Faculte de Médecine de Picardie-80030 Amiens Cedex, FRANCE

Cyclosporin A (Cs A) is one of a family of fungal metabolites which has proved to be a potent immunosuppressive agent. It is extracted from the soil of fungus Tolypocladium inflatum. Cs A has a molecular weight of 1200 daltons and comprises 11 amino acids, one of which is unique and most of which are hydrophobic. Thus the drug is only soluble in lipids or organic solvents. Although first developed as an antifungal agent, its antibiotic activity proved to be very restricted; it was the routine screening of such agents for immunosuppressive activity by Borel et al. (1,2) that revealed this unexpected and powerful activity of Cs A in a variety of in vitro and in vivo assays of immunological reactivity.

The main immunosuppressive action of cyclosporine is selective inhibition of helper T-lymphocytes function. Several lines of evidence support that the immunosuppressive effects of cyclosporine are also attributable to the expansion of specific suppressor T-lymphocyte subpopulations.

International Society for Heart Transplantation Registry (3) indicates that cyclosporine-containinig immunosupressive regimens are associated with a better 5 year actuarial survival than other immunosuppressive regimen. Data from individual centers performing heart tranplantation before and after the introduction of cyclosporine have also shown a decrease in deaths from rejection and infection with the use of this drug (4).While the improvement in survival associated with cyclosporine therapy has been documented, the long-term effects of cyclosporine on the quality of life and pregnancy are not well known and are not very much published neither.

In thisnew field, sexuality and fertility of the transplated patients have an important and particular place. However the problem of innocuity of Cs A over the foetus worths to be asked.

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Yazışma Adresi: Dr. M Vural
Faculté de Médecine de Picardie-80030
Amiens Cedex, FRANCE

CLINICAL EXPERIENCE

Cs A was first used in renal transplantation by Calne et al. (5) after considerable experience with the drug in a number of experimental models. Both the experience of Starzl et al. (6) and Calne et al. (7) with Cs A in liver transplantation has been encouraging.

The most recent data over the heart transplantation is available from the Registry of the International Society for Heart Transplantation (8). Over 12 000 cardiac transplants have been reported to the Registry of which more than 7 000 were performed in the United States. We note an exponential increase in cardiac transplantation in the mid 1980s. Although the exact cause of this Increase can not be documented, it would seem that it coincides with the availibity of the immunosuppressive agent cyclosporine which was made available to the general heart tranplant community in 1983. Almost all cardiac transplants have been orthotopic and the use of the heterotopic technique has remained limited. In 1988 operative mortality was 9,7% and for the first nine months of 1989 has been 7%. Although patient age does not significantly affect overall survival, recipients under 5 years of age have shown a higher mortality (25%) following heart transplantation compared to older reciepents (10%). This may be related to the higher incidence of elevated pulmonary vascular resistance in the young population. In addition, combined heart-lung transpalantation in children, in contrast to heart one alone, has not been associated with increased operative mortality.

The use of cyclosporine has been associated with a modest but significant decrease in the number of deaths due to rejection and infection in cardiac transplant recipients (4). The addition of cyclosporine to the immunosuppressive regimen has increased the 5-year actuarial survival following heart transplant from 73,9% for all cardiac transplant patients to 78,0% for patients receiving cyclosporine. It is reported (9) that women have a higher incidence of rejection and may require higher cyclosporine levels. The dose of cyclosporine was not significantly different for any age group, but there was a definite trend for higher-dose requirement in younger patients.

The use of cyclosporins has undergone many changes since its introduction, including as 80% reduction of the initial dosages used both perioperatively and for maintenance therapy. This change has been brought about multiple factors including early reports of toxicity and malignancy associated with higher doses; and more recently by the development of "triple therapy" (10), the addition of azothioprine (Aza) to the combination of cyclosporins and steroids. This regimen allowed a 30% to 40% reduction in the doses of all three agents, thereby limiting toxicity, while maintaining good immunosuppression (11). The current dose has been reduced over 80% from the 15,0 mg/kg dose used in 1983, to an average of 2-3 mg/kg today.

Blood and plasma Cs A levels are measured by a nonspecific radio immune assay (RIA) capable of detecting parent drug and metabolites and by a newer specific monoclonal RIA assay for the parent drug (12). Therapeutic range of the whole blood cyclosporins A concentration measured by monoclonal RIA is proposed to be 100-300 microg/l.

It is shown (13) on animal study that cyclosporine is distributed widely into the body and the amount in systemic circulation accounts for only a minimal part of the whole body amount, suggesting considsrable binding of the drug in tissues. Thus, blood cyclosporine concentrations may be of only limited use in the difficult task of correlating blood levels with pharmacological and/or side effects. Some authors (9) do not rely on blood levels. They reduce the dose of cyclosporine over time by the msasurement of Interleukin-2 receptor levsls on the surface of circulating lymphocytes.

However, today, practically all of the authors use blood levsls of Cs A as rsference to adjust their trsatmsnt.

It is clsar that with the advent of cyclosporine as an immunosupprsssivs trsatmsnt, cardiac transplantation becams a therapeutic intervention with excellent results. Thus, It is not unusual now for women to become pregnant in the posttransplant period as testified by a few clinical reports (14, 15, 16). To date, however, knowledge concerning drug transfer across the placenta to the fetus and its effects on the newborn is scant and contradictory.

PREGNANCY

The first successful pregnancy in a renal transplant recipient taking cyclosporine A as the only immunosuppressive agent is reported in 1983 (17). In 1988 two casss of prsgnancy in the liver transplanted patients where immunosppression had been achieveJ by cyclosporin, were rsportsd by Vsnkataraman st al. (18).

The first report (14) in the medical literature of a woman with a transplanted heart who completed pregnancy is published in 1988. She underwsnt pregnancy with minimal complications and had a normal vaginal delivery. Outcomes of mother and daughter were excellent.

Today, there is no concencus ovsr ths "triple therapy", which Is mentionsd above, in the hsart transplanted women, because several side effects are attributed to both Aza and prednisone, severe enough to require their withdrawal (19). The results of a study (19) showed that Cs A monotherapy could be safely and effsctivsly used in selected patisnts with Aza intolerance as in the pregnant women. Until now the main problem o ths immunosuppression during prsgnancy was the teratogenscity of the Aza, the drug routinsly used. This study (19) and the others showed ths possibility o pregnancy under Cs A monothsrapy (5,6,17,18,20,21,22) without any graft rejection and no sids sffects in the newborn.

However, no concencus has yet been reached regarding changes in the dosage of cyclosporine required during pregnancy. There are considerabls discrepancies between the observations of different authors. Flechner et al. (23) reported a reduction in the required dosage of cyclosporine during the 4th-6th months of gestation, accompanisd by a grsater concentration of cyclosporine in ths blood. Other authors (14,24) indicated that ths cyclosporins requirement increases during pregnancy until the tims of delivery, whsn ths cyclosporine concentration in ths blood is maintained at the prs-prsgnancy lsvsl.

SIDE EFFECTS

EXPERIMENTAL

Conventional Immunosuppressants, such as azothioprine and cyclophosphamide, have been reported to have cytostatic effscts and mutagenicity. On ths othsr hand, it has been reported that Cs A psr se had no mutagenic effscts in various experimsntal systsms in which Salmonslla, mices, and Chiness hamstsrs were used. A study (25) in ths newborn rats shows that cyclosporine is not only toxic to ths mothers' endocrine beta-cells but also to those of any eventual offspring. Anothsr study in mice (25) showed the structural changes in the livsr, the kidney and the thymus of the mothsr. Embryonic developmsnt and fetal differantiation were not effected considerably by the drug. Neither tsratogsnic nor congenital malformations could be detected experimsntally. To date cyclosporine havs not producsd any chromosomal abnormalities in animals sxpossd to chronic therapy.

As a result, experimentaly shown side effects of cyclosporine are minimal when compared with azothioprine and cyclophosphamide.

in the *mmm.*

The important and frequent advsrse sffects occurring in cydosporins-trsatsd patisnts are:

• *Infection* remains the leading cause of posttransplant death in many programs. The lung has been consistently shown to be the most common site of infection. The pregnancy does not change the incidence of infection in the transplanted women.

• *Coronary artery disease* is the late cause of death In the heart transplanted patient. This accelerated form of coronary disease has been referred to by a number of terms including spontaneous arteriosclerosis, accelerated graft atherosclerosis, coronary occlusive disease, and, with recent observation of involveement of coronary venules, the term transplant coronary vasculopathy has been suggested (27). To date no accelerating affects of pregnacy over this vasculopathy has been shown.

• *Hypertension:* The effects of cyclosporine on the renal tubules and on the renal arterioles may be related to the hyperkalemia and hypertension which frequently occurs after transplantation. Hypertension is a serious and frequent complication of cyclosporine therapy in cardiac transplantation recipient. It is thought to be a result of a vasopressor effect of Cs A, occurring after both acute intravenous and short-term oral treatment. It is most marked with intravenously administered Cs A, causing severe reduction of blood flow to many organs including the lungs. The rise in systemic vascular resistance may be the result of several factors of which local elevation in sympathetic tone, diminished or blocked prostacylin, attenuation of nitrate-based vasorelaxation, and intact innervation appear to be the most important. An increase of posttransplant hypertension requiring modification of the treatment during the pregnancy of a heart transplanted woman, is reported (14).

• *Nephrotoxicity:* The correlation between cyclosporine dose, cyclosporine levels, and renal insufficency is not entirely clear. Cyclosporine induced nephrotoxicity is almost certainly multifactorial. Contributing factors include low preoperative cardiac output; the use of extracorpaoral circulation intraoperatively; decreased renal blood flow due to cyclosporine induced alpha agonist effects and/or reduced prostacycline induced synthesis; and cyclosporine induced tubular damage. Although it is dear that cyclosporine has a toxic effect on the kidney, the use of lower doses of this agent in long maintenance therapy has been associated with a reduction in its toxic properties. An increase In serum creatinine should be interpreted as an indication for a reduction in cyclosporine dose. No significant serum creatinine augmentation has been reported in the pregnancies of the heart-transplated women.

• *Hyperlipidemia* is seen in the patients receiving cyclosporine and corticosteroids. The primary lipid Increased in the cyclosporine-treated heart transplantation recepients is **L D L** cholesterol (16). The major controversy is whether prednisone or cyclosporine is the primary cause of lipid elevation. No measurement of lipids has been reported during the pregnancy of the heart-transplanted woman.

• Another important complication of cyclosporine is its *neurotoxicity* (9). One of the most common manifestations of the neurotoxicity reported is seizures. Hypomagnesemia has been noted by several investigators at the time of the seizures and has been thought to play a role in precipitating the seizures. The cause of the hypomagnesemia is an effect by cyclosporine on the proximal tubule of the kidney, resulting in enhanced renal clearence of magnesium. No seizures have been reported during the pregnancy, because oral magnesium therapy was enough to treat the seizures.

• A unique type of *lymphoma* is seen with cyclosporine therapy (28,29). The etiology of this tumor has been shown to be due to the Epstein-Barr virus. No accelerating effects of the pregnancy on this type of cyclosporine treatament complication has been reported.

• Hepatotoxicity, hirsutism, and gingival hyperplasia have been reduced or relieved by dose reduction.

As a result, it is clear that cyclosporine treatment has its side effects, but pregnancy is not an aggraveting factor of these complications in the pregnant women.

PLACENTAL PASSAGE

Cyclosporine is extensively metabolized by the liver (30). In cardiac transplant patients, the metabolites account for 30-50% of the total cyclosporine level as measured with a nonspecific polyclonal antibody (31). The parent compound is thought to contribute most of the immunosuppressive activity (32). It is shown that cyclosporine crosses the placenta (17). Analysis of cyclosporine levels in the blood of two neonates born to heart-lung transplant recipients showed (33) that parent drug and metabolites were considerably lower in cord blood than maternal blood. The amounts of cyclosporine and metabolites found in cord were half or less that found in the mother. This discrepancy was greater when measuring parent drug alone. In one neonate there was 10 times less parent drug in cord blood compared to maternal blood. Other authors also found the similar descrepancy between maternal and cord blood (13,14,24,34). It can be explained either by the accelerated metabolism of cyclosporine In the fetal liver during the third trimester of pregnancy or by the prevention of its passage by the placenta at the usual concentration range. The drug becomes non detectable in the newborn in one week (14,24,33).

The observations of the disposition of cyclosporine in pregnant rabbits show (13) that there Is no cy-

closporine in the amniotic fluid. It agrres with the case report of a woman by Lewis et al. (23) In another case report detected cyclosporine in human amniotic fluid, using an unspecific assay method.

As a conclusion, it is clear that placental passage of cyclosporine is not important, the fact which can explain its minimal side effects on the fetus.

IN THE NEWBORN

- Indirectly, newborn is affected by the complications of the cyclosporine In its mother (infection, renal insufficiency, hypertension, hyperlipIdemia, seizures, etc.)
- The most important problem faced in the newborn whose mother is treated by cyclosporine Is the severe intrauterine growth retardation, reported by Pickrell et al (35). It should be noted that this pregnancy was marked with a high blood cyclosporine concentration, which can be the cause of this important retardation. Other authors do not agree with this result (17,20,21,22,24,33).
- At this moment there are no reported cases of chromosomal anomalies in children born to mothers receiving Cs A. No modification of DNA synthesis by the Immunosuppressive mechanism of cyclosporine has been reported.
- A study in the babies born to cyclosporine treated mothers (3) showed no differences In total numbers of T cells, B cells, CD8, or $CD8^{+}CD4^{+}$ cells in these babies compared to those born to nontreated mothers. However, babies born to cyclosporine treated mothers had low number of activated T cells compader to normal. It is encouraging that neither of the cord blood or neonatal blood in this study bears the hallmarks of long-term immunodepresslon.
- Until 1989, no pregnancy in women taking cyclosporine had been associated with congenital malformation. But Pujils et al. have reported (26) an hypoplasia of the legs In a baby born to a mother on cyclosporine, which raised questions about Its Interference with the modelling and remodelling processes of bone.

Except the two publications (26,35) where the direct cyclosporine effect is not clear, no other side effects have been reported.

BREAST FEEDING

It is showed (17) that cyclosporine is excreted in breast milk In a maximum amount of 2% of the maternal dose. Therefore mothers taking cyclosporine should avoid breast feeding.

CONCLUSION

It is agreed that cyclosporine Is a very effective immunosuppressive agent, and it remains the cornerstone of the current therapy in cardiac transplantation. The length and quality of survival of patients with heart transplants has become impressive. Thus there is a real chance of pregnancy In female heart transplant reclplents.To date, It Is clear that the best immunodepression during the pregnancy would be by cyclosporine monotherapy, because neither foetal toxitiy, nor rejection have been reported.

The care of the organ transplant recipient during pregnancy requires a team apporach. Not only are the Immediate concerns of the pregnancy Important, but long-term-follow-up of the mother and her Infant will be relevant to fully evaluate the extent of possible complications.

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