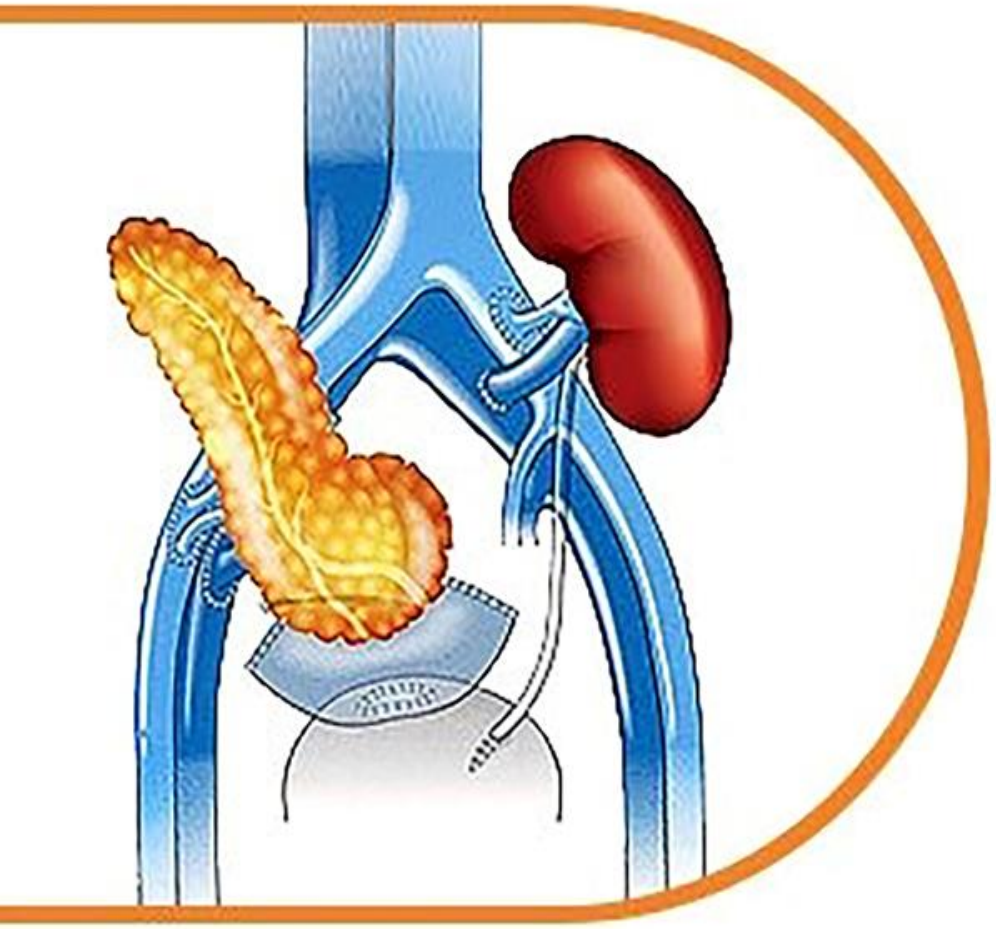
In the Name of GOD



Simultaneous Pancreas & Kidney Transplantation

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Immunosuppression in SPK

The use of biologic agents for induction coupled with combinations of multiple agents with different mechanisms of action for maintenance therapy has become the standard of care in contemporary immunosuppression.

Induction Therapy

Induction Therapy

- Available agents for induction include
  - T cell-depleting antibodies (such as polyclonal rabbit antithymocyte globulin [**rATG]-Thymoglobulin** and
  - monoclonal **Alemtuzumab** [anti-CD52 antibody]) and
  - nondepleting antibodies such as interleukin (IL)-2 receptor antibodies (monoclonal **Basiliximab**).

- **85 percent of pancreas transplants performed in 2016 used T cell-depleting agents for induction; fewer than 10 percent of transplants used IL-2 receptor antibodies or reported no induction agent.**

Induction Therapy

- Administration of intravenous (IV) **rATG-Thymoglobulin** 1 to 1.5 mg/kg intraoperatively (through either central or peripheral venous access) followed by 1.5 to 2 mg/kg of rATG-Thymoglobulin per day for the next two to three days for a total cumulative induction dose of 4.5 to 6 mg/kg.
- rATG-Thymoglobulin is administered if, at presentation, the white blood cell count is greater than 2000/microL and the platelet count is greater than 75,000/microL.
- If rATG Thymoglobulin cannot be given, **Alemtuzumab** is administered.
- Administration of Alemtuzumab as a single IV (or subcutaneous) dose of 30 mg at the time of transplantation.
- rATG-Thymoglobulin was associated with a decreased risk of rejection.

Alemtuzumab vs. rATG induction

Alemtuzumab and **rATG** induction were compared in a randomized, single-center trial of kidney and pancreas recipients:

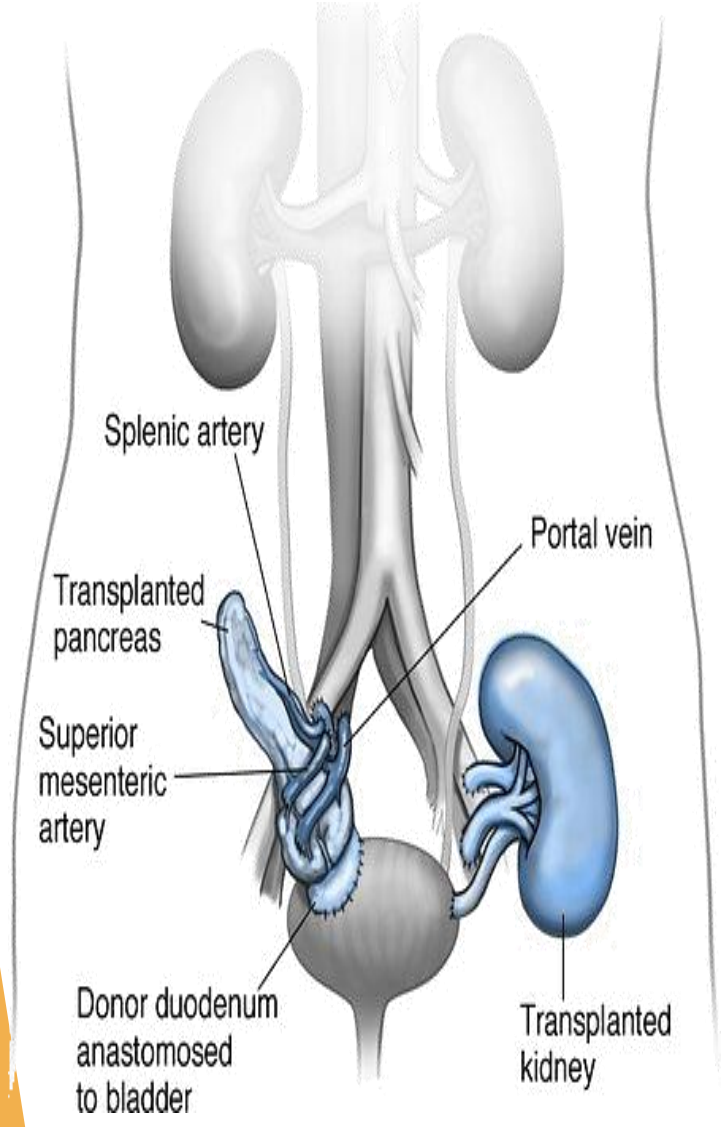
- There were no significant differences between the alemtuzumab and rATG groups in **five-year patient survival kidney graft survival or pancreas graft survival**.
- **Rates of acute rejection** were lower in patients receiving alemtuzumab than in those receiving rATG although this difference was not statistically significant.
- **Cytomegalovirus (CMV) infections** were significantly lower with alemtuzumab compared with rATG.

Belatacept

- **Belatacept** is a soluble fusion protein that selectively blocks a T cell co-stimulation pathway, thereby limiting T cell activation.
- Although studied extensively in kidney transplantation, there are limited data in SPK transplantation.
- An open-label, multi-center, randomized trial of Belatacept in SPK transplantation as a de novo maintenance agent (in combination with rATG induction and mycophenolate) in order to achieve calcineurin inhibitor and glucocorticoid withdrawal was stopped prematurely because of a high incidence of pancreas allograft rejection.
- Belatacept offers appealing benefits, such as avoiding nephrotoxicity, neurotoxicity, and pancreas beta-cell toxicity associated with CNIs. Unfortunately, the use of Belatacept in SKPT patients may be limited by risk of early acute rejection.

Maintenance Therapy

Initiation of Maintenance Therapy



Because recipients of a pancreas transplant are typically "nil per os" (ie, NPO) for the first few days after surgery, maintenance immunosuppression during this period is generally administered IV or per nasogastric tube until patients are able to take oral medications. Alternatively, tacrolimus may be given sublingually as a powder.

Maintenance Therapy

- Maintenance therapy is similar for patients receiving an SPK or PAK transplant and typically includes:
  - a calcineurin inhibitor (**Tacrolimus**)
  - an antimetabolite (**Mycophenolate**) or (mTOR) inhibitor
  - a tapering dose of glucocorticoids (**Prednisone**)

- This approach is generally preferred by most transplant centers, although practice may vary from center to center.

Initiation of Maintenance Therapy

In patients undergoing SPK and receiving **induction therapy with rATG-Thymoglobulin or alemtuzumab**, initiation of **maintenance immunosuppression therapy** as follows:

- Administration of **tacrolimus** on the evening of postoperative day 1 with immediate-release tacrolimus 1 to 2 mg twice daily, with doses adjusted to achieve a 12-hour trough level of 8 to 10 ng/mL for the first three months post-transplant and 6 to 8 ng/mL thereafter. **OR**
- Extended-release **tacrolimus** tablets on postoperative day 1 at 0.08 mg/kg once per day.
- Administration of **mycophenolate** mofetil (MMF) 1000 mg IV twice daily or MMF liquid suspension 1000 mg twice daily per nasogastric tube starting on postoperative day 1. When the patient is able to take oral medications by mouth (typically on postoperative day 2 or 3), we switch from IV or liquid suspension MMF to either enteric-coated.
- Administration of either IV **methylprednisolone** at 7 mg/kg (maximum dose of 500 mg) then switch to oral **prednisone** (20 mg once daily for the first week after transplantation, then tapered to 5 mg daily by one to two months posttransplant.

Initiation of Maintenance Therapy

- **Tacrolimus** and **cyclosporine** selectively inhibit calcineurin, thereby inhibiting the transcription of IL-2 and several other cytokines in T cells by inhibiting cytokine gene transcription.
- **Tacrolimus** it may also increase the risk of CMV viremia and syndrome.
- Most transplant centers administer **mycophenolate** (MMF or EC-MPS) as an antimetabolite agent to SPK recipients rather than azathioprine.
- **Mycophenolate** is teratogenic, and its use is contraindicated in pregnancy. In female recipients of childbearing age, administer mycophenolate as the antimetabolite agent and counsel them against getting pregnant for at least one to two years posttransplant. After this time, if patients wish to conceive, switch them to **azathioprine**.

- This is a study of 39 SPK recipients on standard immediate-release (IR) tacrolimus or LCP-Tacrolimus.
- There was no difference in tacrolimus CV in the IR-TAC and LCPT groups at 1 month or 3 months
  postoperatively; however, a greater difference was observed at 1 year (41.0 vs. 33.1%; p ¼ 0.19).
- Significantly lower rates of rejection were observed in patients receiving LCP-T. The once daily dosing may facilitate medication adherence and result in improved long-term outcomes.

Initiation of Maintenance Therapy

- In the Euro-SPK 001 trial, **205 SPK transplant** patients, pancreas survival being significantly higher with **tacrolimus**.
- **Pancreas survival** remained significantly higher with **tacrolimus** (90 versus 72 percent), with pancreas allograft loss due to thrombosis being markedly increased with cyclosporine (10 versus 2 patients).
- Study of 674 pancreas transplant recipients, the incidence of **redevelopment of diabetes** at 10 years was not increased in those receiving **tacrolimus** compared with **cyclosporine**. The possibility of glucocorticoid sparing or minimization with tacrolimus compared with cyclosporine may counteract some of the purported diabetogenic effects of tacrolimus.

Dosing of Glucocorticoids

- Administer IV **methylprednisolone** at 7 mg/kg (maximum of 500 mg) in the operating room, followed by IV methylprednisolone 20 mg daily until the patient is able to take medications by mouth .
- The daily dose is then tapered every week by 5 mg, resulting in 15 mg daily for one week, 10 mg daily for one week, and then 5 mg daily .
- Some centers prefer early glucocorticoid withdrawal in some SPK recipients. In this setting, some centers may use an mTOR inhibitor as a third maintenance immunosuppressive agent.

mTOR Inhibitors

- **Sirolimus** is administered once daily because of a long half-life, and **everolimus** is administered twice daily; both agents are dosed to achieve target trough levels of 3 to 8 ng/mL .
- A **United Network for Organ Sharing (UNOS) registry study** spanning 1986 to 2016 stratified **25,387 pancreas or SPK transplant recipients** into two groups according to those who either received mTOR inhibitors (at any time posttransplant; n= 4174) or those remaining (n= 21,663) who were managed exclusively with non-mTOR inhibitor-based immunosuppression:
  - The use of mTOR inhibitors was associated with a 7 percent risk reduction in allograft failure and higher patient survival rates up to 10 years.

mTOR Inhibitors

- The available data suggest that the role of mTOR inhibitors may be better suited to replace an antimetabolite rather than a calcineurin inhibitor, which may then permit glucocorticoid weaning and withdrawal.
- There was no difference in NODAT incidence between patients treated with CNI or mTOR inhibitors.
- Despite more dnDSA occurrence and more clinical and histological rejections, the noninferiority of SRL compared to TAC as cornerstone immunosuppression when introduced 3 months after SPK transplantation regarding patient and graft survival at 1 year and 5 years.
- The interest of mTOR inhibitors in combination with CNI at lower doses could be reconsidered after SPK.

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