REPORT 175
Everolimus, Sirolimus and Tacrolimus for Immunosuppression in heart transplantation

Ordinance n° 52/2015 published on 09/30/2015
EXECUTIVE SUMMARY

Technologies: Tacrolimus, Sirolimus and Everolimus.

Indication: Rescue from refractory rejection events in the immunosuppression maintenance period after heart transplantations.

Applicant: Secretariat of Science, Technology and Strategic Inputs/SCTIE/MS.

Context: Heart transplantations save over 250 lives a year, but are among the thirty more expensive therapies universally accessible to the entire Brazilian population, reimbursed by Sistema Único de Saúde of Brazil, SUS, and there is critical self-limitation of available organs. Almost half of them experience episodes of rejection that may not respond to the treatments available in SUS. Approximately 1,000 transplanted patients are estimated to benefit from rescue with therapeutic alternatives.

Questions: Is the incorporation of therapeutic alternatives for immunosuppression maintenance in patients with a transplanted heart, such as tacrolimus, sirolimus and everolimus, able to help in the rescue from episodes of rejection and serious adverse events, at what cost and budget impact to SUS?

Scientific evidence: The meta-analysis on mortality of the 10 and 12 randomized controlled trials, RCTs, comparing cyclosporine and tacrolimus, as well as of 10 and 06 RCTs, respectively, for sirolimus and everolimus combined with reduced doses of cyclosporine and tacrolimus, has shown little or no impact on survival. The empirical analysis of 348 heart transplantations from the InCor-HC/FMUSP [Instituto do Coração-Hospital das Clínicas/Faculdade de Medicina da Universidade de São Paulo] cohort has shown that survival probability was significantly superior in the 1st year of the follow-up period in both age groups, adults and children. In the cohort of transplanted patients surviving in the first year, loss of effect differences and lower mortality in the cyclosporine curve have been observed, reflecting the serious conditions of clinical deterioration and complications that have led to switching these patients to these therapeutic alternatives. In the meta-analysis of these RCTs on rejection, tacrolimus or cyclosporine had no significant difference. There is a significant benefit of rejection occurrence reduction of -8.93% and -7.39% with sirolimus and everolimus combined with reduced doses of calcineurin inhibitors. The use of tacrolimus and alternatives with mTORs in adults and children at InCor-HC/FMUSP has actually provided an efficient control of rejection episodes in patients who have been shown to be refractory or adverse events, such as rejection relapse, renal failure, allergy or intolerance.

Economic assessment: The empirical analysis of total costs for the studied period demonstrates that tacrolimus or cyclosporine have no significant difference. In the model, the average cost-effectiveness was lower: BRL
49,572.19 for tacrolimus versus BRL 58,370.35 with cyclosporine (CE ratio = BRL 1,517.84 between an incremental cost of BRL 171.31 divided by 0.11287 higher effectiveness for the tacrolimus group).

**Budget Impact Assessment:** Reimbursement for procedures “treatment for post-heart transplantation - post-critical transplantation event” may increase between 3% to 33.6% [average of BRL 2,791.89 versus BRL 1,853.87/year for rescue from 01 complication with cyclosporine, excluding drugs reimbursements]. The mean sum of annual follow-up cost with the drugs was = BRL 11,529.05/15% with sirolimus and BRL 9,218.11/3% with everolimus. When using the model for the 1,000 potential patients with the use distribution seen at InCor-HC/FMUSP, the rescue of additional +26% from complications with sirolimus and everolimus combined with reduced doses of calcineurin inhibitors increases to 90% the overall program effectiveness, at the cost of BRL 1.3 million in total required reimbursements to BRL 2.2 million, compared to BRL 1.5 million currently reimbursed for this procedure. The diffusion pressure of everolimus and prevalence of complications may likely increase this number to 10% of patients distributed into each mTOR. In the sensitivity analysis, the additional cost for this scenario may increase + BRL 1.2 million, totaling the same BRL 2.2 million in total annual follow-up program reimbursements for the 1,000 potential patients.

**International Experience:** Approved since April 08, 1994, by FDA, tacrolimus was (and still is) studied in children and adults in the cohort from University of Pittsburg (13 publications). Twelve sites from seven European countries (Austria, France, Germany, Italy, Spain, Sweden, and United Kingdom) have participated in phase II and III studies in adults. These studies supported its approval by the European Medicines Agency on 04/23/2007, where it continues to be used, according to publications of the International Society for Heart & Lung Transplantation Registry (Transplant Registry Quarterly Data Reports Webpage).

**Discussion:** The use of the therapeutic alternatives varies with patient tolerance and may also cause adverse events. For this reason, a dynamics of switches among alternatives, aiming at overcoming episodes of rejection, is observed. Although literature synthesis does not show a different mortality rate among the alternative schedules, these several therapeutic paths allowed seeing a significant mortality reduction among the 348 transplanted patients at InCor-HC/FMUSP, especially in the 1st Year, with the rescue of + 26% of refractory cases. This experience is comparable to the outcome published in the International Society for Heart & Lung Transplantation Registry base analysis, where 69% of transplanted patients are maintained with alternatives.

**Recommendation made by CONITEC:** CONITEC members attending the 35th meeting of CONITEC, held on the days May 6 and 7, 2015, unanimously deliberated in favor of recommending the incorporation of immunosuppressants (everolimus, sirolimus and tacrolimus) in heart transplantations.

**Public Consultation:** 4 contributions have been received during public consultation. All contributions were in favor of incorporating the immunosuppressants (everolimus, sirolimus and tacrolimus). No new scientific evidence on the topic was presented.
Final Deliberation: To recommend the incorporation of the immunosuppressants (everolimus, sirolimus and tacrolimus) in heart transplantation, as per the Clinical Protocol of the Ministry of Health. Deliberation Record nº 137/2015 was signed.

Decision: To incorporate everolimus, sirolimus and tacrolimus for immunosuppression in heart transplantation within the scope of Sistema Único de Saúde-SUS. Ordinance nº 52, published in DOU nº 187, page 71, dated 09/30/2015.