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# Immunosuppressive Therapy After Cardiac Transplantation

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## 1. Introduction

In contrast to renal or pancreas transplantation graft failure after heart transplantation (HTx) is associated with the death of the patient if re-grafting or mechanical support (MCS) is not possible immediately. Since the beginning of modern transplantation medicine one of the highest priorities were preventing and treating graft rejection. Over the last decades experimental, animal and clinical research resulted in the development of new immunosuppressive (IS) drugs leading to an improved patient and graft survival. The efforts of transplant professions to develop new IS protocols trying to reduce the toxic side effects, resulted in an improvement of quality of life (QoL) for transplant recipients.

## 2. Historical consideration

At the beginning of the twentieth century research work by Alexis Carrel on performing surgical anastomosis [1, 2] allowed organ revascularization and marked one of the pre-conditions for organ transplantation. It was the Stanford group of Lower and Shumway who first started to study the problems of HTx [3-5] leading to the first human HTx by Banard in 1967 [6]. Within the next year over 100 HTx were done worldwide. Even if technical successful the great enthusiasm for this new therapy decreased rapidly when the poor survival rate became obvious [7]. One of the biggest problem was preventing and controlling graft rejection. Corticosteroides and Azathioprine (AzA) were the main drugs used for IS at that time. The Standford group added rabbit antithymocyte globulin (ATG) to the protocol gaining acceptable survival rates [8]. The main breakthrough came a decade later with a drug called Cyclosporine (CsA). The great advantage of CsA was the selective immunoregulation of T cells in contrast to the non-selective inhibition of cell proliferation by AzA and corticosteroids. CsA was first used in clinical organ transplantation in 1978 [9] and in 1983 it was approved for clinical use to prevent graft rejection in transplantation. Today transplant professions throughout the world contribute the great success of HTx to the introduction of CsA into clinical practice. Four years after the first use of CsA Kino reported of a new IS agent even more potent compared to CsA called FK 506 [10]. It was Starzl and the Pittsburgh Group who but much effort in the establishment of FK 506 into IS protocols [11]. In the recent FK 506 is more frequently used compared to CsA [12].

As early as 1896, mycophenolate acid (MPA), the activated form of mycophenolate mofetil (MMF) was extracted from Penicillium stoloniferum (Gosio, B. 1896. Ricerche batteriologiche chimiche sulle alterazioni del mais. Riv. Igiene Sanita Pub. Ann.7:825-869. 16. Jaureguiberry). The cytostatic effect was reported by Brewin in 1972 and was first used in the treatment of neoplasia [13]. The first report of MMF use as IS drug in animal research was in a heterotopic HTx model in rats [14].

Lately a new category named proliferation signal inhibitors (PSI), including Rapamycin (Rapa) and Everolimus (EvE) have been introduced to clinical practice. Rapa was discovered in 1965 but it took years before it was introduced to transplantation medicine. The research work of Rapa led to the discovery of the action of the mammalian target of Rapamycin (mTOR).

## 3. Immunosuppressive regimes and agents

Starting with the exploration of CsA the field of IS agents has evolved drastically resulting in the possibility of more combinations for different indications. All IS agents have a narrow therapeutic window in common. Transplant physicians have to find an optimal balance avoiding allograft rejection and avoid toxic side effects. There are mainly three categories for IS therapy: first its use as induction therapy, second to maintain the organ allograft (maintenance therapy) and finally if needed to treat acute rejection episodes (anti-rejection therapy). In the following we focus on the recent used IS agents, acting at T cell mediated processes of rejection. Further agents focusing on the role of antibody mediated rejection may be found in the next chapter.

The highest number of rejection episodes will be within the first months after HTx; therefore up to 50% HTx centres worldwide are using a protocol with high IS for the early post-operative period (=Induction therapy or augmented IS therapy) [12].

Interactions of IS drugs and other medications may be extensively and categorised in minor, moderate and major interactions. Here only the most important and major interactions will be mentioned.

### 3.1 Polyclonal antibodies

Polyclonal Antibodies are derived mainly from rabbits or horses, after the animals have been immunized with human lymphocytes (ALS) or thymocytes (ATG). Polyclonal antibodies have multiple distinct antigen-combining sites resulting in the depletion of circulating T-cells, apoptosis of activated T cells and modulation of cell surface receptor molecules. The IS potential of heterologous antibodies has been demonstrated early [15] and the first clinical use of an antilymphocyte glogulin (ALG) is reported by Starzel in 1967 [16]. The heavily contamination with anti-red cells and anti-platelet antibodies was resolved by the use of human thymocytes as the antigen source, resulting in antithymocyte globulin (ATG). First studied in renal transplantation, ATG was established as fix part in the Stanford protocol for HTx [8]. They used rabbit ATG intramusculary for the first three days after HTx and then every other day. The goal was a reduction of T cells to less than 5% in peripheral blood sample.

Polyclonal Antibodies have strong IS effect but its use is limited by the production of human antibodies against the xenogeny protein fraction allowing only a short term of use. This also explains the need for corticosteroids and the use of histamine antagonist therapy to reduce the rates of anaphylactic shock. Antipyretic medication should be added when ATG/ALS is given as fever and shivering are some of the prominent side effects. Further side effects are thrombocytopenia, leucocytopenia and anemia due to antibody cross reactions. The rate of opportunistic infections might be as high as 30%. It should be administered intravenously using a dialysis catheter or a central venous access. When administered intravenously using a peripheral vein, phlebitis may result and when given intramuscular local painful swelling leading to an abcess can occur. The goals of use of ATG/ALS in modern IS protocols are: Reducing or even avoiding CNIs due to their nephrotoxic side effects for the first days after HTx establishing a CNI free induction therapy, avoiding under-immunosuppression in the first postoperative days and treating acute cellular rejections when other regimes fail. Monitoring of polyclonal antibody treatment is difficult as the effectiveness might vary from charge to charge. Monitoring was done by achieving leucopenia later followed by using the rosette test [18]; nowadays the fluorescence activated cell sorter (FACS) analyses and T cell counts may be used. Most centres use a fixe dose regime.

### 3.2 Anti-Interleuckin 2 receptor antibodies

Agents who specific block the interleukin 2 (IL-2) receptor on activated T-cells, were developed to be more effective compared to non-selective polyclonal or monoclonal antibodies. An activated IL-2 receptor leads to rapid T cells proliferation and finally to the activation of B cells resulting in the production of antibodies against the allograft. The IL-2 receptor consists of three transmembrane protein chains: α (CD25), β (CD122), and γ (CD132). Basiliximab (trade name Simulect) and daclizumab (trade name Zenapax) are humanized antibodies produced by recombinant DNA technology; both composite of about human (90%) and murine (10%) antibody sequences. They are derivate from non-human species and are monoclonal antibodies to the alpha (CD 25) subunit of the IL-2 receptor. The subunit where the IL-2 receptor blocker binds to is only expressed on activated but not on resting lymphocytes. Both drugs were first used in renal transplantation and are now increasingly used in HTx recipients either as induction therapy or for the treatment of graft rejection. FDA approval for dacluzimab was in 1997 and for basiliximab in 1998. Both drugs are given intravenously and should be given within 2 to 24 hours after transplantation. Repetition should be done within 4 days (basiliximab) or 2 weeks (daclizumab). Due to the different half life time of the agents: 7.2 days for basiliximab and 20 days for daclizumab. Serum levels may be measured by ELISA and are recommended for basiliximab 0.2 ug/ml (about 20mg two times in four days) and for daclizumab 5 to 10 ug/ml to achieve a proper saturation of the receptors. When given 2.5 to 25 mg of basiliximab twice (day 0 and 4) approximately 90% of available IL-2 receptors on T lymphocytes are blocked. Saturation maintained with basiliximab for 4 to 6 weeks, with daclizumab for about 90 to 120 days. It was shown that anti-IL-2 receptor antibodies when combined with standard triple druge regime for induction therapy compared to placebo reduces rejection episodes [19, 20]. In a trial using daclizumab 1 mg per kg within 24 hours after HTx and repeated every two weeks

for a total dosage of five, less rejection rates compared to placebo were seen [19]. In a later study it was shown that two doses of daclizumab are similar effective in preventing rejection as five doses, with no negative effects on patient survival [21]. Specific blockade of IL-2 receptor may prevent rejection without inducing global immunosuppression; but even if in the initial studies no increased opportunistic infections rates were observed alike to all IS agents increased risk of infection is still present. Similar to polyclonal antibodies allergic reactions are serious side effects. Anti-IL-2 receptor antibodies are only part of a multiple drug regime. There is a higher risk of lymphoma. Other side effects like nausea, vomiting, diarrhea, tremor, insomnia, headache, tremors, flu symptoms or swelling of peripheral tissue have been reported. A cytocine release syndrome has been reported as well. If anti-IL-2 receptor antibodies are as effective as polyclonal antibodies is still controversial [22, 23].

### 3.3 Calcineurin inhibitors

Calcineurin (CN) is an enzyme dephosphorylating the nuclear factor of activated T-cells complex (NF-ATC) which is in charge for the transcription promotor of Interleukin 2 (IL-2) production. CN is activated when an antigen-presenting cell interacts with a T cell receptor leading to an up-regulation of IL-2 production. IL-2 itself activates T-helper lymphocytes and stimulates the production of cytokines [24]. It is discussed that the absolute amount of produced IL-2 influences the extent of the immune system. Drugs blocking CN are named Calcineurin Inhibitors (CNIs); Cyclosporine A (CsA) and Tacrolimus (TAC) are the most prominent agents out of this group. For all CNIs nephrotoxic and neurologic side effects are an issue and dose reduction or even avoidance of CNIs in HTx protocols have been studied extensively. Nevertheless CNIs are still a major part of IS therapy after HTx.

#### 3.3.1 Cyclosporine A

Cyclosporine A (CsA) is a lipophil, cyclic polypeptide consisting of 11 amino acids. It binds to cyclophylin (CpN), forming a complex which blocks C, resulting it, resulting in a suppression of activated T-cells and B-cell function. In 1971 CsA was isolated from the fungus Tolypocladium inflatum, found at the Hardanger Vidda in Norway. It was first investigated as anti-fungal antibiotic but the antibiotic spectrum was too narrow for clinical use. Its immunosuppressive activity found in 1972 was first reported in 1976 by Borel [25]. Thereafter the effectiveness in animal and human studies was investigated by Calne and his group in Cambridge [26]. They soon discovered that CsA improved heterogenic heart allografts in rats [27]. The effectiveness of CsA was confirmed in human studies in the filed of renal transplantation reported by Calne [28, 29]. These studies already recognizing the disadvantages of CsA, like the high rate of lymphoma [28] and its nephrotoxic side effects [30, 31]. It was the Stanford group who introduced CsA into clinical practice for HTx [17]. After animal research with heterotopic and orthotopic HTx in monkey, they introduced CsA to 66 patients and achieved a one year survival of 80%. At that time the starting dose of CsA was 18mg/kg per day combined with AzA and corticosteroids. European countries followed this protocol [32, 33]. Today when starting CsA recommended dosages are: intravenously (i.v.) application: either 2 to 4 mg/kg once a day continuous over 24 hours or over 4 to 6 hours, 1 to 2 mg/kg twice a day over 4 to 6 hours; oral application: 8 to 12

mg/kg/day in 2 divided doses is common. Afterwards dosage is adjusted to target trough levels and dosage reduction is aimed as low as 3 to 5 mg/kg/day.

When CsA is given per oral it is resorbed in the upper intestinal tract 30 to 60 minutes after the drug intake. The resorption is influenced by ingestion especially by grapefruit juice. The resoprtion half time is about 60 minutes. CsA is metabolized by the p450-3A enzyme in the intestinal wall epithelium. After passing the portal blood stream only 30% of the original CsA suspension will be in the systemic blood stream. The first commercially available oral formulation was very variable on absorption and blood concentration and it was tried to overcome this effect [34]. At the beginning of the 1990ies a new Cyclosporine microemulsion (Sandimmun Neoral, Novartis, Basel, Switzerland) was developed, resulting in a higher bioavailability and reducing the individual deviation attributed to ingestion. The new suspension reaches the maximum blood concentration after 1.5 to 2 hours [35, 36]. CsA is lipophil and the highest concentrations are found in the adipose tissue and in the liver. It is eliminated with a mean half time of 6 to 8 hours mainly across the liver, only 6% across the kidney. Elimination half time in children and lower in women or patients with chronic liver disease [37].

When CsA was introduced to clinical practice the rejection monitoring and drug monitoring was at its beginning. Clinical practice rejection monitoring was done by series of ECG to see voltage drops. Drug monitoring was done by the toxic side effect of AzA, monitoring the absolute T-cell number to see a severe depression. None of these methods were practicable for CsA monitoring as it is not affecting the T cell count. It became clear that a better monitoring of drug availability and a better monitoring of rejection episodes are necessary. The introduction of endomyocardial biopsy (EMB) made histologic examination possible [38]. CsA treatment and rejection monitoring with EMB resulted in a significant reduction of rejection episodes but incidence of malignant lymphoma and early renal dysfunction increased drastically [17, 28, 29, 39]. Measurement of CsA concentration in the blood stream was initiated; at first hindered as there are over 20 metabolits of CsA and the concentration itself in the blood stream is low. Today tow different methods are used for CsA measurement: In clinical practice the immunoassay (IA) is the most practicable. Different IAs have been introduced, like the radioimmunoassy, enzyme-multiplied immunoassay and florescence-polarisations immunoassay; all are using antibodies to CsA. The more specific method is the high-performance liquid chromatography (HPLC) which may be combined with mass spectrometry (MS). Measuring CsA concentration may be done before the patient takes the drug (pre-dose level, C0 measrument) or 2 hours after the intake of the drug (C2 measurement, 2 hours post dose). The C0 level is the more frequent and commonly used measurement but the C2 shows better correlation with the area under the curve and acute rejection episodes. A better prediction of long-term graft survival by C2 measurement was reported as well [40].

Finding the optimal dose and blood level for CsA treatment was and is still a challenge. The The initial Stanford protocol included ATG, corticosteroids and CsA with an initial dose of 18mg/kg followed by 10mg/kg per day [7]. The protocol was modified and CsA was adapted to the measurements of CsA blood trough levels, using a target area of 100 to 300 ng/ml, followed by a further decrease to 100 to 300 ng/ml for the first month and then

lowered to 50 to 150 ng/ml in combination with AzA and ATG (for the first 7 days after HTx). This trend of avoiding high dosage of CsA to reduce the incidence of lymphoma and avoid CNI-induced nephrotoxicity has not ended yet. With the introduction of Everolimus a further dosage reduction of CsA without losing effectiveness was possible [41, 42].

Co-administration with CsA will increase serum levels of HMG-CoA reductase-inhibitors, strong inhibitors of CYP450-3A4 significantly increase the blood concentrations of CsA. Sulfonamides, rifampin and carbamacepine reduce CsA concentrations.

### 3.3.2 Tacrolimus

Tacrolimus (TAC) blocks the CN by forming a complex with the FK506 binding protein resulting in the suppression of T-lymphocyte activation and cytokine production (IL2, 3 , 4, Interferon and tumor necrosis factor [TNF]). The structure of the macrolide antibiotic isolated from Streptomyces tsukubaensis is more similar to Rapamycin than to CsA. TAC was described seven years after the introduction of CsA [10] and found to be 100 times more potent [43]. It was first clinical used in 10 HTx recipients at the University of Pittsburgh in combination with steroids [44, 45]. When given per oral its absorption half-life is about 5 to 6 hours and the bioavailability is about 20%, depending on the intake of food (fat food reduces the bioavailability, grapefruit juice increases the blood concentration); it is mainly absorbed in the duodenum and jejunum, far less in the ileum and colon. 75 – 99% bind to proteins and the elimination half-life is 11.7 hours. Its bioavailability is higher in patients with impaired liver function. TAC has a large inter- and intraindividual variation in the pharmacokinetics. Extraction is mainly through the stool and it can not be removed by dialysis. Similar to CsA TAC should be given in two divided dose every 12 hours starting orally with 0.1 to 0.3 mg/kg/day, intravenously 0.01-0.03 mg/kg/day. Intravenously dosage in pediatric HTx might be raised up to 0.03 to 0.05 mg/kg/day.

Monitoring of the trough level is commercially done by an enzyme-linked immunosorbent assay (ELISA) or microparticulate enzyme immunoassay. Drug interactions are similar to CsA (inhibitor or inducers of P4503A4 may alter TAC level).

TAC seems to reduce the numbers of rejection episodes compared to CsA; in 1992 an actuarial freedom from rejection in the TAC group at 90 days after HTx of 41% and 28% of recurrent rejection was reported [44]. Especially in children TAC is increasingly used [46].

Until recently TAC was marked as Prograf (Astellas Pharma US, Inc., Deerfield, IL) and had to be taken twice a day similar to CsA (Sandimune Neoral, Novartis Pharmaceuticals, Basel, Switzerland); now a retard drug was released named Advagraf (Astellas Pharma US, Inc., Deerfield, IL), which may be taken just once a day. It was studied in renal and liver transplant patients; approval for HTx is investigated.

Even if very close related to CsA there are clinical relevant differences especially regarding side effects of the drug. TAC has a higher incidence of de-novo diabetes mellitus, a higher rate of anaemia and is increasing the tonus of the muscle. CsA on the other side leads to gingival hyperplasia, arterial hypertension, hirsuitsm, and increases liver laboratory values.

### 3.4 Purine synthesis inhibitors

Purine synthesis inhibitors (also called Antimetabolites) can halt cell growth and cell division either in a very unselective way (Azathiporine, [AzA]) or a more specific way (Mycophenolate Mofetil, Enteric-coated mycophenolate mofetil). Since the beginning of modern transplantation medicine purine synthesis inhibitors (AzA) have been part of the IS protocol. Between 2000 and 2009 the reported use of purine synthesis inhibitors to the international registry for heart and lung transplantation (International Society for Heart and Lung Transplantation, ISHLT) as maintenance therapy in HTx recipients was over 85% [12].

#### 3.4.1 Azathioprine

The pro-drug of 6-Mercaptopurin, a thiopurin substance, called Azathioprine (AzA) is a purine analogue IS drug which has antiproliverative effects especially on fast growing cells; i.e. T-cells and B-cells. AzA is metabolized to 6-Mercaptopurin which is less effective [47, 48]. AzA blocks the mitosis of cells resulting in an inhibition of proliferation of activated T and B lymphocytes and it seems that AzA is blocking the production of IL2 too. Nevertheless its complete mechanism of action is still not fully understood. The antiprolivaertive effect is not limited to T and B cells but also on bone marrow, hepatic or other cells. This leads to its severe side effects: bone marrow depression resulting in leucopenia and thrombocytopenia and its hepatotoxic side effects. Other side effects like nausea, vomiting or diarrhoea have been reported mainly at higher doses. Long term treatment might be associated with acute pancreatitis.

AzA was one of the first drugs used to prevent allograft rejection and its first human use in HTx was reported by the Stanford group [49]. The Standford protocol used AzA 1.5-2.5 mg/kg per day combined with corticosteroids. Today starting dosage recommendations is once a day 3 to 5 mg/kg orally or i.v. and may be reduced to 1 to 3mg/kg as maintenance therapy.

Its peak plasma concentration is reached within 1 to 2 hours after oral intake and its plasma half-life time is 3 to 6 hours. AzA is eliminated mainly by the kidney.

One of the weak points of AzA treatment is the unspecific monitoring. Daily dosage administration is still adapted depending on the toxic side effects trying to target the white blood cell count between 4000mm$^3$ and 6000mm$^3$. Lately there are reports of monitoring AzA treatment by blood concentrations of 6-thioguanin [50]. When AzA is combined with allopurinol the dose should be reduced to 75% to avoid severe pancytopenia as allopurinol affects the metabolism of 6-Mercaptopurine. AzA may reduce the anticoagulant effect of Warfarin [51].

AzA had a major positive impact on post-transplant outcome but due to its unspecific way of action, severe side effects and the disadvantage of specific monitoring AzA was replaced in many IS protocols. On the other hand it is increasingly used in evolving countries due to its lower costs.

#### 3.4.2 Mycophenolic acid

Mycophenolic acid (MPA) is the activated IS species of mycophenolate mofetil (MMF). MPA is derived from the fungus Penicillium stoloniferum and was marked as MMF. To improve its

bioavailability mycophenolate sodium was developed (see 3.4.2.1). MMF is a dehydrogenase controlling the synthesis rate of guanine monophosphate resulting in an inhibition of purines. Compared to AzA it specifically suppresses proliferation of T and B lymphocytes without severe bone marrow depression. In large multicentre trails the superiority of MMF over AZA was reported resulting in a progressively replacement of AzA by MMF [2,52,53,54].

Following oral administration it is rapidly metabolised 100% to MPA in the intestinal tract and the liver. No plasma MMF concentration will be measured in the blood, only MPA. MPA is bound 97% to albumin and metabolized in the liver and intestinal tract to a stable phenolic glucuronide (MPAG) which is not pharmacologically active. The maximum plasma concentration of MPA is reached about 1 hour after oral intake and its half-life time is around 16 hours (the same is true for MPAG). Over 90% of MPA is extracted by the kidney but MPAG is extracted by the bile. MPAG enters the enterohepatic cycling process; it is metabolised in the intestinal tract back to MPA and reabsorbed. This leads to a second peak in the plasma concentration after 6 to 12 hours of intake. No dosage adjustment in patient with renal impairment or haemodialysis is needed. In patients with a reduced glomerular filtration rate (GFR) a 3-to 6-fold higher MPAG area under the curve values were reported [55, 56]. In combination with TAC a 50% lower dose of MMF compared to a combination with CsA is recommended as CsA inhibits the hepatic extraction of MPAG leading to a reduced rate of enterohepatic recirculation. . MPA/MPAG can not be removed by hemodialysis. Side effects of MMF are vomiting, diarrhoea and other gastrointestinal side effects [57]. Diabetes and necrosis of bones have been related to MMF. A study were MMF was tested in pediatric HTx recipients showed that genetic polymorphism can directly Influence adverse events of MMF [58].

Initial trials using MMF used standard dosage of 1g in combination with CsA and did not use therapeutic drug monitoring; today dosage recommendation is 1g to 1.5 g twice a day orally or i.v. but when given i.v. dosage shoulkd be given at least over two hours.

Due to the complex pharmacokinetics of MPA and not adequately reflected MPA trough concentrations when combined with TAC, drug level measurement of MPA is still not widely common. HPLC with ultraviolet detection and mass spectrometric may be used to measure free MPA concentrations. Some centres describe the use of an enzyme-multiplied immunoassay technique. Simultaneouse application of acyclovir, ganciclovir and high doses of salicylates are enhancing plasma concentrations of MPAG; antacids, colestyramin and CsA are lowering it. To reduce the gastrointestinal side effects of MMF it was coated (see 3.4.2.1).

#### 3.4.2.1 Enteric-coated Mycophenolate sodium

Enteric-coated Mycophenolate sodiumfortic (EC-MPS) is an enterie formulation of mycophenolate sodium (a prodrug of MPA). MPA reversible inhibits the inosine monophosphate dehydrogenase and the pathway of guanosine nucleotide synthesis which affects B and T lymphocytes whereas other cell types can utilize salvage pathyways for purine synthesis. The coating of mycophenolate sodium should reduce the gastrointestinal side effects [59]. In renal transplant recipients a dosage of 720 mg EC-MPS twice a day was therapeutically equivalent to MMF 1000 mg twice a day with comparable safety profile [60].

Dosage recommendation in HTx recipients is 720mg twice a day either orally or intravenously. Optimal measurement of EC-MPS plasma concentration due to its delay in reaching maximal blood concentrations compared to MMF, is yet not clarify (C0, C2, C4, C6).

### 3.5 Proliferation signal inhibitors

Proliferation signal Inhibitors (PSI) (also named mammalian target of rapamycin (mTOR) inhibitors) include two important drugs currently available for organ transplantation: Rapamycin (Rapa) or Sirolimus (SRL) and Everolimus (EvE). Four decades ago Rapa was extracted and its antifungal effects reported [61]. Intensive research resulted in the discovery of the target of rapamycin named mTOR. mTOR is a serine-threonine kinase which is a transducer of information from growth factors and energy sensors within the cell. Both drugs form a complex with the intracellular binding protein FKBP-12, (similar to FK 506) but contrarily to TAC the PSIs inhibit the activity of mTOR. This leads to an arrest of a cell cycle in the mid-to-late G1 phase [61, 62]. While FK 506 is suppressing lymphokine production and blocking activation of T-cells, PSIs inhibit cells proliferation by impairing their response to growth-promoting lymphokines [63, 64]. They are also used in other areas of medicine like oncology or interventional cardiology (drug eluting stents).

#### 3.5.1 Rapamycin

Rapamycin (Rapa) is a macrocyclic lactone with antifungal, antibiotic and IS properties. It was discovered in 1965, extracted out of soil taken from Rapa Nui in New Zeeland [65]. Its IS effects were discovered in the 1990s [61]. During the approval studies for Rapa the anti-tumor effects of Rapa and its analogues like EvE were found introducing them in oncology and for the prevention of restenosis after percutaneous coronary angioplasty.

Rapa has structural similarities to FK 506 binding protein but it forms complex with FKBP12 which results in an inhibitor of the mTOR [66]. This leads to suppression of T and B cells and decreases the population of dentritic cells who present antigen to T cells during activation [67].

The bioavailability of Rapa is 20% and decreases with food rich in fats (see 3.5.2); 92% of Rapa binds to albumin, is metabolism extensively in intestinal wall via p-glycoprotein and in the liver by CYP3A4. Seven major metabolites are known but 90% of the IS activity is done by Rapa; close to 90% is eliminated by the liver only 2% by the kidney. In contrast to EvE half-life time of Rapa is about 62 hours ± 16 hours allowing one single daily dose.

A loading dose for Rapa on the first post-transplantation day is recommended; in renal transplantation the loading dose should be 3 times the estimated maintenance dose (normally 2mg), in HTx recipients 15mg are given followed by a maintenance dose of 5mg and further guided by trough levels. The total dosage must no exceed 40mg per day; if a higher dose is needed it should be divided over a period of 2 days. In children with a body weight below 40 kg initially a loading dose of 3mg/m$^2$ and a maintenance dose of 1mg/m$^2$ daily is recommended. If CNI therapy is reduced, Rapa dosage should be increased according to the targeted trough levels. In patient with severe hepatic impairment Rapa dosage should be reduced.

Routine clinical measurement is done with chromatographic methods. Major side effects of Rapa are swelling in different tissues, prolonging healing of wounds, increasing cholesterol and triglyceride levels, proteinuria as well as blood pressure. Rapa induced interstitial lung disease like pneumonitis have been observed [68-70]. When combined with CNIs, CNIs dosage reduction is necessary otherwise worsening renal function will develop. Rapa recommended blood trough levels in combination with CNIs is between 4 to 12 ng/ml, without CsA a four times higher Rapa dosage might be needed (CsA/CNIs suppress the metebolizion of Rapa), the recommended blood trough levels is increased between 12 to 20 Ng/ml depending on the time after transplantation. This is also the reason why Rapa intake when combined with CNIs is recommended four hours after CNI administration. Otherwise Rapa enhance the toxic effect of CNIs with an increased risk of CNI induced hemolytic uremic syndrome, thrombotic thrombocytopenic purpura and thrombotic microangiogiopathy. Drugs inducing CYP3A4 (Rifampicin) will decrease, strong inhibitors (Macrolides, Ketoconazole, Itraconazole) will increase Rapa blood levels. Similarly to CNIs grapefruit juice increases plasma concentration of Rapa. According to the last ISHLT report Rapa is currently used up to 20 % of HTx recipients [12].

### 3.5.2 Everolimus

Everolimus (EvE) is an analogue of Rapa and differs only by one extra hydroxyethyl group at position 40; still this leads to some differences. EvE blocks growth factor-mediated proliferation of cells including vascular smooth muscle cell through a CA2+ independent signal [71]. Following oral intake EvE is rapidly absorbed and reaches its maximal blood concentrations after 1 to 2 hours. The oral bioavailability is approximately 30% [72-75] and it is altered by food; a high-fat meal is slowing down the absorption of EvE. It is recommended that EvE is taken constantly either with or without food. EvE undergoes major metabolism with none of the metabolites reaching significantly IS activity. Its half-life time is 28 hours and compared to Rapa (62 hours) much shorter. Initial dose may be 0.75 mg twice a day, no loading dose is necessary.

EvE has a more rapid time to steady state compared to Rapa (4 versus 6 days). EvE binds to plasma proteins about 75% to 80% and is mainly eliminated in the liver, only 5% are extracted across the kidney. In patient with severe hepatic impairment EvE dosage should be reduced. PSIs and CNIs are metabolised by cytochrome P4503A4 (CYP3A4) isoenzyme leading to reduced clearance of EvE when CNI is given. Pre-clinical research reported of no nephrotoxicity of EvE [76] but when it was first clinical used combined with full dose CsA it showed worsening renal function [77, 78]. For that reason FDA approval was refused, but the European Medicine Agency (EMEA) approved EvE for further studies. In a prospective multicentre study the possibility of dose reduction of CsA combined with EvE resulted in stable renal function without loss of efficacy [79]. Further trials confirmed this [41, 42, 80]. Besides this interaction drugs who strong induce CYP3A4 will decrease, strong inhibitors will increase EvE blood levels. Reported EvE blood trough levels are within 3 to 8 ng/ml. Drug monitoring is done by HPLC coupled with mass spectrometry and an immunoassay is being developed. EvE showed to have antiproliferative effects delaying the onset of cardiac transplant vasculopathy and reducing the rate of CMV infections [77, 81]; it is increasingly used, up to 2.6 % in HTx recipients in the years 2008 and 2009 [12]. Due to the favourable effects it may be used in children and is currently investigated (RAD 2313).

### 3.6 Immunosuppressive regimes

At the beginning little was know about interaction, side-effects and combination of IS drugs. Nowadays with many different IS drugs acting at different receptors and stages of the immune system more effective and less toxic regimes may be used.

It was revealed that the combination of different acting IS drugs with adjusted dosage enhance their effectiveness and reduce toxicity. To avoid nephrotoxic side effects of CNIs and to achieve a high IS, over 50% of the centres reporting to the ISHLT are using an induction therapy (20% using polyclonal antibodies, 30% use IL2 receptor antibodies) [12]. Conventionally for maintenance therapy patients are treated with a triple drug regimens, consisting of a CNI (CyC, TAC), antiproliferative agent (AzA, MMF) and corticosteroids. Shortly after the introduction of CsA in 1980 Griffith and colleagues used CsA in combination with low-dose steroids in HTx recipients, tapering steroids from 200mg per day to 15 mg per day similar to the regime used by Starzel in renal and liver transplant recipients [82-84]. Combining CsA, AzA and Cortocosteroides, commonly called triple-drug immunsupression, evolved and showed improved survival for short, medium and long term follow-up [85, 86]. It increased 1 years survival after HTx from 60% to 80% and became the standard regime not only in the US but also in European countries over the next 30 years [87, 88]. The triple-drug protocol, even if modified (many centres skipping corticosteroids after a certain time) is still used around the globe. Adding a forth drug to the regime has been reported but became not standard [19, 89].

Still due to the well know side effects of IS, associated with a significant morbidity, discussion about reducing IS will continue. Reduce IS therapy with a mono or dual drug regimes are investigated. Recently a retrospective study involving 150 patients within 28 days after HTx maintaining recipients only on monotherapy with TAC has been published [90]. One has to notice that in IS monotherapy compliance is paramount and could result in a disastrous outcome. The conviction of currently experts in the field of IS is, that today's "standard" immunosuppression may be replaced by IS individualized for each patient on the basis of genomic profile, baseline risks for rejection and infection, and perhaps serial assessments of immune response after transplantation [91].

## 4. Immunosuppression for acute rejection

Different principles of IS treatment after organ transplantation have been established over time. After HTx numbers of rejection episodes and immune reactivity are highest within the first 3-6 months. Therefore one of the principles is to use the highest intensity of IS immediately after surgery and decrease it over the first year (Induction therapy (see 3.1), corticosteroid weaning (see 4.1.2); lowering blood concentrations of IS agents). The second principle is to rather admit more IS drugs with non-overlapping toxic side effects at a low dose rather than a higher and more toxic dose of a single drug. Therefore monitoring of the IS drug trough levels is of great interest; special caution must be paid to interaction of the drugs (lowering or increasing the blood levels) or i.e. diarrhea when orally taken. The goal is to avoid over-immunosuppression, which leads to infection and malignancy. This on the other hand may lead to late acute rejection episodes even if it is rare [92]. Corner stone of the treatment are corticosteroids, both oral or intravenous, ATG (see 3.1 Polyclonal Antibodies),

IL-2 receptor blockers (see 3.2 Interleukin 2 receptor antibodies) or murine monoclonal antibody (see 4.2). The type of treatment depends on clinical status of the recipients (if the rejection is hemodynamic compromising [reduced cardiac output, decreased pulmonary artery saturation, elevated wedge pressure, reduced cardiac index]) the histology degree and severity of the rejection. Moderate to severe rejection episodes need therapy: intravenous corticosteroids for three to five days, intensify oral maintenance IS therapy and eventually change to another protocol; if there are recurrent rejection episodes TAC or EvE may be considered. In patients with hemodynamic impairment additionally polyclonal or monoclonal antibodies or plasmapheresis should be kept in mind.

### 4.1 Corticosteroids

Corticosteroids inhibit the synthesis of cytokines, but the exact mechanism of action in solving acute rejection is not jet completely understood. Steroids suppress besides i.e. IL-6, interferon gamma, TNF, the production of IL-1 resulting in a diminished production of IL-2 by activated T cells. In animal models it was reported that steroids induce lymphocytolysis which was not proved in humans. Synthetic pharmaceutical drugs with corticosteroid-like effect are used in a variety of treatments. Prednisone is the most used synthetic steroid and is five times more potent compared to cortisol. Its bioavailability is 70% when orally taken and it is metabolised in the liver. Natural steroid hormones have a very short half-life time, synthetic steroids like prednisone have a half-life time of 1 hour. The side effects of long-term corticosteroids are commonly known; dosage reduction below the cushing threshold or even weaning them off are valid options. Nevertheless for acute rejection episodes intravenously high dose corticosteroid treatment is still necessary and effective. After solving the acute phase of the rejection episode orally corticosteroids should be introduced to treatment for at least some time or if already part of the maintenance IS protocol its dosage should be increased.

#### 4.1.2 Corticodsteroid weaning

Over 85% of the centres reporting to the ISHLT are currently using corticosteroids within the first year after HTx, after 5 years about 50% are still using corticosteroids [12, 46]. The negative side effects of steroids are well known such as i.e. weight gain, glucose intolerance, dyslipidemia, osteoporosis, or cartaract. Most of the rejection episodes are within the first year after HTx and most of the steroids can be taken off over a course of a few months. The rationale for diminishing the overall use of corticosteroids is the availability of new IS agents acting more selective compared to synthetic corticosteroids. Numerous protocols were established, most of them use a high dosage of corticosteroids intra-operative (when starting reperfusion) and within the first days (as part of an induction therapy). When oral dosage is given different possibilities are available such as i.e. fixed dose of 15 mg per day or prednisolon 0.05 to 2mg/kg divided by one to four doses per day. After weeks of months the dose is reduced achieving a dose below the cushing threshold. Some study groups report to take off corticosteroids as early as 8 weeks after HTx [90] or over a course for several months following a simple weaning protocol guided by daily cortisol measurments to avoid onset of adrenal insufficiency (level > 8 μg/dl continue to wean, otherwise continue steroid therapy) (Baran DA. A prospective trial of steroid discontinuation in stable heart

transplant patients as guided by serum cortisol measurement. International Society for Heart and Lung Transplantation 2009, Abstract 431). Other weaning protocols decrese the daily prednisone dosage by 1mg each month starting at month 6 post HTx [93].

The question why long-term use of corticosteroids is still that present may have several reasons i.e. avoiding adrenal insufficiency or other potential effects when treatment is stopped but also the 'heritage' of this therapy as steroids once were nearly the only immunosuppressant choice for transplant recipients.

### 4.2 Monoclonal muromonab CD3 antibody

Muromonab-CD3 (brand name: OKT3) is a monoclonal antibody against CD3 antigen resulting in an inhibition of T-cell function by down regulation of CD3 positive cells. It was the first monoclonal antibody to be approved for clinical use in humans. Similar to polyclonal antibodies its way of administration is only intravenously. Recommended dosage is 5 mg per day, in pediatric patients (< 30kg body weight) initial dosage may be lowered to 2.5mg per day. The human body will produce human anti-mice antibodies, as OKT3 is like a mice-antibody explaining the loss of effectivity if given repeatedly. Toxic side effects besides the well know from all IS agents (higher infection rate higher rate of lymphoproliferative disorders) have been reported: cytokine-mediated first-dose reaction, pulmonary edema, aseptic meningitis, haemolytic-uremic syndrome. The first-dose reaction may include fever, rigors, nausea, vomiting, and diarrhea which will decrease with repeated exposure. Nevertheless steroids, antihistamines and antipyretics should be given along with OKT3 to minimize these side effects. It takes about a week after ending the OKT3 treatment until the T cell function returns to normal.

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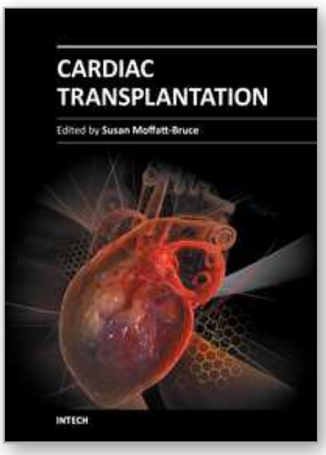
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We are truly in an era of change not only in terms of technology but in the type of patient we are caring for. That is why I feel this book is exciting in that it presents the team approach to the transplant patient. I am confident that the pioneers of cardiac transplantation would be pleased with our response to challenges in healthcare today and be pleased with the final product.

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