Mei 2002

**An overview of reports on sirolimus**

**Introduction**

Sirolimus (Rapamune®) was granted a marketing authorisation in the EU on 17 May 2001 with the following therapeutic indication: *Rapamune is indicated for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant. It is recommended that Rapamune be used initially in combination with cyclosporine microemulsion and corticosteroids for 2 to 3 months. Rapamune may be continued as maintenance therapy with corticosteroids only if cyclosporine can be progressively discontinued.* Sirolimus (or rapamycine) is produced by Streptomyces hygroscopicus. It inhibits the proliferation of T and B lymphocytes. Despite comparable chemical structure, its mechanism of action differs from calcineurin inhibitors like cyclosporine or tacrolimus, especially in relation to nephrotoxicity. Combined administration of sirolimus and cyclosporine results in substantial enhanced bioavailability of both compounds. In the section on undesirable effects the SPC mentions: lymphocele, various infections, tachycardia, abdominal pain, diarrhoea, stomatitis, pancreatitis, anaemia, thrombocytopenia, leukopenia, thrombotic thrombocytopenic purpura, haemolytic uraemia syndrome, post transplant lymphoproliferative disorder, hyperlipidaemia, hypokalaemia, abnormal liver function tests, arthralgia, bone necrosis, epistaxis, pneumonia, acne, rash, urinary tract infection, pyelonephritis, pneumonitis[1].
Sirolimus has been on the market for one year. Since it is a new chemical entity with immunosuppressive action, we considered it useful to prepare an overview of reported adverse events, including Dutch reports from the industry. Prescription data are not available. Per 1 January 2001, there were 4765 patients with a functioning renal graft in the Netherlands. In 2000 565 renal transplantations were performed, including 169 living donor procedures[2].

**Reports**

Table 1 provides a summary of the reported adverse events. Eleven out of 14 reports were made available by the marketing authorisation holder. One patient was reported by both the industry and the specialist, although the description of the adverse event differs. Three patients were reported with dyspnoea, although the reports revealed bilateral interstitial pneumonitis. Four patients died due to the immunosuppressive activity, myocardial infarction, interstitial pneumonitis and hepatic failure, respectively.
Generally, the industry reports were incompletely documented.

**Other sources of information**

*Literature*

A Medline search on “sirolimus/adverse effects [MESH]” yielded 89 hits. As derived from the titles, the clinically relevant adverse events comprised de novo haemolytic syndrome, interstitial pneumonitis, impaired phosphate handling, eyelid oedema, thrombocytopenia and leukopenia, hyperlipidaemia, and capillary leak syndrome.

**Discussion and conclusion**

All reports were classified as serious adverse events. This may be due to the fact that most reports originated from the industry.
The number of fatal outcomes warrants alertness. One patient died of myocardial infarction, which may be due to the underlying disease. The fatal interstitial pneumonitis and the fatal hepatic failure may have a stronger relationship with sirolimus.

In most reports, the adverse events can be considered as unwanted but pharmacological plausible effects.

References

1. Summary of product characteristics of sirolimus (Rapamune) http://www.eudra.org/humandocs/humans/epar/rapamune/rapamune.htm (21st April 2002).
2. Personal communication. Stichting Renine. http://www.renine.nl
3. Lennon A, Finan K, FitzGerald MX, McCormick PA. Interstitial pneumonitis associated with sirolimus (rapamycin) therapy after liver transplantation. Transplantation. 2001;72: 1166-7.
4. Singer SJ, Tiernan R, Sullivan EJ. Interstitial pneumonitis associated with sirolimus therapy in renal-transplant recipients. N Engl J Med. 2000; 343:1815-6.
5. Morelon E, Stern M, Kreis H. Interstitial pneumonitis associated with sirolimus therapy in renal-transplant recipients. N Engl J Med. 2000; 343:225-6.

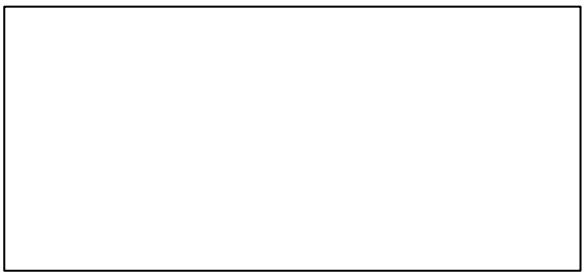

Table 1. Summary of reported suspected adverse events at Lareb

| no | sex | age | date of birth | ADR | latency | outcome | immunosuppressive co-medication | indication | dose | source |
|---|---|---|---|---|---|---|---|---|---|---|
| I | F | ? | ? | pancytopenia | 16 days | recovered | MMF | liver | ? | industry |
| II | M | 63 | 17-12-1937 | infection, pancytopenia, DIC, convulsions, acute circulatory failure, death | 27 days | fatal | prednisone, CsA | renal | 5 mg/day | industry |
| IIIa | M | 3 | 1-5-1998 | encephalopathy, temporary blindness [a] | 7 weeks | disappearance | prednisolone | liver | 0,2 mg/day | specialist |
| IIIb | M | 3 | ? | myoclonic jerks, restlessness, visual disturbance, ataxia | ? | ? | ? | liver | 0,2 mg/day | industry |
| IV | ? | ? | ? | mouth ulceration | ? | ? | ? | ? | ? | industry |
| V | ? | 59 | 18-9-1942 | lymphoproliferative disorder | 7.5 months | ? | ? | renal | ? | industry |
| VI | ? | ? | | renal impairment | ? | ? | ? | | | industry |
| VII | M | 49 | 27-1-1952 | myocardial infarction, death | 6 weeks | fatal | CsA, prednisone, methylprednisolone, MMF | renal | 6 mg/day | industry |
| VIII | F | ? | ? | pneumonia, sinusitis | 3 months | not yet recovered | prednisolone | renal | ? | industry |
| IX | M | 52 | 25-5-1949 | thrombocytopenia, chest pain, dyspnoea (interstitial pneumonitis) | 4 weeks | recovered | MMF, tacrolimus | renal | 2 mg/day | industry |
| X | M | 55 | 24-1-1946 | renal failure, thrombocytopenia, haemorrhage, sepsis | ? | ? | CsA, prednisone | renal | ? | industry |
| XI | M | 55 | 8-8-1946 | dyspnoea, death, (interstitial pneumonitis) | 1 month | fatal | prednisolone | renal, CsA toxicity | 8 mg/day | specialist |
| XII | M | 54 | 20-4-1947 | dyspnoea. (interstitial pneumonitis) | 33 days | recovered | prednisolone | renal | 5 mg/day | specialist |
| XIII | M | ? | ? | hepatic disease, death | ? | fatal | prednisolone | renal | ? | industry |

a During recovery from the encephalopathy, patient seemed to have cortical blindness: consciousness and pupil reflex were intact, but no menace reflex was observed. Visual evoked potentials were not measured. The blindness gradually disappeared in a few days.
IIIa and IIIb Same patient, reported by specialist (IIIa) and by industry (IIIb)
? not reported
DIC diffuse intravascular coagulation
MMF mycophenolate mofetil (Cellcept®)
CsA cyclosporine A (Neoral®)