PRS33

COST-EFFECTIVENESS ANALYSIS OF TACROLIMUS AS PRIMARY IMMUNOSUPPRESSION FOR LUNG TRANSPLANT RECIPIENTS IN THE CZECH REPUBLIC

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BACKGROUND

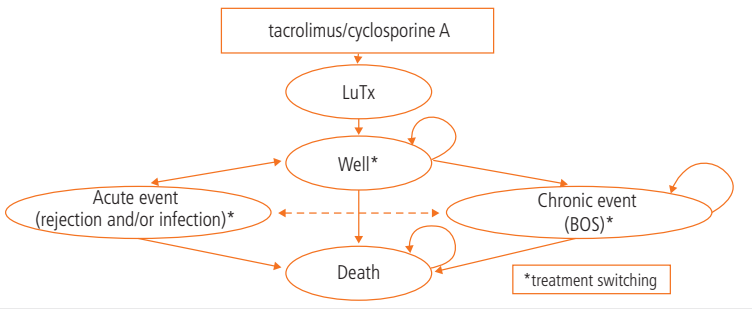
Tacrolimus is commonly used in accordance with SmPC[1] for the prophylaxis of transplant rejection in adult kidney or liver graft recipients or for the treatment of adults with organ rejection resistant to treatment with other immunosuppressive agents.

However, recent study (Treede et al.[2]) has also demonstrated the benefits of de novo tacrolimus use by lung graft recipients, which primarily lead to significant reduction of chronic graft rejection manifested as bronchiolitis obliterans syndrome (BOS).

OBJECTIVE

The objective of this study was to assess the cost-effectiveness of tacrolimus as primary immunosuppressive therapy after lung transplantation in comparison with cyclosporine A (CsA) which is an alternative calcineurin inhibitor established as historical standard in Czech clinical practice.

Figure 1. Model scheme



METHODS

A developed 20-year Markov cohort model in TreeAge Pro 2017 with one-year cycle length projects outcomes (Quality-Adjusted Life-Years, QALYs; Life-Years Gained, LYGs) and costs of care including primary prophylaxis of graft rejection in adult lung transplant recipients with mean age of 45 years from healthcare payers' perspective.

Model health states are defined by occurrence of acute and/or chronic complication (e.g. rejection, infection) and death. **Figure 1** shows the model scheme.

Transition probabilities between health states were sourced from Treede et al.[2] **Figure 2** shows mortality of lung transplant patients treated with tacrolimus-based therapy and CsA-based therapy. **Figure 3** and **Figure 4** present incidence of acute and chronic graft rejection in time. Incidence rate of the other complications (e.g. infection) together with withdrawal rate of immunosuppressive therapy is shown in **Table 1**.

Utilities and disutilities were taken from published literature (Sullivan et al.[3], Anyanwu et al.[4], Oppong et al.[5]) and were combined using multiplicative approach (Ara et al.[6]). Utility of common population derived by formula[3]: $utility_{xy\text{-}year} = 0.93170 - 0.00003 * age^2 - 0.00060 * age$ is affected by (dis)utilities of post-transplant conditions (**Table 2**) and occurrence of complications (**Table 3**).

Time dependent costs associated with organ transplantation, post-transplantation care (including immunosuppressant agents – tacrolimus/cyclosporine A & mycophenolate mofetil (MMF) & corticosteroids, monitoring, anti-infectious prophylaxis, supplementation therapy) and management of complications were based on KOLs' statement[7] or Treede et al.[2] (in case of dosing scheme of immunosuppressive drugs) and reimbursement lists[8-12] (**Table 4**).

Costs and outcomes were discounted by 3%.

One-way sensitivity analysis (OWSA) accompanied with scenario analysis (SA) were conducted (**Figure 6**).

Probabilistic sensitivity analysis (PSA; 10,000 iterations) was performed with Czech Willingness-To-Pay (WTP) threshold of €45,000/QALY gained. **Table 6** summarizes the PSA setting.

RESULTS

Tacrolimus compared with CsA demonstrates an incremental cost-effectiveness ratio (ICER) of €31,703/QALY gained over a 20-year time horizon (**Table 5**).

Both calcineurin inhibitors bring in total 10.924 LYGs and 6.890 QALYs, however, complications associated with tacrolimus-based therapy and CsA-based therapy decrease QALYs by 0.359 and 0.573 respectively (i.e. incremental QALYs: 0.214; **Table 5**).

Total costs of tacrolimus-based therapy and CsA-based therapy are €160,219 and €153,434 (i.e. incremental costs: €6,784), of which only 24.9% and 20.6% respectively, are costs of immunosuppressive drugs (**Table 5**).

Primary prevention of graft rejection with tacrolimus-based therapy leads to the highest net monetary benefit compared to CsA-based therapy (i.e. incremental NMB: €106,592; **Table 5**).

PSA showed that probability of tacrolimus being cost-effective is 83.4% at selected WTP threshold (**Figure 5**). Average probabilistic ICER is very close to base-case deterministic ICER (**Figure 5**).

OWSA and SA also confirmed the robustness of the base-case setting of analysis (**Figure 6**).

Figure 2. Cumulative mortality with optimal extrapolation in time[2]

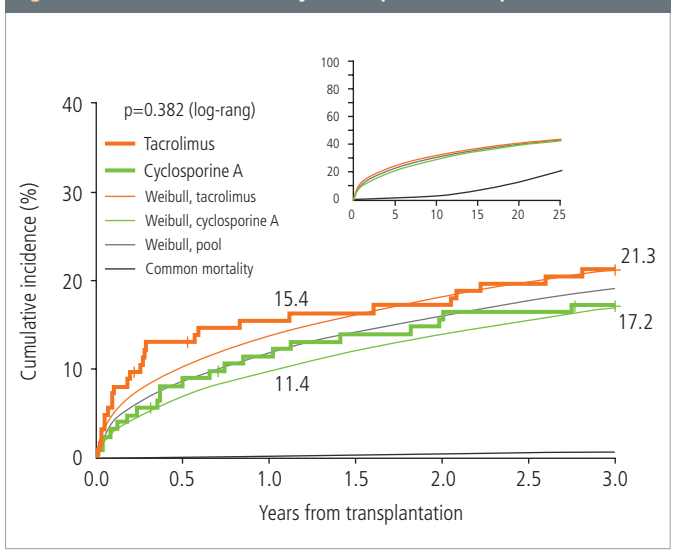


Figure 3. Cumulative incidence of chronic rejection with optimal extrapolation in time[2]

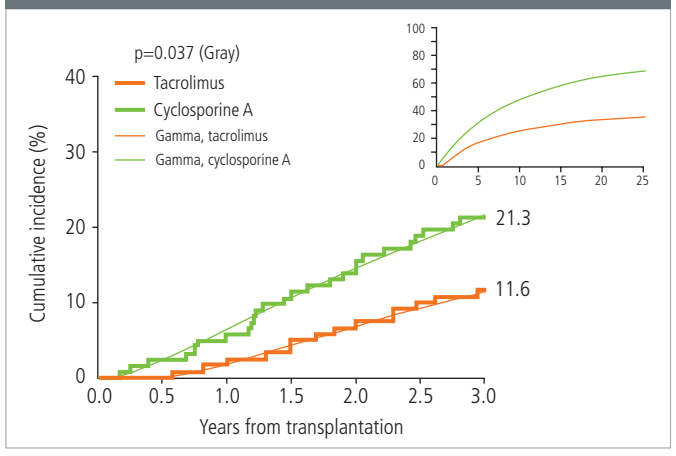


Figure 4. Cumulative incidence of acute rejection with optimal extrapolation in time[2]

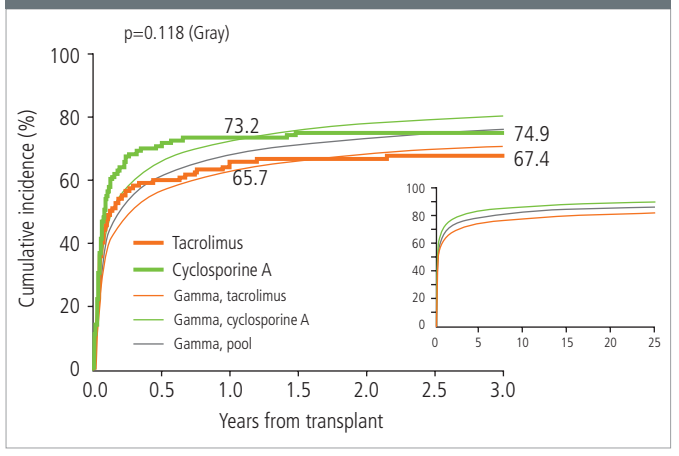


Table 1. Incidence rate of the other complications and withdrawal rate of immunosuppressive therapy[2]

	Tacrolimus	Cyclosporine A
Infection per 1,000 patient-years	0.0092	0.0094
Renal failure per 1 patient-years	0.0760	0.0560
Treatment withdrawal per 1 patients-years	0.0376	0.1333

Table 2. Utility after lung transplantation[2,4]

	Utility after lung transplantation, weighted average
0–6 months from transplantation	0.734
7–18 months from transplantation	0.795
19–36 months from transplantation	0.778
> 36 months from transplantation	0.778

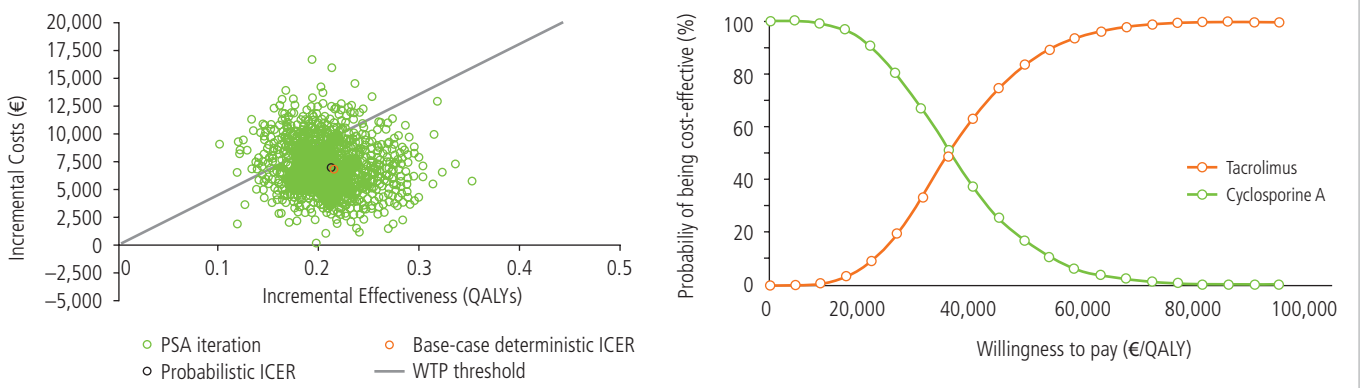
Table 3. Disutility of complication[3,5]

	Disutility of complication
Acute rejection, ICD–9 496	–0.078
Chronic rejection, ICD–9 518	–0.134
Infection, ICD–9 466	–0.156
Renal failure, ICD–9 586	–0.101

Table 4. Costs[7-12]

	Cost (€/month)
Lung transplantation	76,156
Immunosuppressive therapy	tacrolimus: 601–282 cyclosporine A: 387–197
Monitoring	tacrolimus: 455–28 cyclosporine A: 421–25
Anti-infectious prophylaxis	934–2
Supplementation therapy	10
Complication	
– infection	2,265
– acute rejection	2,872
– chronic rejection	157–34
– renal failure	2,571

Figure 5. Cost-effectiveness scatter plot (left) and Cost-effectiveness acceptability curve (right)



CONCLUSIONS

Tacrolimus is a cost-effective immunosuppressive therapy in lung transplant recipients, protecting them from chronic lung graft dysfunction, which manifests as bronchiolitis obliterans syndrome. Deterministic ICER of €31,703/QALY is well below WTP threshold equal to €45,000.

As tacrolimus results in the highest net monetary benefit, this is rank as the most cost-effective strategy in primary prevention of lung transplant rejection.

To our knowledge, this is the first cost-effectiveness analysis of tacrolimus as primary immunosuppression after lung transplantation.

Table 5. Base-case results of cost-effectiveness analysis

	Tacrolimus	Cyclosporine A	Difference
Total costs (€)	**160,219**	**153,434**	**6,784**
Transplantation costs (€)	73,289	73,289	0
Immunosuppression costs (€)	39,947	31,623	8,324
– tacrolimus (€)	27,212	8,914	18,298
– cyclosporine A (€)	0	9,974	–9,974
– MMF & corticosteroids (€)	12,735	12,735	0
Complication costs (€)	34,603	36,489	–1,886
Other costs (e. g. monitoring, supplementation; €)	12,381	12,034	347
QALYs	**6.531**	**6.317**	**0.214**
– utility after transplantation	6.890	6.890	0.000
– disutility associated with complication	–0.359	-0.573	0.214
LYGs	**10.924**	**10.924**	**0.000**
ICER (€/QALY)	–	–	**31,703**
NMB (€)	**169,292**	**165,280**	**4,013** $NMB_{tacrolimus} > NMB_{CsA}$

Figure 6. Tornado diagram - one-way sensitivity analysis & scenario analysis

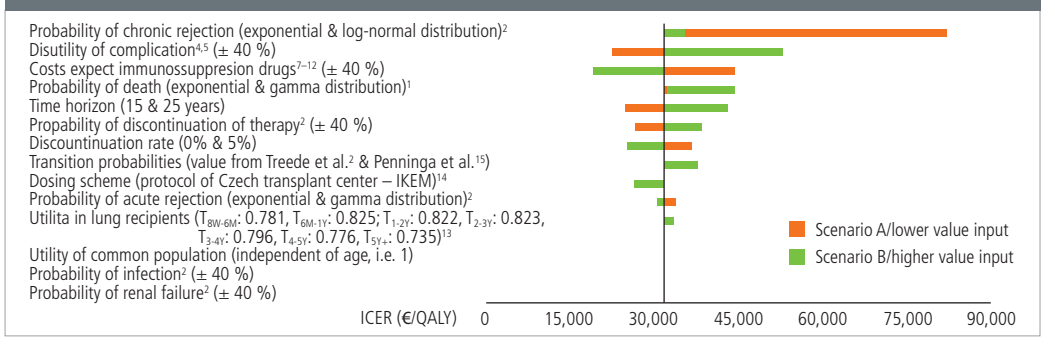


Table 6. Setting of PSA

Parameter	Distribution
Probabilities – coefficients of parametric models & rates[2]	Normal
Utility of common population[3], utility in lung recipients[2,4], disutility of complication[3,5]	Beta
Costs[2,7–12]	Gamma

REFERENCES

1 EMEA. Summary Of Product Characteristics – Advagraf. 2015 Oct. • 2 Treede et al. J Heart Lung Transplant. 2012 Aug;31(8):797–804. • 3 Sullivan et al. Med Decis Making. 2011 Nov–Dec;31(6):800–4. • 4 Anyanwu et al. Thorax. 2001 Mar;56(3):218–22. • 5 Oppong t al. Eur J Health Econ. 2013 Apr;14(2):197–209. • 6 Ara et al. Value Health. 2012 Sep–Oct;15(6):971–4. • 7 Expert panel. 2017 Feb. • 8 Ministry of Health of the Czech Republic. Decree No. 348/2016. • 9 General Health Insurance Company of the Czech Republic. List of medical services. 2017 Mar. • 10 General Health Insurance Company of the Czech Republic. List of medical devices. 2017 Mar. • 11 State Institute for Drug Control. List of reimbursed medicinal products. 2017 Mar. • 12 State Institute for Drug Control. List of reimbursed individually prepared medicinal products. 2017 Mar. • 13 Kugler et al. Transplantation. 2010 Aug 27;90(4):451–7. • 14 Institute for Clinical and Experimental Medicine. Lung Transplantation – Immunosupresive Protocols. 2016 Feb. • 15 Penninga et al. Cochrane Database Syst Rev. 2013 May 31;(5):CD008817.

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