Diplomarbeit

Retrospective evaluation of the rate of infectious complications in recipients of expanded-criteria donor kidney transplants

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Linz, am 24.08.2018 *Matthias Neuböck, eh.*

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Zusammenfassung

Hintergrund: Auf Grund von steigender Nachfrage von Spendernieren kommen Organe von Spenderinnen/Spendern mit erweiterten Kriterien (i.e. Spender >60 Jahre; oder 50-59 Jahre und Kreatinin > 1,5 mg/dl oder Hypertonus oder eine zerebrovaskuläre Todesursache) – "expanded criteria donors (ECD)" – zum Einsatz. Es wird angenommen, dass diese älteren Nieren anfälliger für nephrotoxische Effekte von Calzineurininhibitoren (CNI) sind. Deswegen erhalten in unserem Zentrum seit September 2014 Empfängerinnen/Empfänger solcher ECD-Nieren eine Induktionstherapie mit Anti-thymozytenglobulin (ATG), um niedrigere CNI-Spiegel zu erreichen. Im Zuge dieser Studie wurden Patientinnen/Patienten, bei denen derartige Induktionstherapie zur Anwendung kam, mit früheren Empfängerinnen/Empfängern verglichen, die eine Standard-Immunsuppression mit IL-2 Rezeptorantagonisten (IL-2RA) erhielten.

Material und Methoden: Empfängerinnen/Empfänger von ECD-Nieren wurden erhoben und sowohl klinische Daten als auch Laborparameter aus digitalen Arztbriefen und medizinischen Dokumenten entnommen. Verglichen wurde die Rate an schweren Infektionen, welche definiert waren als infektbedingte stationäre Aufnahmen. Die beobachtete Zeitspanne war das erste Jahr nach der Transplantation.

Ergebnisse: Zwanzig Empfängerinnen/Empfänger (mittleres Alter 54±11 Jahre, n männlich/weiblich 18/2, durchschnittliche Dialysedauer 37±21 Monate) wurden in der IL-2RA-Gruppe erhoben und mit zwanzig Empfängerinnen/Empfängern (mittleres Alter 57±10 Jahre, n männlich/weiblich 9/11, durchschnittliche Dialysedauer 44±40 Monate) in der ATG-Gruppe verglichen. Es wurden keine signifikanten Unterschiede zwischen den Spenderinnen/Spendern der IL-2RA-Gruppe (mittleres Alter 58±12 Jahre, letztes gemessenes Kreatinin 0,8±0,25 mg/dL, Hypertonus 35%, zerebrovaskuläre Todesursache [CVA] 80%) und der ATG-Gruppe (mittleres Alter 63±7 Jahre, letztes gemessenes Kreatinin 0,76±0,17 mg/dL, Hypertonus 40%, CVA 65%) gefunden. Die FK506 Spiegel nach drei (10,5±8,96 vs. 6,6±3,23 ng/mL; $p<0,05$), aber nicht nach sieben (8,1±2,21 vs. 7,86±3,86 ng/mL; $p=0,25$) Tagen waren signifikant höher in der IL-2RA-Gruppe, verglichen mit Patientinnen/Patienten, die mit ATG induziert wurden. Insgesamt 13 Patientinnen/Patienten (6 (30%) in der IL-2RA-Gruppe, 7 (35%) in der ATG-Gruppe)

mussten während des Beobachtungszeitraumes auf Grund eines Infektes stationär aufgenommen werden, 1 Patientin/Patient (5%) der IL-2RA-Gruppe litt an zwei schweren Infektionen. Im ersten Monat nach der Transplantation musste in der IL-2RA-Gruppe niemand stationär aufgenommen werden, während 1 Empfängerin/Empfänger (5%) der ATG-Gruppe an einem schweren Infekt litt. Zwischen dem zweiten und sechsten Monat nach der Transplantation wurden 5 Patientinnen/Patienten (3 (15%) in der IL-2RA-Gruppe, 2 (10%) in der ATG-Gruppe) auf Grund eines Infekts hospitalisiert. Im zweiten Halbjahr nach der Transplantation gab es keine Unterschiede zwischen den beiden Gruppen, es wurden 8 Patientinnen/Patienten (4 (20%) in der IL-2RA-Gruppe, sowie 4 (20%) in der ATG-Gruppe) hospitalisiert.

Conclusio: Diese Studie zeigt, dass es keine signifikanten Unterschiede in der infektbedingten Hospitalisierungsrate von ECD-Nieren-Empfängerinnen/Empfängern gibt, wenn man Patientinnen/Patienten, die mit IL-2RA induziert wurden mit ATG-Empfängerinnen/Empfängern vergleicht. Obwohl die FK 506 Spiegel in der IL-2RA-Gruppe drei Tage nach der Transplantation signifikant höher waren, zeigten sich keine Unterschiede in Patientinnen/Patienten in Bezug auf delayed graft function oder in der Langzeit-Nierenfunktion. Mehr Patientinnen/Patienten müssten in die Studie inkludiert und analysiert werden, um konkrete Empfehlungen zu machen.

Abstract

Background: An increasing demand for renal allografts has led to the use of kidneys from expanded criteria cadaveric donors (i.e. donors >60 years; or 50-59 years and creatinine > 1.5mg/dL or hypertension or death from cerebrovascular accident). These older grafts are thought to be more susceptible to nephrotoxic effects of calcineurin inhibitors (CNI). Therefore, at our center, starting in September 2014, recipients of ECD allografts received induction therapy with anti-thymocyte globulin (ATG), while targeting lower CNI through levels. This study evaluated recipients in whom this strategy was employed and compared them to prior recipients who received standard immunosuppression (IL-2RA) using anti-IL-2 receptor antibodies. Recipients of allografts from non-heart beating donors were included. Rates of hospitalisations and infectious complications were compared

Material and methods: Recipients of ECD allografts were identified and clinical as well as laboratory parameters extracted from electronic medical records. Major infections were defined as infections requiring hospitalisation. The follow-up period was one year after transplantation.

Results: Twenty recipients (mean age 54±11 years, n male/female 18/2, mean dialysis vintage 37±21 months) were identified in the IL-2RA group and compared to twenty recipients (mean age 57±10 years, n male/female 9/11, mean dialysis vintage months 44±40) in the ATG group. There were no significant differences between donors in the IL-2RA (mean age 58±12 years, last creatinine 0,8±0,25 mg/dL, hypertension 35%, cerebrovascular cause of death [CVA] 80%) and the ATG (mean age 63±7 years, last creatinine 0,76±0,17 mg/dL, hypertension 40%, CVA 65%) group. FK506 through levels after three (10,5±8,96 vs. 6,6±3,23 ng/mL; p<0,05) but IL-2RA seven days (8,1±2,21 vs. 7,86±3,86 ng/mL; p=0,25) were significantly higher in IL-2RA compared to ATG patients. A total of 13 patients (6 (30%) in IL-2RA group, 7 (35%) in ATG group) required hospitalisation during the follow-up, 1 patient (5%) of IL-2RA group suffered from 2 major infections. During the first month after transplantation IL-2RA group showed no hospitalisations, while 1 patient (5%) of ATG group was hospitalised. Between month 2 and 6 post transplantation 5 patients (3 (15%) in the IL-2RA group, 2 (10%) in the ATG group) suffered from a major infection. There was no difference in major infection rates

during the time between month 7 and 12 of the follow-up with 8 patients (4 (20%) in IL-2RA group as well as 4 patients (20%) in ATG group) being hospitalised.

Conclusions: This study shows that when comparing recipients of ECD renal allografts who were induced using IL-2RA compared to ATG there was no difference in the rate of major infections. Importantly, while early CNI through levels were significantly lower in ATG-induced patients, there was no difference in rates of delayed graft function or long-term graft function. To make any firm recommendations these data would have to be expanded and more patients would have to be included in the analysis.

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Glossary and abbreviations

ACEi	angiotensin-converting enzyme inhibitor
ACR	albumin-to-creatinine ratio
AER	albumin excretion rate
APC	antigen-presenting cells
ARB	angiotensin receptor blocker
AS	Alport Syndrome
ATG	antithymocyte globulin
BMI	body mass index
CKD	chronic kidney disease
CMV	cytomegalovirus
CNI	calcineurin-inhibitor
COPD	chronic obstructive pulmonary disease
CVD	cardiovascular disease
DM	diabetes mellitus
EBV	Epstein-Barr virus
ECD	expanded criteria donor
eGFR	estimated glomerular filtration rate
ESP	Eurotransplant senior programme
ESRD	end stage renal disease
ET	Eurotransplant
FSGS	focal segmental glomerulosclerosis
GFR	glomerular filtration rate
HIS	hospital information system
HIV	human immunodeficiency virus
HLA	human leucocyte antigen
IL-2	interleukin-2
IL-2RA	interleukin-2 receptor antagonist
IQR	interquartile range
KDIGO	kidney disease: improving global outcome
KDPI	kidney donor profile index
KDRI	kidney donor risk index
LKH	Landeskrankenhaus

M	mean
MDMD	modification of diet in renal disease
MDN	median
NHBD	non-heart-beating-donor
OEDTR	österreichisches Dialyse- und Transplantationsregister
OGDT	observatory on donation and transplantation
PCR	polymerase chain reaction
PTLD	post-transplant lymphoproliferative disorder
PVAN	polyoma-BK associated nephropathy
RAS	renin-angiotensin system
RRT	renal replacement therapy
SCD	standard criteria donor
SD	standard deviation
SGLT2	sodium-glucose cotransporter 2
VZV	varicella zoster virus

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1 Introduction

1.1 Chronic kidney disease

1.1.1 Definition

The function of the kidney is multifaceted including excretory, endocrine and metabolic processes. The Kidney Disease: Improving Global Outcomes (KDIGO) initiative defined chronic kidney disease (CKD) as abnormalities of kidney structure, function or both affecting one individual's health and lasting for at least three months. Possible structural alterations include but are not limited to cysts, malformations and tumours, while functional disorders may appear as, for instance, hypertension, oedema, altered output or altered quality of urine (1).

Given the fact that usually all functions of the kidney deteriorate in parallel, the glomerular filtration rate (GFR) as a component of the excretory function is widely considered as the best overall indicator of current kidney function. Therefore, provided that the abnormalities last longer than three months making it a chronic disease, either decreased GFR or the presence of at least one marker of kidney damage is needed to fulfil the criteria for CKD as shown in table 1 (2).

A confirmed decrease in kidney function leads to a broad range of complications derived from the kidney's various features. These complications not only include pharmacokinetic alterations in renally excreted drugs and metabolic and endocrine complications such as anaemia or metabolic acidosis, but also frailty and increased susceptibility to infections (3,4). Besides the risk of progression to end stage renal disease (ESRD), the increased risk of cardiovascular disease (CVD) constitutes a major complication of CKD. Individuals with decreased GFR and albuminuria show a remarkable increase of 10-year-risk of developing CVD compared to populations with normal kidney function, while they also show higher risk of progression to ESRD, which is the final stage for CKD (5,6). In fact, a CKD patient who has not yet been on renal replacement therapy (RRT) has the same risk of cardiovascular events as a patient with established coronary artery disease (7).

table 1: Criteria for CKD according to KDIGO 2012

either of the abnormalities present for ≥ 3 months	
decreased GFR	GFR < 60 ml/min/1,73m²
markers of kidney damage	albuminuria (AER ≥ 30 mg/24h; ACR ≥ 30 mg/g [≥ 3 mg/mmol]) history of kidney transplantation structural abnormalities detected by imaging abnormalities detected by histology electrolyte and other abnormalities due to tubular disorders urine sediment abnormalities

note: (2); abbreviations: CKD = chronic kidney disease; KDIGO = kidney disease: improving global outcome; GFR = glomerular filtration rate; AER = albumin excretion rate; ACR = albumin-creatinine ration

1.1.2 Classification

With the intention to consolidate a classification comprising cause and severity KDIGO strongly recommends categorizing CKD using Cause, GFR and Albuminuria referring to it as CGA staging. The cause was added to the classification to do justice to its role both for the prognosis of CKD and for the choice of treatment. Albuminuria, on the other hand, constitutes a good additional marker for severity and supplements GFR as an indicator of risk of CKD progression (2).
To achieve the categorisation of albuminuria, KDIGO chose a threshold of an albumin excretion rate (AER) of ≥ 30 mg/24 hours lasting for more than three months to be evaluated as CKD. An albumin-to-creatinine ratio (ACR) of ≥ 30 mg/g or ≥ 3 mg/mmol is regarded to be approximately equivalent to this threshold and thus is likewise applicable.

By sorting GFR into six and albuminuria into three severity levels, KDIGO developed a way of assigning each patient to one out of eighteen categories, each representing an assessment of both the risk and outcome of CKD, ranging from a low to a very high risk, as shown in figure 1.

It is important to mention at this point that the kidney undergoes profound changes in both structure and function during the process of ageing. Macroscopically one can observe a roughening surface, waning cortical volume masses and a rising number of renal cysts, while microscopically the histological signs of nephrosclerosis progress (8). Therefore, the physiological age-associated GFR decline must be considered when it comes to evaluating kidney function.

The mean natural GFR decline amounts to approximately 1 ml/min/1,73m² per year, being 0,75 ml/min/1,73m² in a study population in Marocco using estimated GFR (eGFR) as assessed by the modification of diet in renal disease (MDRD) equation and 0,95 ml/min/year in another study population in Norway using measured GFR (9,10). Nevertheless, an increased risk can be observed with decreased GFR or increased ACR regardless of the cause. Therefore, persistently decreased GFR or increased albuminuria are always inclusion criteria for CKD (2).

figure 1: prognosis of CKD according to KDIGO 2012
assessed by GFR and albuminuria categories

				GFR categories (ml/min/1.73m²) description and range						legend
				G1	G2	G3a	G3b	G4	G5	
				Normal or high	Mildly decreased	Mildly to moderately decreased	Moderately to severely decreased	Severely decreased	Kidney failure	low risk *(if no other sign of kidney disease or CKD)*
				≥90	*60-89*	*45-59*	*30-44*	*15-29*	*<15*	
persistent albuminuria categories description and range	**A1**	Normal to mildly increased	*<30 mg/g <3 mg /mmol*							**moderately increased**
	A2	Moderately increased	*30-300 mg/g 3-30 mg/mmol*							**high risk**
	A3	Severely increased	*>300 mg/g >30 mg/mmol*							**very high risk**

note: (2); abbreviations: CKD = chronic kidney disease; GFR = glomerular filtration rate; KDIGO = kidney disease: improving global outcome

1.1.3 Epidemiology

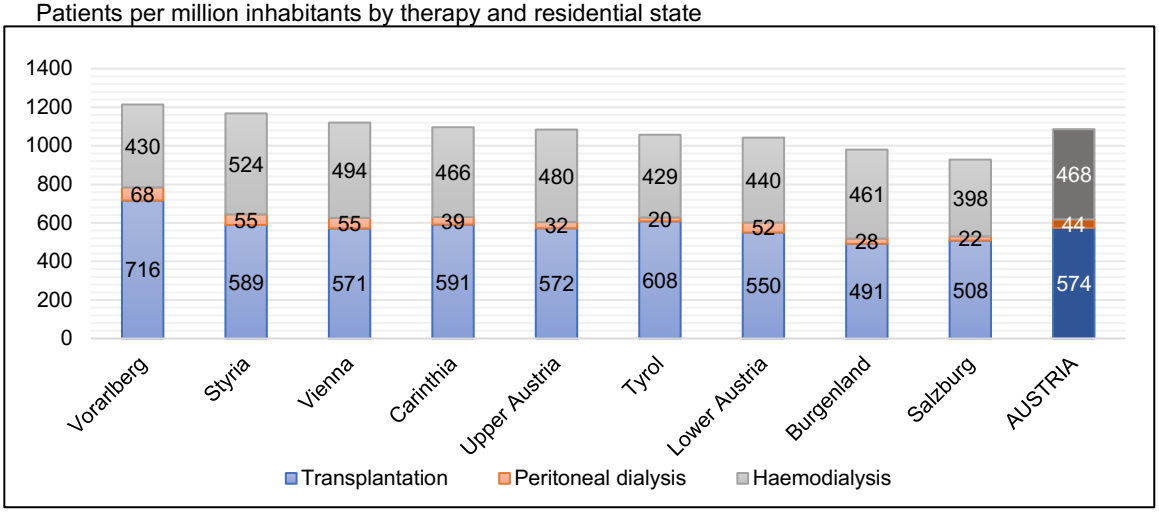
The overall mortality burden due to CKD rose by more than 80% from 1990 to 2010, making it a prevalent and substantial health burden (11,12).

According to a meta-analysis of the current epidemiological data, the global CKD prevalence is estimated to be in a range between 11 to 13%. However, studies concerning the prevalence of CKD still show great differences and high heterogeneity making a direct comparison difficult (13). Additionally, the differentiation essential for risk and outcome between the eGFR G3a and G3b stages has not been assessed in many studies. With more than half of the patients being categorised as stage G3 but not further specified in the meta-analysis, an exact assignment for the prevalence is pending (13).

In many countries, including Austria, it is not CKD prevalence but rather prevalence and incidence of RRT that are collected on a regular basis. The Austrian dialysis and

transplant register “Österreichisches Dialyse- und Transplantationsregister (OEDTR)” keeps accurate and systematic records of RRT patients in Austria. The annual report of 2016 revealed an average prevalence of RRT in Austria of 1086 patients per million inhabitants as shown in figure 2.

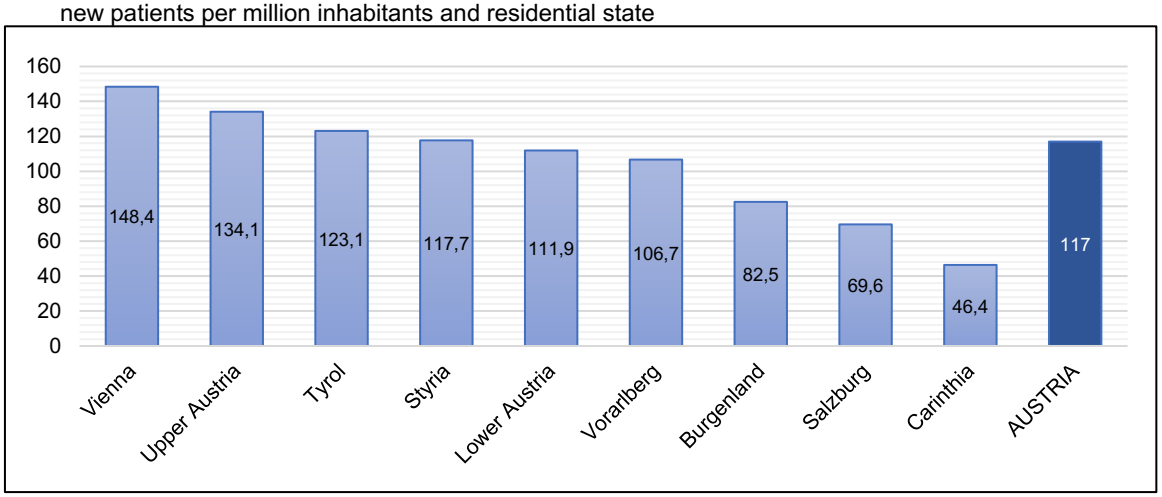
figure 2: prevalence of RRT in Austria on 31.12.2016 according to OEDTR
Patients per million inhabitants by therapy and residential state



note: (www.nephro.at); abbreviations: RRT = renal replacement therapy; OEDTR = österreichisches Dialyse- und Transplantationsregister

For 2016 that makes 9492 RRT patients in Austria thus an increase of more than 22% was noted compared to 2007. This corresponds to an annual incidence of 117 new patients per million inhabitants that were registered in Austria in 2016, as can be seen in figure 3 (14).

figure 3: incidence of RRT in Austria in 2016 according to OEDTR
new patients per million inhabitants and residential state



note: (www.nephro.at); abbreviations: RRT = renal replacement therapy; OEDTR = österreichisches Dialyse- und Transplantationsregister

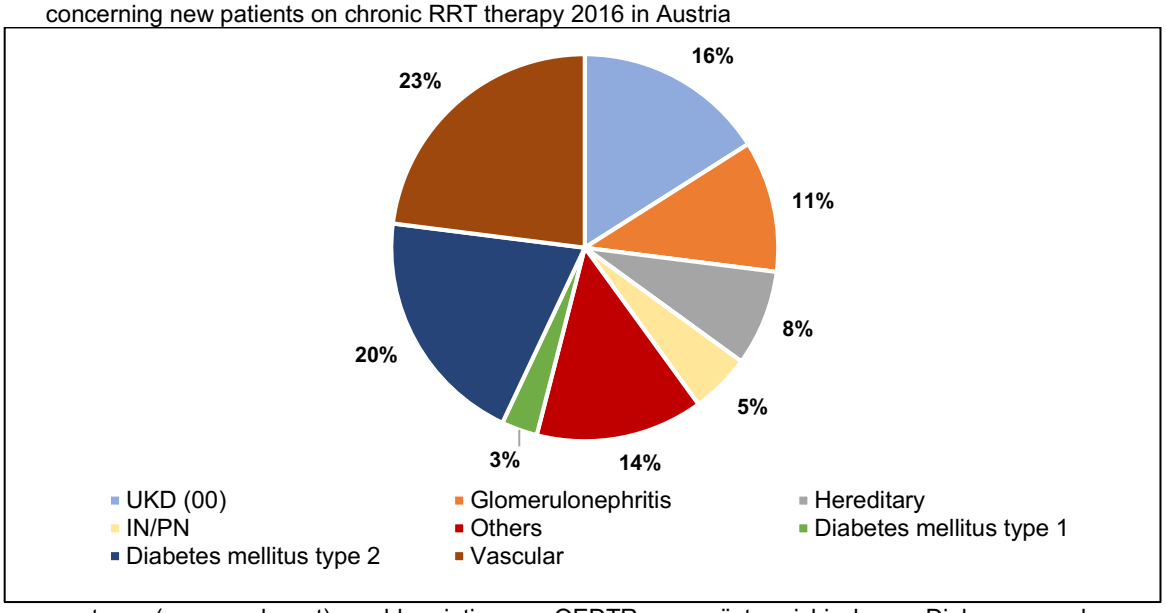
1.1.4 Aetiology

The causes of CKD vary widely between different countries and regions, depending, among other things, on socio-economic status and different life expectancies. As mentioned before, the prevalence of CKD is rising globally, which is attributable to the increase in the prevalence of the main risk factors for CKD led by diabetes mellitus (DM), hypertension and ageing population (15).
Parallel to this tremendous increase in prevalence especially in economically developing countries, one can observe a shift in the burden of disease from infectious causes, glomerulonephritis and the inappropriate use of medications to lifestyle-related causes. This explains the large differences between high-income and low-income countries (16).

From a global perspective, DM is the main cause of CKD with a further increase in the number of people affected still to be expected (15). With big differences due to variable ethnicities, healthcare systems and further factors, the prevalence of CKD among type 2 DM was reported to range from 27,9 to 77% (17). Furthermore, a meta-analysis of Tsai et al. suggests that substantial proteinuria and the male sex represent significant perpetuating factors for the advancement of CKD, while the prevalence of CKD is actually higher in women (18,13).

In Austria, conclusions about the causes of CKD can be drawn based on the primary renal diagnosis of new patients on chronic RRT. As shown in figure 4, vascular alterations and DM constitute the main causes for RRT reported in 2016 and together represent the disease leading to CKD in nearly 50% of cases.

figure 4: primary renal diagnoses according to OEDTR
concerning new patients on chronic RRT therapy 2016 in Austria



note: (www.nephro.at); abbreviations: OEDTR = österreichisches Dialyse- und Transplantationsregister; RRT = renal replacement therapy; UKD = unknown kidney disease; IN/PN = interstitial nephritis / pyelonephritis

1.1.5 Pathophysiology

The kidney consists of approximately one million single nephrons, which cannot be regenerated if lost. Each of these nephrons has a functional reserve which counteracts a decreasing total GFR by hyperfiltration in the case of loss of kidney mass occurring during the progression from CKD to ESRD. If a state of glomerular hypertension, equivalent to an increased filtration pressure, and elevated GFR in the remnant nephrons, endures, these nephrons start to hypertrophy (1,19).

Angiotensin II, a peptide hormone taking part in the renin-angiotensin system (RAS) initiating aldosterone secretion and vasoconstriction, plays a major role in the development of hyperfiltration. It is also considered to be associated with effects that lead to focal segmental glomerulosclerosis (FSGS) and, moreover, to increased permeability of the remaining glomeruli implicating proteinuria. Such tubular protein overload is associated with eventual tissue scarring and GFR loss (20).

By resulting in consecutive renal atrophy and thus more loss of kidney mass, a vicious cycle is evolving forcing the remaining nephrons to further increase their single GFR and therefore leading to even more loss of nephrons (1).

1.1.6 CKD progression

The rate and presence of renal function decline is different in CKD patients. Thus, it is important to recognise and for that matter define CKD progression. KDIGO suggests defining it based on either a drop in GFR category accompanied by a drop of at least 25% in eGFR from baseline, or based on rapid progression, which is the case with a sustained reduction in the eGFR of more than 5ml/min/1,73m²/year (2).

For clinicians it is difficult to predict CKD progression as there are many factors influencing likelihood and rate of it. These include the cause of CKD, GFR and albuminuria category, continuous exposure to nephrotoxic agents, hypertension, age, obesity, ethnicity and further laboratory parameters, for instance haemoglobin and bicarbonate (2). Although it is not yet clear how strong the impact of the individual factors on the progression of CKD is, KDIGO claims it to be essential to identify them, since some of them can be treated if present (2).

In some cases, CKD progresses to a point at which the kidney is not able to fulfil its functions anymore and is then called ESRD. The term is not synonymous with kidney failure but rather indicates that the function of the kidney has to be compensated for, and thus does not precisely define a certain level of kidney function (21). Patients suffering from ESRD account for more than 1% of the health-care spending in high-income countries, although not even 0,1% of the total population are affected (22). Levey et al. claimed that RRT patients are even consuming up to 5% of health care budgets (23). However, there is not enough evidence that clearly shows the financial benefit of early intervention in CKD patients; still it is possible that early diagnosis, treatment and management could generate big cost savings (22).

1.2 Management of CKD progression

CKD management is composed of several aspects. In addition to the controlling of further kidney injury, a normalisation of the single-nephron hyperfiltration, the management of CKD related complications and the preparation of the patient for RRT are goals of treatment (1). As mentioned before, there are numerous factors having an impact on CKD progression. To control further nephron injury, these factors must be recognised and, if possible, treated.

At the core of renocardioprotective therapy in patients with proteinuria stands the inhibition of the RAS with angiotensin-converting enzyme inhibitors (ACEis) and/or angiotensin receptor blockers (ARBs) (20). By reducing the GFR of the individual nephrons and also their glomerular filtration pressure, they lead to a decrease in proteinuria (1). The renoprotective effect is both reached by blood pressure control but also by the reduction of proteinuria and the resulting renal fibrosis.

The “renoprotection of optimal antiproteinuric doses (ROAD)” study by Fan Fan Hou et al. showed that, for that matter, an uptitration of the dosages of the ACEi benazepil and the ARB losartan to a maximum antiproteinuric effect rather than the conventional antihypertensive dosages resulted in a reduction of primary outcomes such as death, ESRD or doubling of serum creatinine for patients without diabetes (24).

However, not only the individual GFR and proteinuria, but also the total GFR decreases leading to a relief of the nephrons and on the other hand to elevated creatinine levels. This induced fall of GFR is important to be recognised as such by the physician and further must be explained to the patient, since it does not show a deterioration but rather inversely correlates with the renal function decline during long-term follow-up (25).

When it comes to non-proteinuric forms of CKD, however, inhibition of the RAS possibly has a benefit on CVD complications but does not impact progression to ESRD (1).

Obesity has long been known to be a risk factor in association with CKD. It is shown that bariatric surgery can substantially reduce filtration load, proteinuria and glomerular hypertension, although there is not enough data that shows whether the correction of obesity totally reverses CKD or rather delays its progression to ESRD (26). It is clear, though, that lifestyle modifications leading to normal body mass index (BMI) have a positive effect on the outcome of CKD patients and are therefore arealways a treatment target.

Patients who additionally suffer from DM have a special role when it comes to CKD management. Hyperglycaemia induces low sodium concentration at the macula densa by stimulating the reuptake of filtered glucose and sodium to a maximum leading to glomerular hyperfiltration (27). The underlying vasodilatation in the afferent arterioles is driven by the sodium-glucose cotransporter 2 (SGLT2) and cannot be controlled by inhibition of RAS but only by SGLT2 inhibitors. These show, in addition to beneficial effects on biomarkers such as blood pressure, glycaemia and albuminuria, significantly lower rates of cardiovascular events and also of CKD progression (28).

Regardless of the type of therapy, time is proven to be a decisive factor for the patient's outcome when it comes to CKD management. In Göttingen (Germany) 283 patients suffering from Alport syndrome (AS) have been followed for more than 20 years, as AS inevitably leads to ESRD. Gross et al. wanted to determine whether the RRT onset can be delayed and life-expectancy can be improved by early use of ACEi. The study showed that ACEi delay the progression to ESRD in a time-dependent manner. The authors further compared 15 sibling pairs, in which the younger siblings received earlier therapy and diagnosis than the older ones, since they got tested as soon as the older siblings first got their diagnosis. The median age at RRT onset in the younger siblings was 13 years higher than in the older ones (29). While the effects on the outcome are enormous when patients get treated before symptoms start, therapy onset once CKD stage G3 is reached only delays progression to ESRD (29).

1.2.1 Complications of CKD

The loss of endocrine and exocrine function of the kidney comes along with several complications which increase in parallel with the deterioration of the kidney function. The most important complications the patients experience are metabolic acidosis, hypertension, hyperuricaemia, anaemia and mineral bone disorder, which is associated with vitamin D deficiency, hyperparathyroidism, hyperkalaemia and hyperphosphataemia (1). All these complications contribute to the heavy symptom burden of CKD and strongly affect the patients' lives, which is why they require management (2). The individual prevalence of each of them depending on the GFR category is listed in table 2 underlining their relevance in consideration of treatment.

table 2: CKD complications according to KDIGO 2012

		GFR category (ml/min/1.73m²)				
		≥ 90	***50-89***	***45-59***	***30-44***	***< 30***
Anaemia	*[< 12g/dl for women; < 13,5 g/dl for men]*	4,0%	4,7%	12,3%	22,7%	51,5%
Hypertension	*[syst. ≥ 140 mmHg; dias. ≥ 90 mmHg; antihypertensive medication]*	18,3%	41,0%	71,8%	78,3%	82,1%
25(OH) Vit. D deficiency	*[<15 ng/ml]*	14,1%	9,1%	10,7%	78,3%	82,1%
Acidosis	*[serum bicarbonate < 21 mEq/l]*	11,2%	8,4%	9,4%	18,1%	31,5%
Hyperphosphataemia	*[serum phosphate ≥ 4,5 mg/dl]*	7,2%	7,4%	9,2%	9,3%	23,0%
Hypoalbuminaemia	*[serum albumin < 3,5 g/dl]*	1,0%	1,3%	2,8%	9,0%	7,5%
Hyperparathyroidism	*[PTH levels ≥ 70 pg{ml]*	5,5%	9,4%	23,0%	44,0%	72,5%

note: (2); abbreviations: CKD = chronic kidney disease; KDIGO = kidney disease: improving global outcome; GFR = glomerular filtration rate; PTH = parathyroid hormone

1.2.2 Renal replacement therapy

Once renal disease has advanced to ESRD, usually RRT in form of haemodialysis, peritoneal dialysis or kidney transplantation is needed. Depending on the patient's life expectancy and other factors including remaining renal function, a conservative therapy can be considered as a possible alternative (1).

Experts are still discussing the right time to initiate RRT. KDIGO recommends timely referral for planning it in people with progressive CKD who show a risk of kidney failure within one year of 10 to 20% or higher (2). This is accompanied with the big difficulty in predicting the further progression of CKD which, as mentioned before, nephrologists are struggling with.

Combined with the risks of RRT and the possible measuring inaccuracies this creates the strong suggestion of treating patients by symptoms rather than by

laboratory results. Thus, KDIGO recommends initiating RRT when one of the following are present (2):

- Symptoms or signs attributable to kidney failure
    - Such as acid-base or electrolyte abnormalities, pruritus or serositis
- Uncontrollable volume status or blood pressure
- Constantly deteriorating nutritional status, which cannot be controlled dietarily
- Cognitive impairment

Although it is impossible to predict precisely, these symptoms can usually be expected in a GFR range between 5 and 10 ml/min/1,73m² (2).
However, preparing a patient for RRT is not only a matter of timing, but also of access and planning. Patients who are about to get haemodialysis, for example, need vascular access, where of the different possibilities a functional arteriovenous access is preferable.
On the other hand, for peritoneal dialysis a transcutaneous catheter needs to be implanted into the peritoneal cavity, and of course also a transplantation of the kidney takes a lot of evaluation and planning. All this should be considered by the multidisciplinary team managing the CKD patient, which is usually coordinated by a nephrologist (1).

It has been mentioned before that there are selected patients for whom a conservative management is the most reasonable treatment option. This does not only apply to patients who do not have access to RRT, but more importantly is medically indicated for patients who would not benefit from dialysis or transplantation. A study published in 2009 by Carson et al. showed that people older than 70 years with ESRD receiving RRT commonly survived approximately two years longer than those choosing conservative therapy (30). However, this survival advantage is lost when patients are older than 80 years as recently shown by Verberne et al. (31). Such a conservative management includes full medical treatment and symptom burden alleviation as well as appropriate palliative care and must focus on prompting patient values and shared decision making (31).

1.2.3 Dialysis

As mentioned before, at the stage of ESRD insufficient renal function must be replaced to prevent the several possible systemic complications. The two possibilities besides transplantation are haemodialysis and peritoneal dialysis, both showing similar rates in survival according to a review by Merchant et al. from 2015 (32). However, with approximately 80% of the world's ESRD patients being treated with it, conventional, facility-based three times weekly dialysis is the most common treatment option (32). There is a controversy going on in current literature with some papers showing better survival rates for patients treated with peritoneal dialysis compared to haemodialysis especially in the first year after initiation of dialysis. However, as the review by Merchant and colleagues points out, there is a good chance that these findings are being driven by selection bias and the authors underlined the fact that adequately powered randomised controlled trials are missing to end this controversy (32).

Concerning elderly patients, Han et al. obtained approximately 1300 Korean patients older than 65 for a meta-analysis comparing patients receiving haemodialysis with those receiving peritoneal dialysis. They came to the conclusion that elderly patients being treated with peritoneal dialysis showed a higher risk of death compared to those receiving haemodialysis (33).

In contrast, in a meta-analysis by Zazzeroni et al. published in 2017, the quality of life in patients undergoing haemodialysis and peritoneal dialysis were compared. The authors came to no unanimous conclusion reflecting current literature, as their only quantitative difference concerning the quality of life regarded the effect of kidney disease (34).

Peritoneal dialysis is only received by a minority of global ESRD patients. Nevertheless, it must be mentioned that there is a huge heterogeneity among different countries all over the world. A study by Jain et al. published in 2012 focused on the global trends of peritoneal dialysis and showed this huge variety with Hong Kong having 79,4 per cent of dialysis patients treated with peritoneal dialysis but Luxembourg having only 0,4 per cent (35). Their assessment included 130 countries

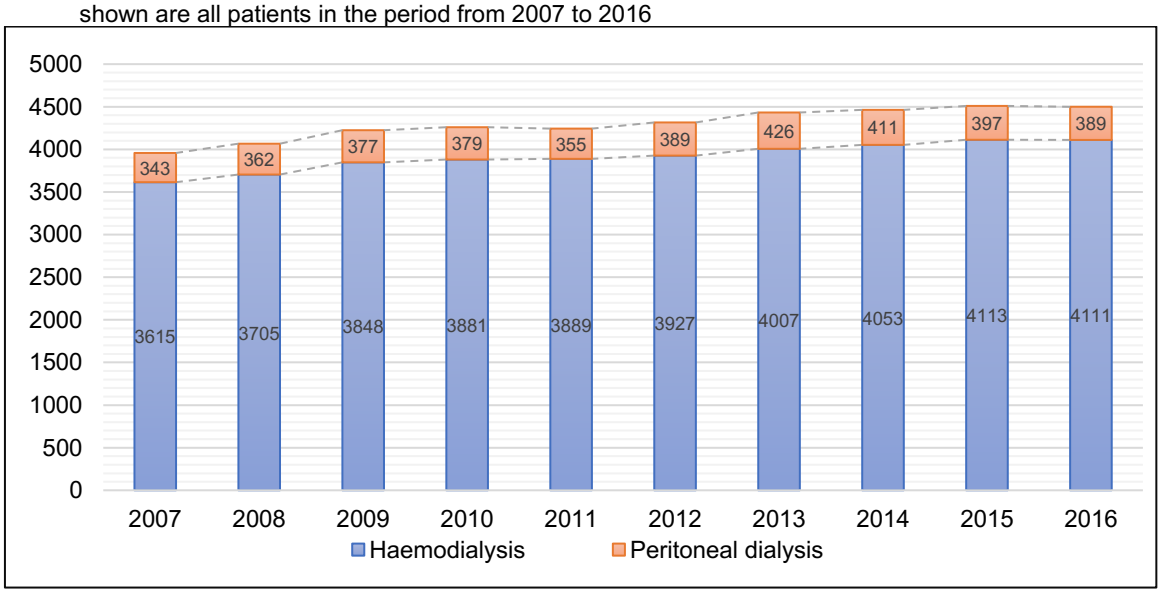
obtaining dialysis patients from 1997 to 2008 and the result showed a global average of 11% of the dialysis population being treated with peritoneal dialysis (35).

In Austria, peritoneal dialysis has encountered for an even smaller proportion in the last 10 years, as can be seen in figure 5 taken from the OEDTR's annual report. It shows that only an average 8,9% of patients receiving dialysis in Austria between 2007 and 2016 were being treated with peritoneal dialysis (14).

Same as with CKD therapy, it is not possible to define the perfect GFR level or the perfect time to start dialysis. However, a meta-analysis by Susantitaphong et al. from 2012 regarding slightly over a million patients, shows that there is a correlation between GFR level at initiation of dialysis and mortality. Paradoxically, higher GFR levels are accompanied by a higher adjusted mortality risk in observational studies, unaffected by nutritional status (36).

Due to the lack of significant data that provide information about a preferred time to initiate dialysis, it is suggested though to make the decision when to start dialysis clinically. More precisely, it is recommended to add clinical symptoms to measurable proxies of uraemia, which is the dominant indication for the initiation of dialysis (37).

figure 5: chronic dialysis patients in Austria according to OEDTR
shown are all patients in the period from 2007 to 2016



note: (www.nephro.at); abbreviations: OEDTR = österreichisches Dialyse- und Transplantationsregister

1.3 Kidney transplantation

The alternative therapy for ESRD patients besides dialysis and conservative management is kidney transplantation. It is often divided into three types of donation, which are live donation, donation after brain death and donation after circulatory death (38).

Current literature strongly suggests aiming for a transplant as soon as possible considered availability is given, as the outcome for kidney transplantation is significantly superior to any modality of dialysis. This applies to both mortality and quality of life, as Tenelli et al. could show in a review published in the American Journal of Transplantation in 2011. Considering almost 2 million patients suffering from CKD they found especially patients having received transplantation more recently to have reduced risk of cardiovascular events and mortality as well as increased quality of life, independent of dialysis modality and health system (39).

What must be taken into account, though, is that the superiority in mortality rates of transplantation compared to dialysis is not reached until approximately one year after transplantation due to raised mortality rates during the immediate post-transplant period (40).

Quality of life is an outcome measure that has gained increasing importance. In a 2008 systematic review conducted by Liem et al., the different therapy options for RRT have been investigated regarding the associated quality of life by comparing the utility of the patients. The authors also concluded that utility in transplant patients was significantly higher than in patients receiving haemodialysis or peritoneal dialysis (41).

1.3.1 Epidemiology

Due to the reasons outlined above, the number of kidney transplants worldwide each year has been increasing dramatically over the last decades. In 2016 the annual report of the Global Observatory on Donation and Transplantation (OGDT) counted 78.519 kidney transplants worldwide including both deceased and living

donors. In comparison, in the year 2000 only 7.544 kidney transplants have been registered by the OGDT. This corresponds to an approximately tenfold increase with a rate of 10.63 per million population in 2016 compared to 1.25 back in 2000, as shown in figure 6 (42).

In the last ten years though, the number of transplantations has not been increasing much. The official Eurotransplant (ET) annual report, which includes all transplantations from Austria, Germany, Slovenia, Croatia, Hungary and the Benelux-countries, counted 3.207 kidney transplants from deceased donors in 2008, while the annual report from 2016 counted only 3.074 (43,44). The data provided by the OEDTR confirm this trend with 432 kidney transplants in 2009 and 433 registered kidney transplants in 2016, as shown in figure 7 (14).

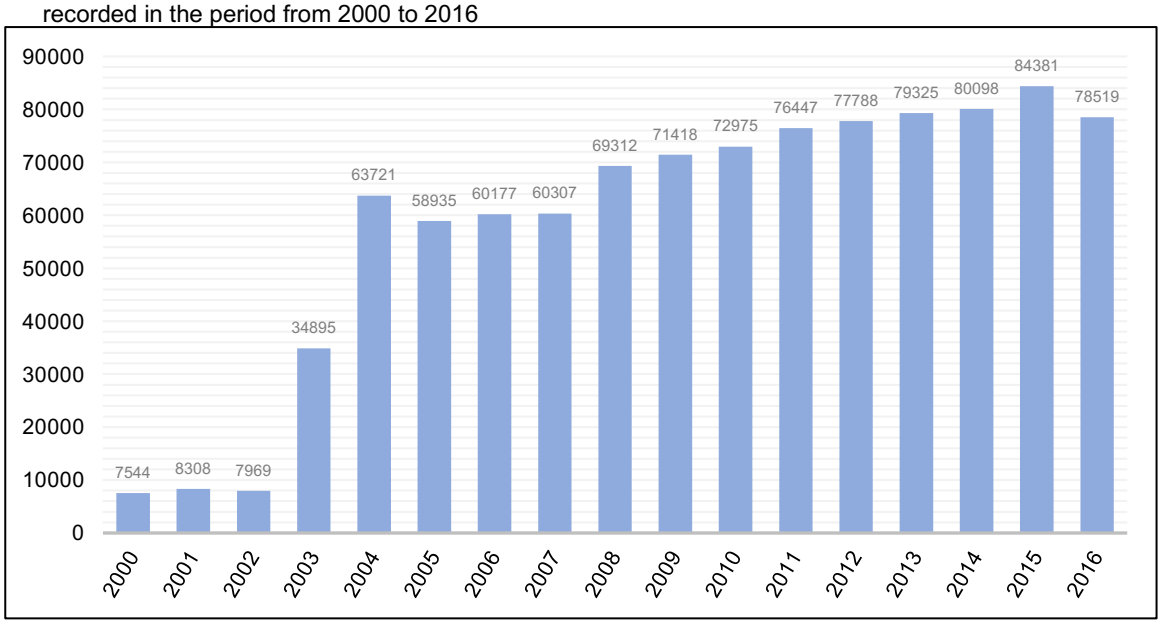
This implies that while the prevalence of CKD and subsequently ESRD is continuously increasing, the number of transplantations is stagnating. The reason for this stagnation is the limited number of donors and thus the number of available organs is stagnating. This can also be seen from the long waiting lists that prevail worldwide; the active waiting list of all Eurotransplant countries together at the end of 2016 counted 10.476 patients, for example (44).

Additionally, the patients receiving organs are getting older in parallel with the increasing average life expectancy that can be observed (38). A study conducted in the united states (USA) by Schold and colleagues could point out that almost half of the patients older than 60 years would die before receiving a transplant from a deceased donor while on the waiting list (45).

However, it has long been known that there is a significant effect of donor age and recipient age on the outcome of kidney transplant, as older age is associated with worse graft outcome (46). A higher mortality rate during long waiting periods therefore contrasts with worse outcomes when older organs or extend criteria for donors in general are used. In 2001 a ground-breaking study by Ojo and colleagues compared life expectancy of people on transplant waiting lists with the life expectancy of patients receiving organs they then called “marginal” kidneys, defined as kidneys from old donors with for example diabetes or hypertension as a comorbidity (47). They found that recipients of these “marginal” kidneys had a 5

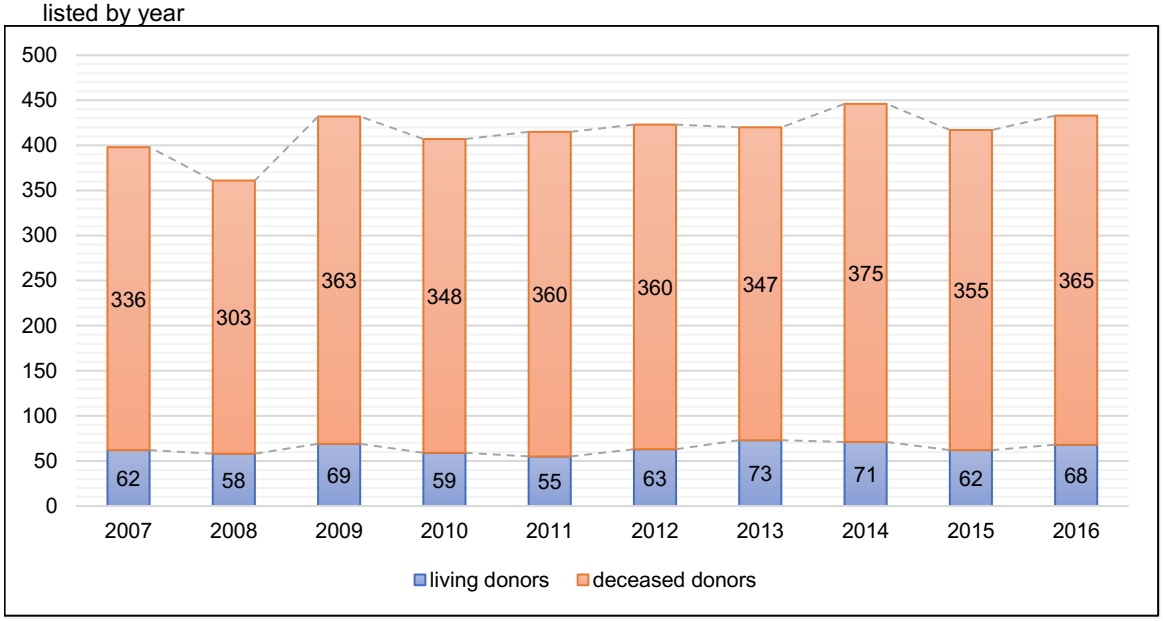
year longer overall survival compared to transplant candidates who did not receive a graft (48).

figure 6: number of worldwide kidney transplantations according to GODT
recorded in the period from 2000 to 2016



note: (http://www.transplant-observatory.org/); abbreviations: GODT = global observatory on donation and transplantation;

figure 7: number of kidney transplantations in Austria according to OEDTR
listed by year



note: (www.nephro.at); abbreviations: OEDTR = österreichisches Dialyse- und Transplantationsregister

1.3.2 Extended criteria donors

After first research results justified the use of these kidneys that would previously have been sorted out, there was an effort to rid the literature of the term “marginal” and try to classify organs with extended criteria using known key factors for the graft outcome. For that matter, a group of donors aged 10 to 39 years having neither hypertension history, nor a pre-donation serum creatinine level higher than 1,5 mg/dl or a cerebrovascular event as cause of death, was compared with donors showing one or more of these risk factors to evaluate the relative risk of graft loss (49,50).
Only those factors showing an increased relative risk of graft loss of 1,7 or more were considered for the definition, leading to the following inclusion criteria for extended criteria donors (ECD) defined by the United Network for Organ Sharing:

- Donor aged older than 60 years
- Donor aged 50 to 59 with two of the following:
    - Hypertension history
    - Pre-donation serum Creatinine > 1,5 mg/dl
    - Cerebrovascular event as cause of death

Back in 2009 Rao and colleagues developed a different approach for organ allocation. Instead of the dichotomy of either being ECD or standard criteria donor (SCD), they established “a continuous kidney donor risk index (KDRI)” identifying ten donor and four transplant characteristics that are associated with transplant failure (51).

A modification of this index is the so-called kidney donor profile index (KDPI), for which only the donor-related characteristics are considered. It is expressed as the percentage of transplants of the prior calendar year, which is deemed better than the judged organ (52). The classification was not congruent with the ECD classification, but rather showed an overlap, which is due to the huge variety in quality of ECD organs. According to a study published by Woodside et al. in 2012, the distinction between SCD and ECD has no relevance for the outcome in the different KDRI levels (53).
However, even the kidneys scoring a high KDPI, which equals a high risk of organ failure, have a survival benefit compared to staying on the waiting list for a better

organ (52). What Merion and colleagues concluded in a study in 2005, though, was that the cumulative survival benefit of ECD transplants compared to staying on the waiting list or getting a SCD organ was not reached until 3,5 years after transplantation (54).

Beginning in 1999, the Eurotransplant senior programme (ESP) aimed for an age-matching policy rather than human leucocyte antigen (HLA) -based allocation as is used in other allocation schemes. Within the Eurotransplant region (Austria, Croatia, Germany, Belgium, Luxembourg, The Netherlands and Slovenia) organs from donors ≥65 are allocated to recipients ≥ 65 years with the shortest possible cold ischaemia time and non-immunised first transplant recipients as inclusion criterion. (55). Frei et al. compared the ESP to standard allocation and showed that graft and patient survival were comparable in the groups, although age-matched organs had shorter ischaemia times, less delayed graft function but 5-10% higher rejection rates (56).

Patients older than 60 years generally benefit from ECD kidney transplantation, but this does not apply to patients with comorbidities such as malignancy or chronic obstructive pulmonary disease (COPD) with limited survival prognosis, as mortality rates significantly increase in these patients (57). Either way, this patient group of elderly patients receiving ECD organs constitutes a particular one exhibiting increased risk of infections, poor graft outcome, malignancies and nephrotoxicity caused by calcineurin-inhibitors (CNIs) (49).
For that matter, a special and adapted immunosuppressive therapy may be of benefit in patients with ECD kidney transplantation.

1.4 Immunosuppressive Drugs for Kidney Transplantation

A lot of time has passed since the first successful kidney transplant was performed by Dr. Lawler in 1950 in Chicago. Still, the core question in allograft transplantation is the prevention of allograft rejection and therefore sufficient immunosuppressive therapy. The development of new immunosuppressive drugs and regimens led to reduced rejection rates. However, this reduction of allograft rejections comes at the

expense of increased susceptibility to infections caused by opportunistic germs and to malignancies (58).
Therefore, successful immunosuppressive therapy is a balancing act between successful prevention of allograft rejection and the lowest possible side effects such as nephrotoxicity, opportunistic infections and cancer.

1.4.1 Alloimmune responses and three-signal model

To understand the mechanisms of immunosuppressive medications it is important to look at the alloimmune responses and the processes that are targeted by the different immunosuppressive therapies.
Among other authors, Halloran et al., who published a review about immunosuppressive drugs in the New England Journal of Medicine in 2004, refer to the alloimmune response as a reaction that can be described using the so called "three-signal model" (59).

"Signal 1" is constituted by antigen-bearing dendritic cells triggering T-cells with cognate T-cell receptors. Simultaneously, antigen-presenting cells (APC) induce "signal 2", which is also referred to as "co-stimulation", as co-stimulatory receptors such as CD28 are engaged on T-cells (60). The result of these two signals is the activation of transcription factors and therefore the expression of, amongst other new molecules, Interleukin-2 (IL-2). These effects are achieved via three signal transduction pathways, one of which is the calcium-calcineurin pathway. Together with other cytokines IL-2 further leads to "signal 3" by activating a pathway called "target of rapamycin" pathway and as a result T-cell proliferation, which makes a lot of effector T-cells available.
Besides effector T-cells, the second type of agents of allograft rejection are alloantibodies against donor HLA antigens. They are produced by B-cells, which are activated through their antigen receptors after antigen engagement, usually taking place in lymphoid follicles or extrafollicular sites (59).
In T-cell mediated rejection, inflammation in the transplanted organ is generated by infiltrating effector T-cells, while in B-cell mediated rejection alloantibody targeting donor antigens cause the inflammatory response.

1.4.2 Classification of immunosuppressive drugs

Depletion of lymphocytes, diversion of lymphocyte traffic and blockage of the response pathways of lymphocytes are the possible approaches of the many different immunosuppressive agents. In the review just mentioned before by Halloran et al. the authors classified the various immunosuppressive drugs as such:

- **glucocorticoids**
- **small-molecule drugs**
    - immunophilin-binding drugs
        - CNIs (*e.g. cyclosporin, tacrolimus*)
        - target-of-rapamycin inhibitors (*e.g. sirolimus*)
    - inhibitors of nucleotide synthesis
        - purine synthesis inhibitors (*e.g. mycophenolate mofetil*)
        - pyrimidine synthesis inhibitors
    - antimetabolites (*e.g. azathioprine*)
- **protein drugs**
    - depleting antibodies against T-cells, B-cells or both
        - polyclonal antibody (*e.g. horse or rabbit antithymocyte globulin*)
        - mouse monoclonal anti-CD3 antibody
        - humanised monoclonal anti-CD52 antibody
        - B-cell-depleting monoclonal anti-CD20 antibody
    - nondepleting antibodies and fusion proteins
        - humanised or chimeric monoclonal anti-CD25 antibody (*e.g. daclizumab, basiliximab*)
        - fusion protein with natural binding properties
    - intravenous immune globulin

1.4.3 Glucocorticoids

Glucocorticoids are classified as nonspecific cytokine inhibitors, as they inhibit all cytokine transcription through the blockage of transcription factors. This leads to several various effects on the immune system, such as T-cell depletion, induction

of apoptosis, apoptosis of the eosinophils and dysfunction of macrophages. Since glucocorticoids are not specific and come with a lot of side effects, a reduced use is aimed for and agents with the same efficacy but fewer side effects are focused on in organ transplantation (61). Recently, it has been shown that maintenance immunosuppression in low-risk renal allograft recipients can quite safely be performed steroid free and leads to significantly reduced rates of post-transplantation DM (62).

1.4.4 Small-molecule drugs

Before Cyclosporin was established in kidney transplantation, azathioprine, a small-molecule drug that inhibits the purine nucleotide biosynthesis and thus downregulates DNA and RNA synthesis, was the first immunosuppressive agent to be widely used in organ transplantation (59,63). Since the widespread application of calcineurin inhibitors, azathioprine has lost its importance in organ transplantation and became a second-line drug.

1.4.4.1 Calcineurin inhibitors

As agents targeting “signal 1”, CNIs belong to the T-cell directed therapy. Cyclosporin, the best-known representative, has revolutionised immunosuppression in transplantation in the 1980s by reducing the rejection rates drastically (61). Two decades later, tacrolimus reduced rejection rates even further and established itself in kidney transplantation (64). Both agents prevent calcineurin-dependent gene transcription, Tacrolimus being the agent that shows more molecular potency, although recent studies suggest the efficacy of both to be about the same (65,66). What they both have in common is a dose-dependent direct vascular effect leading to reduced perfusion of the kidney and possibly resulting in chronic kidney injury or in acute tubular necrosis and renal ischaemia (61). The nephrotoxicity of CNIs is undisputed, but while acute nephrotoxicity is considered reversible and its existence is not doubted, chronic nephrotoxicity as a side effect of CNIs is considered irreversible and still controversial (67).

Other side effects shared by both cyclosporin and tacrolimus are the thrombotic microangiopathy, hypertension, skin changes, hirsutism, hyperlipidaemia, neurotoxicity and post-transplantation DM, although the incidence of the latter two

is higher in Tacrolimus and the incidence of hypertension, hyperlipidaemia, skin changes, hirsutism and gum hyperplasia is higher in Cyclosporin (61).

In order to reduce chronic CNI nephrotoxicity, many CNI-sparing protocols have been tested in clinical trials, trying minimisation, avoidance or even total elimination (67). Probably the most prominent of these studies is the randomised prospective trial called “ELITE-Symphony study” which randomised patients into four different groups each being treated with a different CNI avoiding or minimisation protocol. One of the regimens contained daclizumab induction plus low-dose cyclosporin, one used low-dose sirolimus, one group of patients received standard cyclosporin doses without daclizumab induction and one group was treated by a regimen consisting of daclizumab, mycophenolate mofetil, corticosteroids and low-dose tacrolimus. Ekberg et al. could show, that after 12 months of treatment, the last-mentioned regimen with daclizumab induction, low-dose tacrolimus, mycophenolate mofetil and corticosteroids lead to better renal function and lower rejection rates than the other protocols while showing adequately low rejection rates (64).

1.4.4.2 Mycophenolate

Another agent that showed decreased rejection rates compared to azathioprine is mycophenolate mofetil, a mycophenolate-acid-releasing prodrug (68–70). Mycophenolate acid further inhibits inosine monophosphate dehydrogenase, which is considered a key enzyme in the purine synthesis, which in turn is essential for B-cells and T-cells. It shows no cardiovascular risk and is easy to monitor and its nonimmune toxicity is restricted to gastrointestinal and haematologic problems, mainly diarrhoea, anaemia and leucopenia (59).

1.4.5 Polyclonal antibody

Polyclonal antithymocyte globulin (ATG) products contain antibodies to human lymphocyte antigens that result in, mainly but not exclusively, T-cell depletion, although mechanisms are not fully understood yet. It is usually used for 3 to 10 days as induction therapy, in order to induce lasting lymphopenia (59).

As mentioned before, T-cell depletion both in blood and lymphoid tissues caused by apoptosis, complement-dependent lysis and T-cell activation remains not the only

effect of ATG. Additionally, it induces apoptosis in B-cell lineages and myeloma cell lines but also interferes with dendritic cell functional properties and leads to the induction of natural killer T-cells and regulatory T-cells (71).

Polyclonal ATG can be produced in different ways, which is why there are three different agents available on the market. Thymoglobulin® is produced by immunisation of rabbits using human thymocytes, for the production of atgam®, horses are immunised with human thymocytes and Fresenius-ATG® is made by using lymphocytes from a Jurkat T-cell leukaemia line to immunise rabbits (61).
After immunisation, the serum of either horse or rabbit is harvested and the immunoglobulins against thymocytes are isolated and purified before they are pooled, usually from thousands of horses or rabbits (72).

Unlike in CNIs, no nephrotoxic effects are found in either of the polyclonal ATG agents. Nevertheless, considering they are of non-humanised immunoglobulins, they all show side effects caused by cytokine release such as anaphylaxis, fever, chills, hypo- or hypertension, dyspnoea, rash or pulmonary oedema. Other possible acute side effects that can occur are haemolytic anaemia, thrombosis, thrombocytopenia and neutropenia. Besides acute reactions, serum sickness and infection are possible delayed reactions caused by polyclonal ATG agents (72).

1.4.6 Humanised or chimeric monoclonal anti-CD25 antibody

IL-2 plays an important role in “signal 3” and therefore the proliferation of effector T-cells. As antibodies against the α-subunit of the IL-2 receptor, Interleukin-2 receptor antagonists (IL-2RAs) interfere with “signal 3” and impede the proliferation of the activated T-cells. There used to be two agents that were used widely in organ transplantation, namely basiliximab and daclizumab, although the latter is not produced anymore. Basiliximab is still very popular, especially in patients with low immunologic risk, as it needs no monitoring, has few toxic effects and is moderately effective (59,73).

1.4.7 Immunosuppressive therapy and ECD

When it comes to the evaluation of immunosuppressive drugs, the focus lies not only on the therapeutic effects: The effectiveness in preventing rejection faces the consequences the immunosuppression itself brings with it, such as infection and cancer, as well as the individual non-immune toxicity to other tissues each immunosuppressive agent has (59). Due to the great variety in available immunosuppressive regimens and patient groups, the immunosuppressive management differs not only from centre to centre, but also between the different patient populations.

The diversity of the recipients and their needs is pointed out, when the change of immunity with age is looked at, as rejection rates of 28% in 18 years old patients occurred compared to 14% in patients aged 70 (74). Still, older recipients are, independent of the baseline immunosuppression, at a higher risk to lose their transplant from rejection, no matter the real rejection rates (55). Thus, the management for transplants with ECD aims at the best possible nephron protection, which in the case of immunosuppression, means nephrotoxicity minimisation and infection prophylaxis (75). Especially older patients receiving ECD kidneys may be frailer to the nephrotoxic side effects of CNI, which is why many attempts at improvement in immunosuppressive regimens aim at withdrawal or avoidance of CNIs.

Besides delayed usage and complete avoidance of CNIs, the two common strategies for minimisation of CNI toxicity, lower CNI levels compared to SCD are another option and in the practice of, for example, the group surrounding Lionaki et al. (76). More data is available concerning delayed CNI introduction, a long-term study by Stratta et al. that included 101 ECD kidney recipients, is considered one of the best long-term experiences (55). Either ATG or alemtuzumab were used together with mycophenolate mofetil and steroids and tacrolimus was not introduced unless creatinine levels lower than 4 mg/dl occurred. After 24 months of follow-up, actual patient (93%) and graft (83%) survival rates were similar and rates of delayed graft function, as well as infection and rejection were comparable (77).

The optimal immunosuppressive regimen both for induction and maintenance, however, is still subject of discussion, since a lot of trials have ECD as an exclusion criterion and sufficient validation through studies is missing (55).

1.4.7.1 Induction

When comparing induction therapy with ATG and IL-2RAs, ATG seems to have superiority both over basiliximab and daclizumab concerning the incidence and severity of acute rejection in recipients with high immunologic risk (78,79).

In a study published by Gill et al. in 2011, 14.820, elderly patients received either rabbit ATG, IL-2RAs or alemtuzumab as induction therapy. The results suggested, that it is preferable to use rabbit ATG among high-risk recipients with high-risk donors and possibly low-risk recipients with high-risk donors (80). Low doses of ATG also turned out to be more effective than basiliximab in preventing rejections in recipients of ECD transplants, although short-term complications including cytomegalovirus (CMV) infections were higher in the ATG group (81).

1.4.7.2 Maintenance

The optimal maintenance therapy is still discussed controversially in recent papers. Gill and colleagues, for example, suggested mycophenolic acid and tacrolimus to be the immunosuppressive agents of choice for patients older than 60 years (80).

Due to a lack of randomised trials dealing with the question of maintenance therapy in ECD recipients, there are only general guidelines for transplant recipients, which take no regard on ECD. As far as the KDIGO guidelines are concerned, they suggest a combination therapy including CNIs and an anti-proliferative agent, specifically, tacrolimus and mycophenolate as first-line therapy (82).

1.5 Infections after kidney transplantation

The advancement in immunosuppressive therapy and its widespread use led to both higher infection rates and a shift in infection patterns. Infection is hard to detect in immunocompromised patients, as the natural signs of infection are oppressed, and organ recipients often show non-infectious causes of fever. In a detailed review published in the New England Journal of Medicine in 2007, Jay A. Fishman, M.D. states the current standard of knowledge on infection in solid-organ transplant

recipients. He describes the risk of infection of a transplant recipient as “a continuous function” of the interplay between many factors (58).

1.5.1 Risk of infection

A patient’s risk of infection is not measurable and constantly changing due to its many variables. Prophylaxis is built on known and anticipated exposures of the individual patient using serologic tests and epidemiologic history.
Fishman divides the epidemiologic exposures into four overlapping categories, namely donor-derived infections, recipient-derived infections, nosocomial infections, and community infections (58).

The transmission of pathogens from donor to recipient is made easier through immunosuppression in transplantation, examples are cytomegalovirus (CMV) infection and tuberculosis. Furthermore, the detection is limited by the short time period in which an organ is usable and by the current standard of technology and of serologic tests, all together implicating that there are always going to be infections that remain undetected.
On the other hand, infections already existing in the recipient can undergo reactivation after transplantation. Mycobacterium tuberculosis, some parasites, viral infections such as herpes simplex or varicella zoster virus, endemic fungi hepatitis B or C virus and human immunodeficiency virus (HIV) belong to the pathogens most common.
Transplant recipients are hospitalised for extended periods of time and are therefore susceptible for nosocomial infections. Additionally, pathogens that would not do any harm to an immunocompetent person can lead to major infections in immunocompromised patients. Concluding all these risk factors, a dynamic assessment of the risk of infection is needed, with dose, duration and sequence of immunosuppression as main determinants, referred to by Fishman as “net state of immunosuppression” (58).

1.5.2 Prevention

Prophylaxis has proven to be a cornerstone in reduction of infection rates and severity of infections after transplantation. The availability of oral antiviral medication represents a breakthrough in prevention. There are three therapy regimens that proved to be effective, namely universal prophylaxis including surgery, vaccination and pre-symptomatic therapy (83). Vaccinations can be less protective concerning both time and extent in immunocompromised patients, due to the inhibition of B- and T-cell proliferation and responses (84,85). Also, live vaccinations are contraindicated in organ transplant recipients.

Universal prophylaxis follows the concept of providing antimicrobial therapy to every patient after transplantation for a certain period, no matter the individual risk. Pre-symptomatic therapy, on the other hand, uses monitoring, such as antigen detection, at certain time intervals, to detect and treat infections at their very beginning (58).

Change of lifestyle is another aspect often considered important as prophylaxis for immunosuppressed patients. This refers to the avoidance of exposure, for example by washing hands properly after possible contamination and by shunning risky environments.

1.5.3 Infection patterns

In parallel with the extensive development in immunosuppression, patterns of infection changed a lot over time. Immunosuppression used to be consistent at its beginning in organ transplantation, which led to a consistent infection pattern resulting in a predictable timeline for infections after transplantation. This timeline has altered, as have prophylaxis strategies and immunosuppressive regimens. Concordant to KDIGO guidelines, most transplantation centres prefer a triple maintenance therapy with CNI, an antimetabolite and prednisone (82). With the introduction of T-lymphocyte-depleting agents, a prolonged risk of viral and fungal infection due to a long-lasting lymphocyte deficit was produced. To illustrate this altered “timeline of infection”, Fishman divided the time after transplantation into three time periods, defined as such (58):

- Early post-transplantation period (1 - 4 weeks after transplantation)
- Intermediate post-transplantation period (1 - 6 months after transplantation)

- Late post-transplantation period (> 6 months after transplantation)

1.5.3.1 Early post-transplantation period

Immunosuppression takes time to reach its full extent, which is why there are usually no opportunistic infections during this early period. Instead, infectious complications are generally donor-, or recipient derived, but also nosocomial infections and technical ones are common during these first four weeks.

1.5.3.2 Intermediate post-transplantation period

The main causes of febrile episodes during this period are allograft rejections on the one hand, and viral infections on the other. The main cause of infectious complications in this second phase after transplantation is activation of latent infections. Opportunistic infections and urinary tract infections are largely controlled by trimethoprim-sulfamethoxazole prophylaxis and herpes virus infections have become uncommon due to viral prophylaxis. However, with BK polyomavirus and other emerging viral complications, direct and indirect effects often occur during this phase. While direct effects occur immediately and invade the tissue, indirect effects can be systemic or local and encourage other opportunistic infections through immunosuppression. Other indirect effects can be increased risk of allograft rejection and graft injury, as well as the post-transplantation lymphoproliferative disorder (PTLD) (58).

1.5.3.3 Late post-transplantation period

When the graft functions well several months after transplantation, the immunosuppression is usually adjusted and softening. In that case, risk of infection is also decreasing, although community-acquired pathogens always keep the risk of a transplant recipient above the risk of people without compromised immune system. However, some patients develop recurrent infection all the less, making themselves susceptible for opportunistic infections like invasive fungal pathogens, uncommon pathogens or listeria nocardia species.

If immunosuppression needs to be kept at a higher level of course, the risk of recurrent infection is not diminishing as it is with tapered immunosuppression.

1.5.4 Common infections

In renal transplant recipients, herpes virus infection is a common cause of morbidity and complications. Whereas herpes simplex and varicella zoster cause mostly local problems, but may cause fulminant, potentially lethally disease if left untreated. CMV and Epstein-Barr virus (EBV) are considered to have other important clinical, systemic effects (86). The timetable of the dynamic risk assessment of organ recipients defined by Fishman is reproduced in figure 8.

1.5.4.1 CMV

Without prophylaxis, CMV infection occurs in 30 to 80% of solid organ transplant recipients (87). Direct effects of CMV are usually observed during the first 12 months of immunosuppression and mostly occur in the form of fever and neutropenia. On the other hand, indirect effects come along with increased risk of additional infections and also EBV-associated PTLD (58). CMV infection can occur as viral superinfection, reactivation or primary infection, where of the latter one is considered the most severe form. There are meta-analyses that could show that risk of CMV infection and associated mortality can be reduced by antiviral prophylaxis and that pre-emptive treatment for CMV viraemia reduces CMV disease rates (88,89). Antigen-detecting methods and molecular assays such as the polymerase-chain-reaction (PCR) are considered very important quantification methods for the control and management of CMV infection.

1.5.4.2 EBV and PTLD

Primary EBV infection is one of the main risk factors for PTLD, which is why it has an important role in management of organ recipient patients. PTLD is defined as a heterogeneous group of lymphoproliferative disorders found in 3 to 10% of solid-organ recipients. Mortality rates of monoclonal forms have been recorded up to 80% for patients with PTLD diagnosis (90).

Other risk factors include CMV coinfection, allograft rejection and exposure to antilymphocyte antiserum.

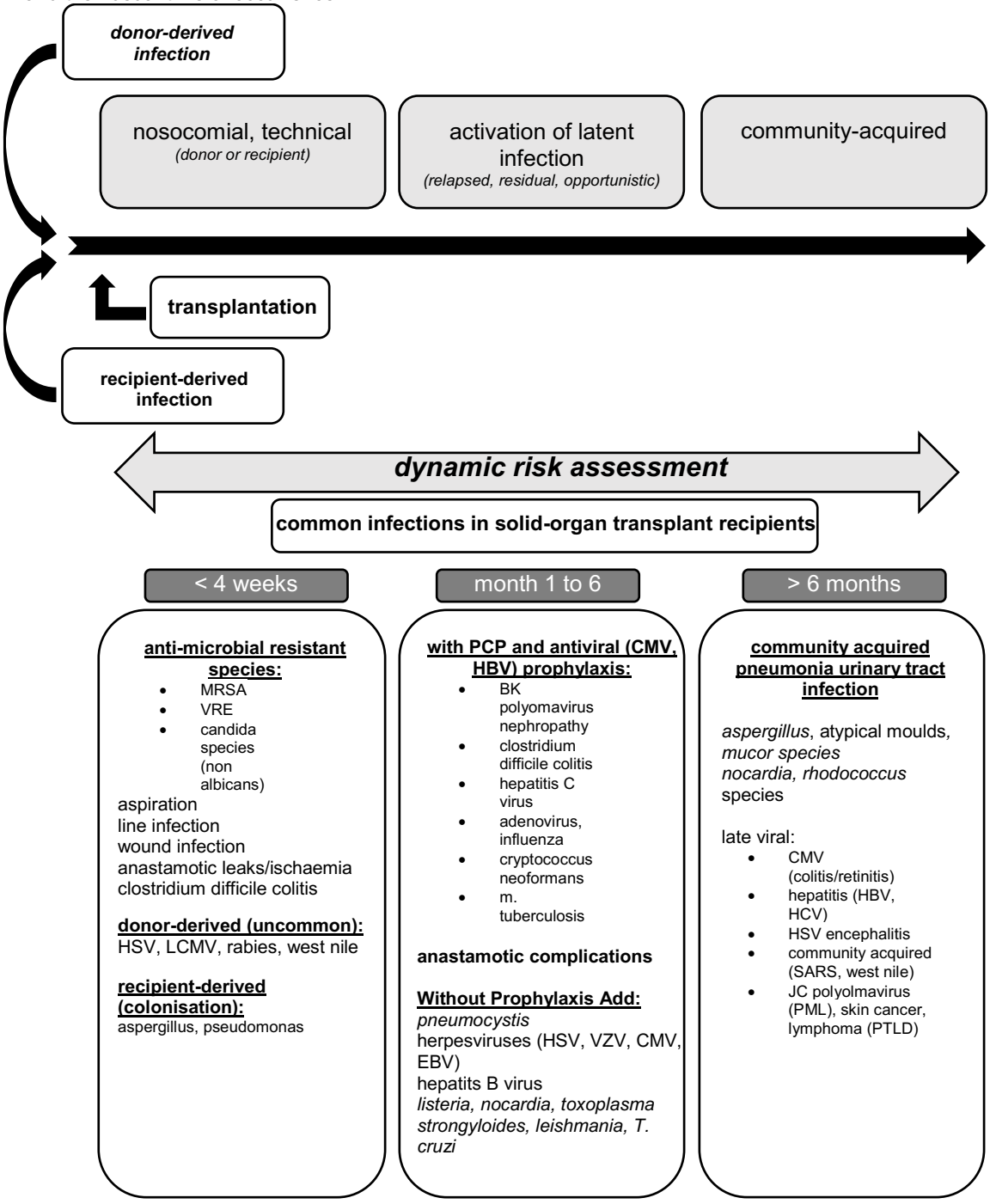
1.5.4.3 Polyomaviruses BK and JC

For polyomaviruses, there is no known effective antiviral therapy. Therefore, the immunosuppression must be adapted and reduced in the case of polyomavirus

infection. Especially polyomavirus BK is considered a common complication for its association with the polyoma BK-associated nephropathy (PVAN) after transplantation. Up to 10% of organ transplant recipients are diagnosed with it and the associated graft failure can reach rates of 80% (91,92).

figure 8: timetable of post-transplant infection risk according to Fishman et al.

The timetable shows the dynamic risk assessment in transplant recipient patients plus common infections and their usual time of occurrence



note: (58); abbreviations: MRSA = methicillin-resistant staphylococcus aureus; VRE = vancomycin resistant enterococcus; HSV = herpes simplex virus; LCMV = lymphocytic choriomeningitis virus; PCP = pneumocystis pneumonia; CMV = cytomegalovirus; HBV = hepatitis B virus; VZV = varicella zoster virus; EBV = Epstein-Barr virus; HCV = hepatitis C virus; SARS = severe acute respiratory syndrome; PML = progressive multifocal leucoencephalopathy; PTLD = post-transplant lymphoproliferative disorder

1.5.5 ATG vs IL-2RA

It has been pointed out before that ATG might be superior to IL-2RA as induction therapy regarding efficacy in high risk patients (79). Similar findings were published by Tabor et al. showing acute rejection rates being significantly lower in rabbit ATG-induced patients compared to a group receiving basiliximab (93).
However, these reduced rejection rates must be weighed against infection rates that seem to be higher than in IL-2RA-induced transplant recipients. Recent data suggest that this superiority could come at the expense of increased infection rates in cardiac transplantation, as well as in kidney transplantation with living-related donors and with donors after cardiac death (94–97). Considering the fact, though, that around 70% of all kidney transplant patients in in the last decade received either ATG or IL-2RAs as induction therapy, research is largely required in this field, especially in ECD recipients (98).

2 Materials and Methods

2.1 Study design

In this study, we conducted a retrospective data analysis. Data gathering was carried out during the period from November 2016 to May 2018.
This study was approved by the ethics committee of the Medical University of Graz (29-245 ex 16/17). Due to its retrospective character, no written informed consent on the part of the patients was needed. All the collected data were pseudonymised for the analysis.

2.2 Immunosuppressive Regimens

The ATG patients in this study received immunosuppressive therapy as prescribed by a standard operating procedure in use at the Clinical Division of Nephrology, Department of Internal Medicine, Medical University of Graz:

- Thymoglobulin 1,5 mg/kg day 0 - 3 (intraoperatively for the first time)
- Adaption of dosage according to blood count and in case of infection
- Prograf (tacrolimus) 0,02 – 0,03 mg/kg bodyweight = half daily dose starting on day 0 (aimed levels of 4 – 6 ng/ml per day)
- Myfortic (mycophenolate mofetil) 360 mg starting with 2x1 on day three, 3x1 on day 4 and 2x2 on day 5 (in case of no infectious, wound-, or blood count related complications)
- Solu Dac (prednisolon) 500 mg pre-, and intraoperatively; then taper “normally” according to pattern
- Valcyte (valganciclovir) if D+/R- starting on day 5 – 7
- Lidaprim (trimethoprim/sulfametrol) forte pneumocystis prophylaxis (at least 3x ½ per week up to 1x1 each day according to kidney function and tolerability) starting on day 5 – 7
- Rocephin (ceftriaxone) 2g once daily until surgical drains are removed

2.3 Patient population

All patients who received a kidney transplant with expanded criteria in the time between 2009 and 2016 at the Landeskrankenhaus (LKH) Graz were eligible for this study. Patients who had undergone induction therapy with either IL-2RAs or ATG could be enrolled.
Exclusion criteria included other forms of induction therapy or immunosuppressive regimens, as well as withdrawal throughout the one-year follow-up due to insufficient data caused e.g. by a patient's switch to another health institution.
Recruitment was planned to ensure that the population included 50% ATG recipients and 50% patients who received IL-2RAs for induction therapy.

We used the criteria used by the Clinical Division of Nephrology, Department of Internal Medicine, Medical University of Graz to define ECD:

- donor age > 60
- or donor age > 50 + history of hypertension or terminal creatinine > 1,5 mg/dl
- non-heart-beating-donor (NHBD)
- cerebrovascular cause of death

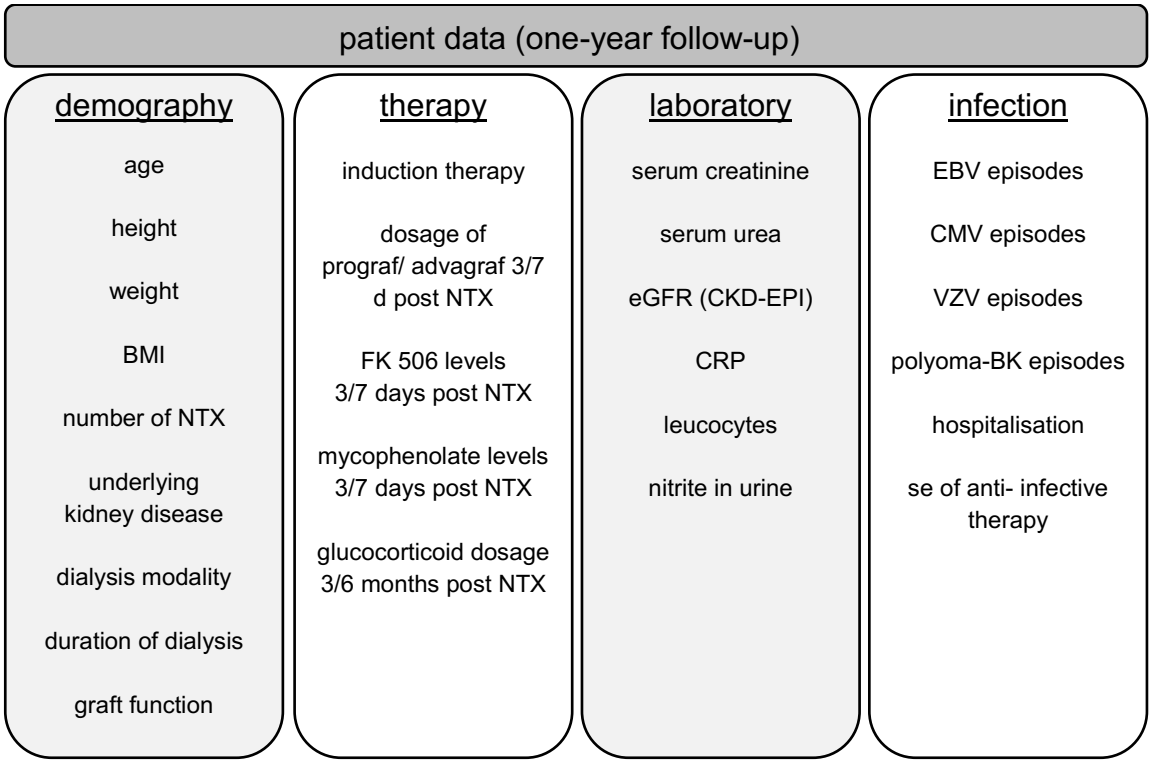
2.4 Data collection

In a first step, we collected and digitalised data on all 494 patients who received a kidney transplant during the period from 2009 to 2016 at the LKH Graz. Collected data included: ET number, age of the recipient and date of transplantation. By using the ET number, donor data was then extracted from the ET database (www.eurotransplant.org). Donor age, sex, history of hypertension, HLA-mismatch, cerebrovascular cause of death, terminal creatinine levels and history of DM were collected.

For the considered period 316 patients met the criteria for receiving an ECD organ. In the context of this diploma thesis we included 40 of these patients for further data collection, observing 20 patients who received IL-2RAs and 20 patients who received ATG for induction therapy. The hospital information system (HIS)

openMEDOCS was used for a comprehensive data collection for the follow-up period of one year after transplantation. The data that was collected is shown in figure 9.

figure 9: collected patient data



abbreviations: BMI = body mass index; NTX = kidney transplantations; eGFR (CKD-EPI) = estimated glomerular filtration rate (chronic kidney disease epidemiology collaboration); CRP = c-reactive protein; EBV = Epstein-Barr virus; CMV = cytomegalovirus; VZV = varicella zoster virus

The underlying kidney diseases were divided into either autoimmune, DM, hypertension, glomerulonephritis, Polycystic kidney disease, unknown kidney disease or others. The graft function was classified as immediate, delayed or primary non-function.
We defined delayed graft function as ≥ 1 acute haemodialysis treatment during the first week after transplantation.

The induction therapy was either IL-2RAs (Basiliximab or Daclizumab) or ATG.
Episodes with EBV, CMV, varicella zoster virus (VZV) and Polyoma-BK were defined as positive PCR-values. Major infections were defined as hospitalisations caused by infectious complications within one year of follow-up. The number of and reasons for hospitalisations and anti-infective therapies were collected from medical records.

The data were then processed and inserted into a pre-designed Microsoft EXCEL-file (Microsoft Excel 2016 MSO [16.0.10228.20080], Microsoft Corporation, Redmond, Washington, USA) and later into IBM SPSS tables (IBM SPSS statistics 23, International Business Machines Corporation [IBM], Amon, New York, USA).

2.5 Statistical analysis

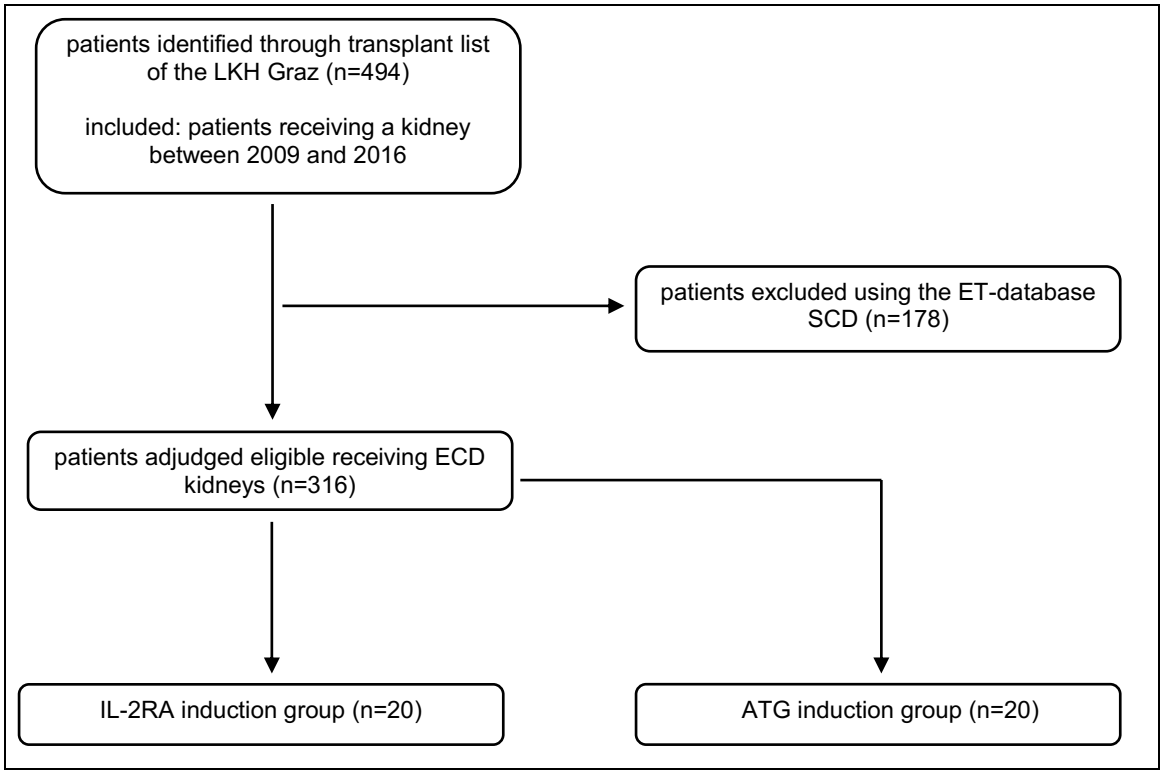
The statistical analysis for this thesis was conducted in June 2018 using IBM SPSS statistics. The assumption of normality was checked using the Kolmogorov-Smirnov test. Normally distributed numerical data were presented by means and standard deviations, non-normally distributed data by medians and interquartile ranges.
Categorical data were analysed by calculating absolute figures and relative shares in per cent. When comparing the patients based on their induction therapy, the t-test for independent samples for parametric data and the Man-Whitney-U-test for nonparametric data came to use. No multiple testing correction was made. All p-values below 0,05 were considered significant.

3 Results

3.1 Study characteristics

figure 10 shows how patients were recruited for this thesis. In the kidney transplant list of the LKH Graz we found 494 patients who underwent transplantation. A total of 316 of these patients received an ECD organ and were eligible, 40 of which were included for further data collection. Patients were chosen so that 20 patients who received IL-2RA induction faced 20 patients who were induced with ATG.

figure 10: flow chart for the recruiting of included patients



abbreviations: LKH Graz = Landeskrankenhaus Graz; N = number; ET = Eurotransplant; SCD = standard criteria donor; ECD = extended criteria donor; IL-2RA = interleukin-2 receptor antagonist; ATG = antithymocyte globulin

3.2 Baseline Characteristics

3.2.1 Recipient baseline characteristics

For this thesis 40 patients were included, divided into 20 patients receiving induction therapy with ATG and 20 patients inducted with IL-2RA agents. Data collection was done together with fellow medical student Andreas Würtz, whose analysis focused on another aspect of ECD kidney transplantation (99). Since we analysed the same cohort of patients, baseline characteristics are identical. The baseline characteristics of these 40 organ recipients are shown table 3, sorted by induction therapy. No significant differences concerning age, height, weight BMI or duration of pre-transplant dialysis were found between the induction therapy groups. For the statistical analysis, normally distributed data is presented by mean (M) and standard deviation (SD) was analysed using a t-test for independent samples. Data that are not distributed normally are shown by median (MDN) and interquartile range (IQR) and were analysed using a Man-Whitney-U-test for independent samples.

table 3: baseline characteristics of the organ recipients

recipient baseline characteristics			
	IL-2RA	**ATG**	**p-value**
age M (SD)	54,3 (11,4)	57,5 (10,3)	0,347
male N (%)	18 (90%)	9 (45%)	
female N (%)	2 (10%)	11 (55%)	
height [cm] M (SD)	173,3 (9,9)	171,4 (7,1)	0,493
weight [kg] M (SD)	79,8 (14,7)	80,9 (16,5)	0,834
BMI [kg/m²] M (SD)	26,5 (3,9)	27,6 (4,8)	0,447
duration of dialysis [months] MDN (IQR)	37 (34)	33,5 (30)	0,945
haemodialysis N (%)	15 (88,2 %)	19 (95%)	
peritoneal dialysis N (%)	2 (11,8%)	1 (5%)	
number of transplantations			
1 TX N (%)	17 (85%)	13 (65%)	
2 TX N (%)	3 (15%)	5 (25%)	
3 TX N (%)	0	1 (5%)	
4 TX N (%)	0	1 (5%)	
underlying renal disease			
autoimmune N (%)	2 (10%)	1 (5%)	
hypertension N (%)	2 (10%)	1 (5%)	
DM N (%)	3 15%)	4 (20%)	
glomerulonephritis N (%)	4 (20%)	4 (20%)	
PCKD N (%)	3 (15%)	2 (10%)	
unknown Kidney Disease N (%)	3 (15%)	2 (10%)	
others N (%)	3 (15%)	6 (30%)	

statistical analysis: Man-Whitney-U-test (exact significance); abbreviations: M = Mean; SD = standard deviation; N = number; MDN = median; IQR = interquartile range; TX = transplantation; DM = diabetes mellitus; PCKD = polycystic kidney disease; IL-2RA = interleukin-2 receptor antagonist; ATG = antithymocyte globulin

3.2.2 Donor baseline characteristics

In table 4, the baseline characteristics of the corresponding organ donors are presented. There was no significant difference when age and terminal serum creatinine were compared between the induction therapy groups. Again, M and SD were used to describe normally distributed data, which were further analysed with t-test for independent samples. MDN and IQR were used to present not normally distributed data to further analyse them using the Man-Whitney-U-test.

table 4: baseline characteristics of the organ donors

donor baseline characteristics			
	IL-2RA	**ATG**	**p-value**
age M (SD)	58,2 (11,8)	63,3 (7,5)	0,114
male N (%)	12 (60%)	8 (40%)	
female N (%)	8 (40%)	12 (60%)	
terminal serum creatinine [mg/dl] MDN (IQR)	0,82 (0,28)	0,73 (0,2)	0,738
previous Illness			
hypertension N (%)	7 (35%)	8 (40%)	
no hypertension N (%)	13 (65%)	12 (60%)	
cerebrovascular cause of death			
yes N (%)	16 (80%)	13 (65%)	
no N (%)	4 (20%)	7 (35%)	
non-heart-beating Donor			
yes N (%)	1 (5%)	3 (15%)	
no N (%)	19 (95%)	17 (85%)	

statistical analysis: Man-Whitney-U-test (exact significance); abbreviations: M = Mean; SD = standard deviation; N = number; MDN = median; IQR = interquartile range; IL-2RA = interleukin-2 receptor antagonist; ATG = antithymocyte globulin

3.3 Hospitalisations caused by infection

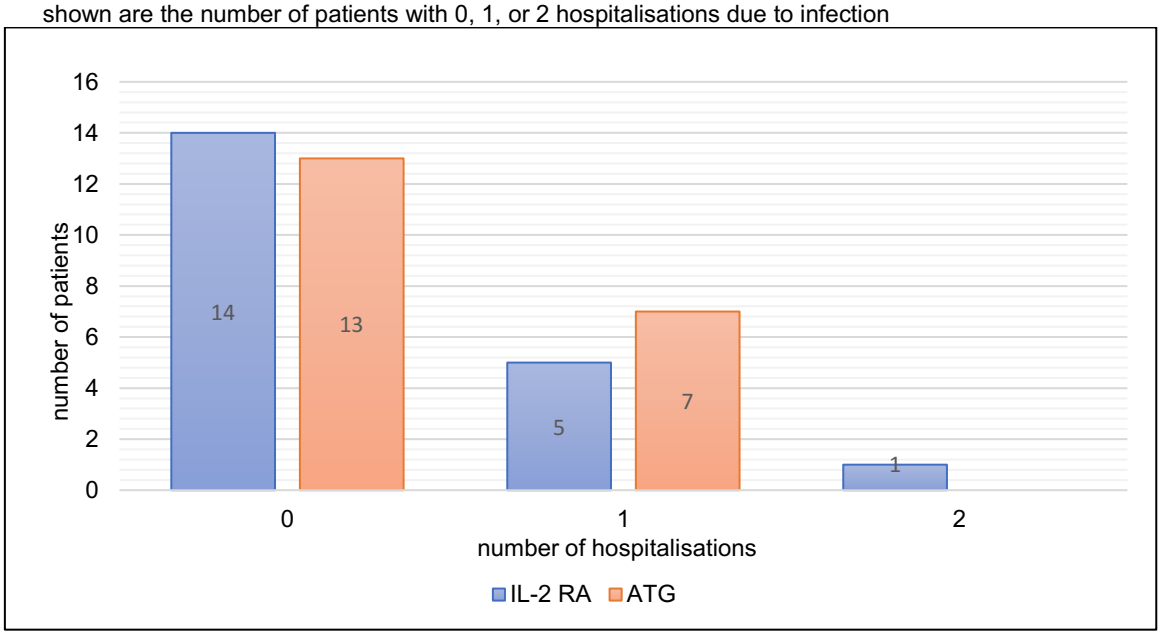
Major infections were defined as hospitalisation due to infection. The information was gathered from medical records for the follow-up period of one year after kidney transplantation. As shown in table 5, in the IL-2RA group 5 patients (25%) were hospitalised once and 1 patient (5%) was hospitalised twice with infectious indications. Within the ATG group, there was no patient that had to be hospitalised twice, but 7 patients (35%) that were hospitalised one time during the one-year follow-up. The Man-Whitney-U-test came to use, to compare the induction therapy groups. The follow-up period is shown in total and separately for the first month, month 2 to 6 and month 7 to 12 after the transplantation. It can be seen below, that there is no significant difference between the induction therapy groups in all the periods (p-values = 0,829; 1,0; 0,283; 0,382). figure 11 presents all major infections due to infectious indication during the one-year follow-up, sorted by induction therapy group.

table 5: major infections

total major infections			
	IL-2RA	**ATG**	**p-value**
number of patients within one-year follow-up showing			
no hospitalisation N (%)	14 (70%)	13 (65%)	
1 hospitalisation N (%)	5 (25%)	7 (35%)	*0,829*
2 hospitalisations N (%)	1 (5%)	0	
first month post TX			
	IL-2RA	**ATG**	**p-value**
number of patients within first month post TX showing			
no hospitalisation N (%)	19 (95%)	19 (95%)	*1,000*
1 hospitalisation N (%)	1 (5%)	1 (5%)	
month 2 - 6 post TX			
	IL-2RA	**ATG**	**p-value**
number of patients within month 2 - 6 post TX showing			
no hospitalisation N (%)	16 (80%)	18 (90%)	*0,382*
1 hospitalisation N (%)	4 (20%)	2 (10%)	
month 7 - 12 post TX			
	IL-2RA	**ATG**	**p-value**
number of patients within month 7 - 12 post TX showing			
no hospitalisation N (%)	18 (90%)	16 (80%)	*0,382*
1 hospitalisation N (%)	2 (10%)	4 (20%)	

statistical analysis: Man-Whitney-U-test (asymptomatic significance); abbreviations: N = number; TX = transplantation; IL-2RA = interleukin-2 receptor antagonist; ATG = antithymocyte globulin

figure 11: major infections during one-year follow-up
shown are the number of patients with 0, 1, or 2 hospitalisations due to infection



abbreviations: IL-2RA = interleukin-2 receptor antagonist; ATG = antithymocyte globulin

3.4 Infectious complications without hospitalisation

Infectious complications that did not lead to hospitalisation were cumulated as minor infections. They were made up of the sum of CMV, EBV and polyoma BK viraemia, as well as anti-infective agent use (except prophylaxis) and other infectious complications that were documented in the medical records. The results can be seen in table 6. Within the IL-2RA induction group, 78 minor infections occurred during the total follow-up period of one year, compared to 65 infectious complications without hospitalisation in the ATG group, making no significant difference (p = 0,228). What is interesting, is that during the first month after transplantation patients receiving ATG as induction therapy had, with a total of 30, significantly more minor infections, than IL-2RA recipients, in which 16 minor infections occurred (p=0,033). After the first post-transplant month, IL-2RA recipients showed more minor infections than patients induced with ATG (40 compared to 23, p =0,382; 22 compared to 12, p = 0,088). Again, the Man-Whitney-U-test was used for comparison between the different induction therapy groups.

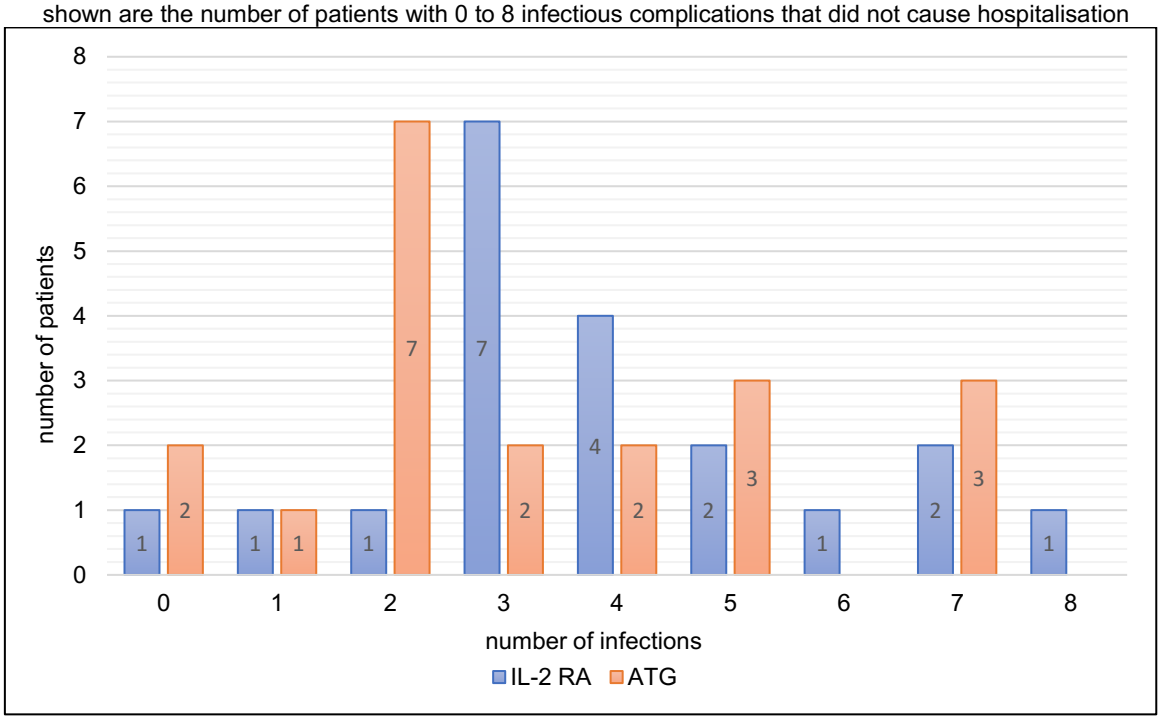
table 6: minor infections

total minor infections			
	IL-2RA	**ATG**	**p-value**
number of patients within one-year follow-up showing			
no complication without hospitalisation N (%)	1 (5%)	2 (10%)	
1 complication without hospitalisation N (%)	1 (5%)	1 (5%)	
2 complications without hospitalisation N (%)	1 (5%)	7 (35%)	
3 complications without hospitalisation N (%)	7 (35%)	2 (10%)	
4 complications without hospitalisation N (%)	4 (20%)	2 (10%)	*0,228*
5 complications without hospitalisation N (%)	2 (10%)	3 (15%)	
6 complications without hospitalisation N (%)	1 (5%)	0	
7 complications without hospitalisation N (%)	2 (10%)	3 (15%)	
8 complications without hospitalisation N (%)	1 (5%)	0	
total minor infections within induction group N	**78**	**65**	
first month post TX			
	IL-2RA	**ATG**	**p-value**
number of patients within first month post TX showing			
no complication without hospitalisation N (%)	11 (55%)	4 (20%)	
1 complication without hospitalisation N (%)	5 (25%)	8 (40%)	
2 complications without hospitalisation N (%)	2 (10%)	2 (10%)	***0,033***
3 complications without hospitalisation N (%)	1 (5%)	6 (30%)	
4 complications without hospitalisation N (%)	1 (5%)	0	
total minor infections within induction group N	**16**	**30**	
month 2 to 6 post TX			
	IL-2RA	**ATG**	**p-value**
number of patients within month 2 - 6 post TX showing			
no complication without hospitalisation N (%)	4 (20%)	8 (40%)	
1 complication without hospitalisation N (%)	2 (10%)	6 (30%)	
2 complications without hospitalisation N (%)	6 (30%)	3 (15%)	*0,382*
3 complications without hospitalisation N (%)	6 (30%)	2 (10%)	
4 complications without hospitalisation N (%)	2 (10%)	0	
5 complications without hospitalisation N (%)	0	1 (5%)	
total minor infections within induction group N	**40**	**23**	
month 7 to 12 post TX			
	IL-2RA	**ATG**	**p-value**
number of patients during month 7 - 12 post TX showing			
no complication without hospitalisation N (%)	6 (30%)	11 (55%)	
1 complication without hospitalisation N (%)	8 (40%)	6 (30%)	*0,088*
2 complications without hospitalisation N (%)	4 (20%)	3 (15%)	
3 complications without hospitalisation N (%)	2 (10%)	0	
total minor infections within induction group N	**22**	**12**	

statistical analysis: Man-Whitney-U-test (asymptomatic significance); abbreviations: N = number; TX = transplantation; IL-2RA = interleukin-2 receptor antagonist; ATG = antithymocyte globulin

In figure 12, the number of patients showing 0 to 8 infections during the follow-up period of one year are presented, sorted by induction group.

figure 12: minor infections during one-year follow-up
shown are the number of patients with 0 to 8 infectious complications that did not cause hospitalisation



abbreviations: IL-2RA = interleukin-2 receptor antagonist; ATG = antithymocyte globulin

3.4.1 CMV episodes

Patients receiving ATG showed slightly more CMV viraemia throughout the follow-up, than patients induced with IL-2RA (p =0,441). Each episode of PCR-positive CMV viraemia after negative PCR results in the previous laboratory was counted as one CMV episode. Episodes that spanned several periods of the follow-up were counted to the first episode they occurred in. The Man-Whitney-U-test was used for group comparison. The only period that showed significant differences, was the late post-transplant period of 7 to 12 months after transplantation. During this period, 4 patients (20%) suffered from CMV viraemia, while within the ATG group no patient had PCR-positive results (p =0,037). table 7 lists all CMV viraemia per induction group divided into the different periods after transplantation.

In figure 13, the PCR-positive CMV viraemia episodes during the follow-up period of one year are presented.

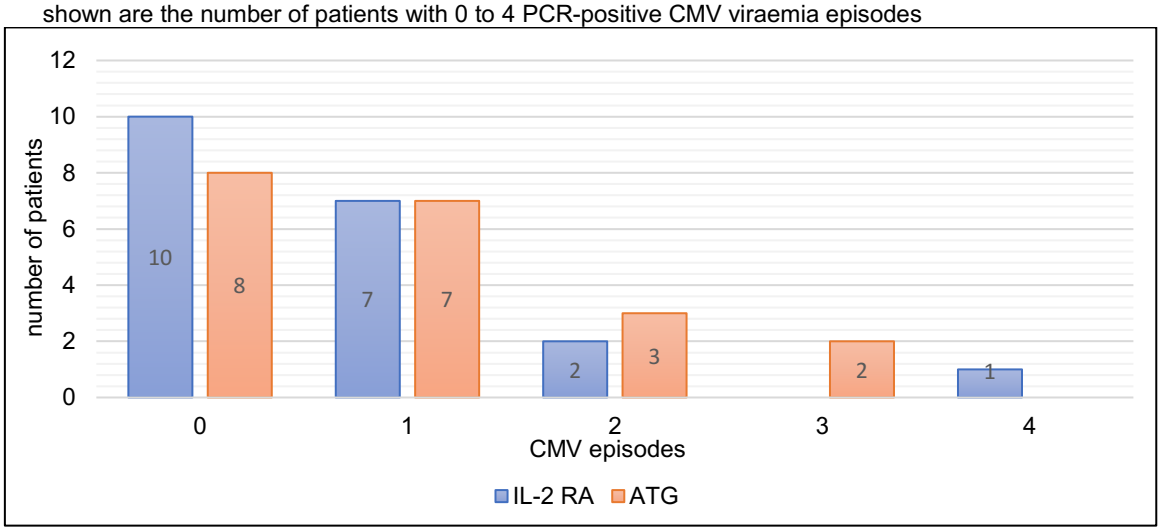
table 7: CMV viraemia

shown are numbers of patients with episodes of PCR-positive CMV viraemia results

total CMV episodes			
	IL-2RA	**ATG**	**p-value**
number of patients within one-year follow-up showing			
no PCR-positive CMV episodes N (%)	10 (50%)	8 (40%)	
1 PCR-positive CMV episode N (%)	7 (35%)	7 (35%)	
2 PCR-positive CMV episodes N (%)	2 (10%)	3 (15%)	*0,441*
3 PCR-positive CMV episodes N (%)	0	2 (10%)	
4 PCR-positive CMV episodes N (%)	1 (5%)	0	
total PCR-positive CMV episodes within induction group N	**15**	**19**	
first month post TX			
	IL-2RA	**ATG**	**p-value**
number of patients within first month post TX showing			
no PCR-positive CMV episodes N (%)	16 (80%)	11 (55%)	*0,096*
1 PCR-positive CMV episode N (%)	4 (20%)	9 (45%)	
total PCR-positive CMV episodes within induction group N	**4**	**9**	
month 2 to 6 post TX			
	IL-2RA	**ATG**	**p-value**
number of patients within month 2 - 6 post TX showing			
no PCR-positive CMV episodes N (%)	14 (75%)	12 (65%)	
1 PCR-positive CMV episode N (%)	5 (20%)	6 (25%)	*0,478*
2 PCR-positive CMV episodes N (%)	1 (5%)	2 (10%)	
total PCR-positive CMV episodes within induction group N	**7**	**10**	
month 7 to 12 post TX			
	IL-2RA	**ATG**	**p-value**
number of patients within month 7 - 12 post TX showing			
no PCR-positive CMV episodes N (%)	16 (80%)	20 (100%)	***0,037***
1 PCR-positive CMV episode N (%)	4 (20%)	0	
total PCR-positive CMV episodes within induction group N	**4**	**0**	

statistical analysis: Man-Whitney-U-test (asymptomatic significance); abbreviations: CMV = cytomegalovirus; PCR = polymerase chain reaction; N = number; TX = transplantation; IL-2RA = interleukin-2receptor antagonist; ATG = antithymocyte globulin

figure 13: CMV viraemia episodes during one-year follow-up
shown are the number of patients with 0 to 4 PCR-positive CMV viraemia episodes



abbreviations: CMV = cytomegalovirus; PCR = polymerase chain reaction; IL-2RA = interleukin-2 receptor antagonist; ATG = antithymocyte globulin

3.4.2 EBV episodes

Significant differences were found between the two induction groups, when PCR-positive EBV viraemia episodes were compared, as shown in table 8. During the complete one-year follow up, 12 EBV episodes occurred within ATG group, while 4 were recorded in IL-2RA group (p =0,047). While no differences can be seen from the second post-transplant month on, 9 patients (45%) receiving ATG showed one EBV viraemia compared to 0 patients with 1 episode and 1 patient (5%) with 2 episodes within IL-2RA recipients (p = 0,007). Again, each episode of PCR-positive EBV viraemia after negative PCR results in the previous laboratory was counted as one EBV episode. Episodes that spanned several periods of the follow-up were counted to the first episode they occurred in. For statistical analysis, the Man-Whitney-U-test came to use. In figure 14, EBV viraemia episodes within the complete follow-up period of one year are presented.

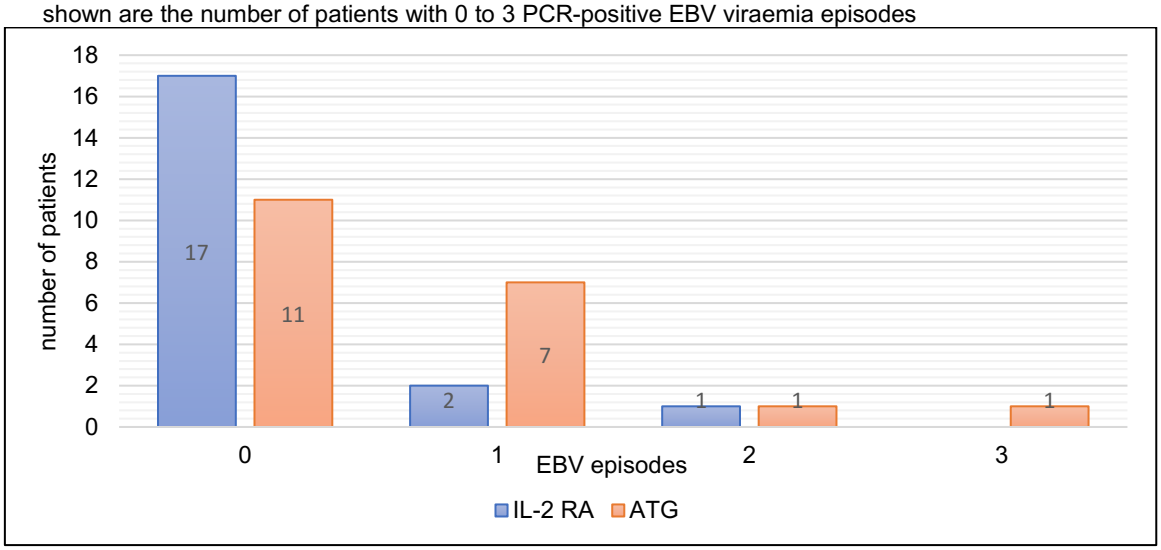
table 8: EBV viraemia

shown are numbers of patients with episodes of PCR-positive EBV viraemia results

total EBV episodes			
	IL-2RA	**ATG**	**p-value**
number of patients within one-year follow-up showing			
no PCR-positive EBV episodes N (%)	17 (85%)	11 (55%)	
1 PCR-positive EBV episode N (%)	2 (10%)	7 (35%)	***0,047***
2 PCR-positive EBV episodes N (%)	1 (5%)	1 (5%)	
3 PCR-positive EBV episodes N (%)	0	1 (5%)	
total PCR-positive EBV episodes within induction group N	**4**	**12**	
first month post TX			
	IL-2RA	**ATG**	**p-value**
number of patients within first month post TX showing			
no PCR-positive EBV episodes N (%)	19 (95%)	11 (55%)	
1 PCR-positive EBV episode N (%)	0	9 (45%)	***0,007***
2 PCR-positive EBV episodes N (%)	1 (5%)	0	
total PCR-positive EBV episodes within induction group N	**2**	**9**	
month 2 to 6 post TX			
	IL-2RA	**ATG**	**p-value**
number of patients within month 2 - 6 post TX showing			
no PCR-positive EBV episodes N (%)	18 (90%)	18 (90%)	
1 PCR-positive EBV episode N (%)	2 (10%)	1 (5%)	*0,959*
2 PCR-positive EBV episodes N (%)	0	1 (5%)	
total PCR-positive EBV episodes within induction group N	**2**	**3**	
month 7 to 12 post TX			
	IL-2RA	**ATG**	**p-value**
number of patients within month 7 - 12 post TX showing			
no PCR-positive EBV episodes N (%)	20 (100%)	20 (100%)	*1,000*
total PCR-positive EBV episodes within induction group N	**0**	**0**	

statistical analysis: Man-Whitney-U-test (asymptomatic significance); abbreviations: EBV = Epstein-Barr virus; PCR = polymerase chain reaction; N = number; TX = transplantation; IL-2RA = interleukin-2 receptor antagonist; ATG = antithymocyte globulin

figure 14: EBV viraemia episodes during one-year follow-up
shown are the number of patients with 0 to 3 PCR-positive EBV viraemia episodes



abbreviations: EBV = Epstein-Barr virus; PCR = polymerase chain reaction; IL-2RA = interleukin-2 receptor antagonist; ATG = antithymocyte globulin

3.4.3 BK-Polyoma-Virus episodes

No significant difference was found between the induction groups concerning BK-polyomavirus viraemia episodes (p values = 0,275; 1,0; 0,515; 0,152). Comparison was made using the Man-Whitney-U-test. Detailed numbers are listed in table 9. An episode was defined as a PCR-positive lab result after the previous result were negative. When an episode spread over more than one period of the follow-up, it came to count in the period it first appeared in. figure 15 shows the number of patients showing 0 to 4 episodes during the follow-up period of one year.

table 9: BK-polyomavirus viraemia

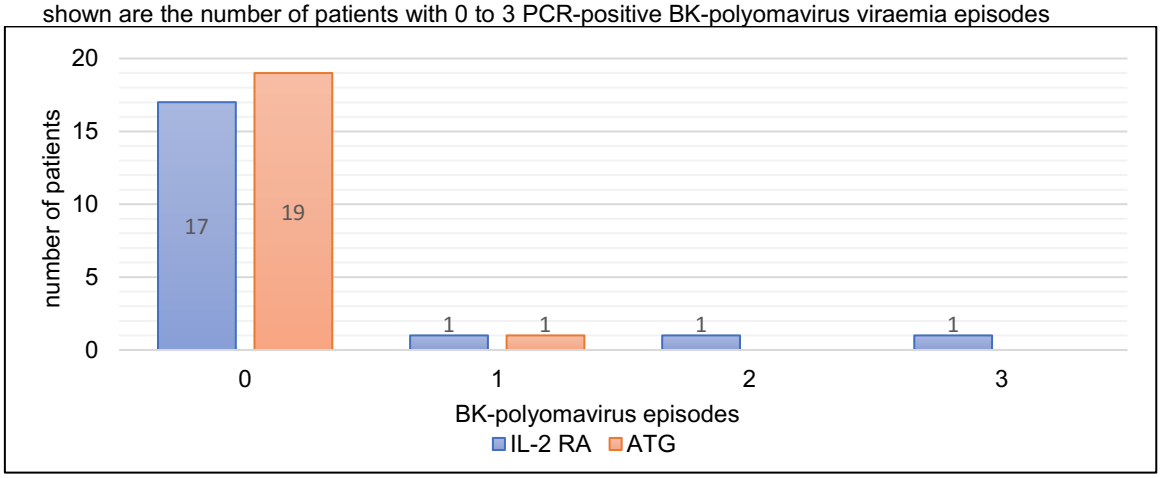
shown are numbers of patients with episodes of PCR-positive BK polyomavirus viraemia results

total BK-polyomavirus episodes			
	IL-2RA	**ATG**	**p-value**
number of patients within one-year follow-up showing			
no PCR-positive BK-P-V episodes N (%)	17 (85%)	19 (95%)	
1 PCR-positive BK-P-V episode N (%)	1 (5%)	1 (5%)	*0,275*
2 PCR-positive BK-P-V episodes N (%)	1 (5%)	0	
3 PCR-positive BK-P-V episodes N (%)	1 (5%)	0	
total PCR-positive BK-P-V episodes within induction group N	**6**	**1**	
first month post TX			
	IL-2RA	**ATG**	**p-value**
number of patients within first month post TX showing			
no PCR-positive BK-P-V episodes N (%)	20 (100%)	20 (100%)	*1,000*
total PCR-positive BK-P-V episodes within induction group N	**0**	**0**	
month 2 to 6 post TX			
	IL-2RA	**ATG**	**p-value**
number of patients within month 2 - 6 post TX showing			
no PCR-positive BK-P-V episodes N (%)	18 (90%)	19 (95%)	
1 PCR-positive BK-P-V episode N (%)	0	1 (5%)	*0,515*
2 PCR-positive BK-P-V episodes N (%)	2 (10%)	0	
total PCR-positive BK-P-V episodes within induction group N	**4**	**1**	
month 7 to 12 post TX			
	IL-2RA	**ATG**	**p-value**
number of patients within month 7 - 12 post TX showing			
no PCR-positive BK-P-V episodes N (%)	18 (90%)	12 (100%)	*0,152*
1 PCR-positive BK-P-V episode N (%)	2 (10%)	0	
total PCR-positive BK-P-V episodes within induction group N	**2**	**0**	

statistical analysis: Man-Whitney-U-test (asymptomatic significance); abbreviations: BK-P-V = BK-polyomavirus; PCR = polymerase chain reaction; N = number; TX = transplantation; IL-2RA = interleukin-2 receptor antagonist; ATG = antithymocyte globulin

figure 15: BK-polyomavirus viraemia episodes during one-year follow-up

shown are the number of patients with 0 to 3 PCR-positive BK-polyomavirus viraemia episodes



abbreviations: PCR = polymerase chain reaction; IL-2RA = interleukin-2 receptor antagonist; ATG = antithymocyte globulin

3.4.4 Anti-infective medications

Using medical records, the number of complications that indicated anti-infective medication was assessed. Excluded were anti-infective agents that were used for prophylaxis, when antibiotics had to be adapted and switched, it was not counted as new anti-infective medication. There was a significant difference between the induction group when total number of the one-year follow-up are regarded (p = 0,031). While there were no differences in the first month and after a half year after transplantation, during the intermediate post-transplant period from 2 to 6 months after transplantation 26 anti-infective usages in IL-2RA group face 9 in ATG group (p = 0,005). Among the patients receiving IL-2RA, 7 (35%) needed anti-infective treatment once, while 5 (25%) showed 2 and 3 (15%) showed 3 indications for the usage of antibiotics, antiviral or antifungal medication. Compared to this, 3 (15%) patients receiving ATG needed one and 3 (15%) patients needed 2 interventions with anti-infective agents. The Man-Whitney-U-test came to use for comparison, the results are listed in table 10, figure 16 shows a bar chart showing the complications that led to anti-infective treatment during the one-year follow-up period.

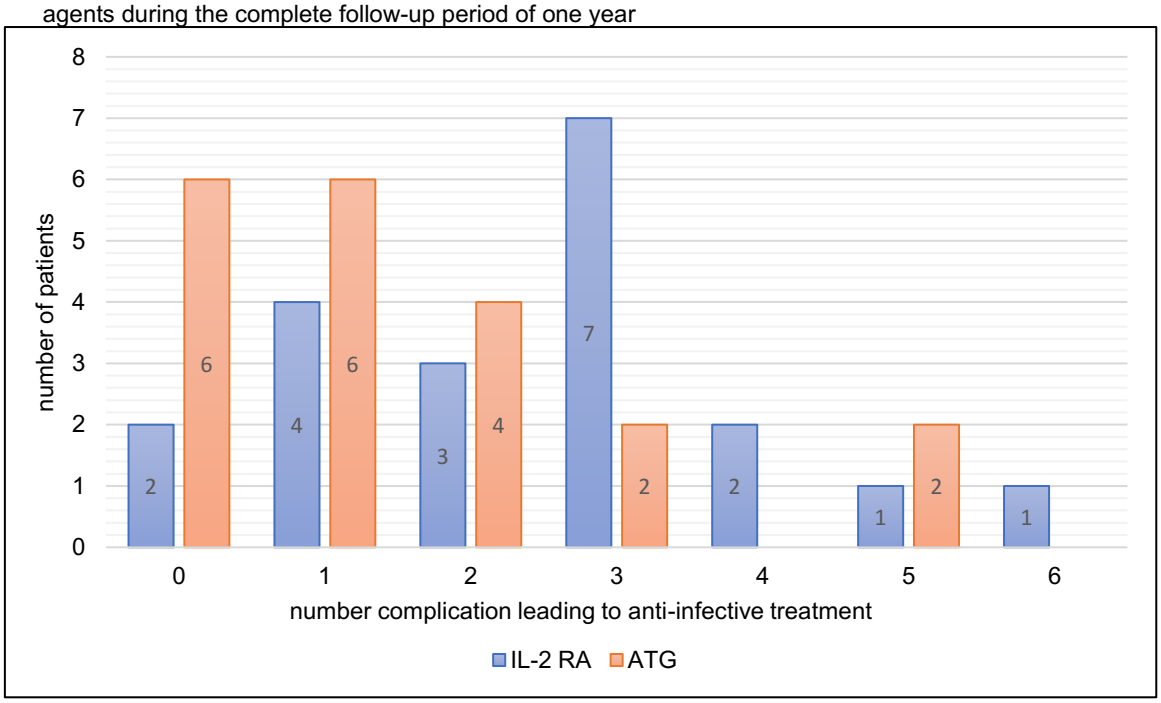
table 10: anti-infective medications

total anti-infective medications			
	IL-2RA	**ATG**	**p-value**
number of patients within one-year follow-up being treated with			
no anti-infective medications N (%)	2 (10%)	6 (30%)	
1 anti-infective medication N (%)	4 (20%)	6 (30%)	
2 anti-infective medications N (%)	3 (15%)	4 (20%)	
3 anti-infective medications N (%)	7 (35%)	2 (10%)	***0,031***
4 anti-infective medications N (%)	2 (10%)	0	
5 anti-infective medications N (%)	1 (5%)	2 (10%)	
6 anti-infective medications N (%)	1 (5%)	0	
total anti-infective medications within induction group N	**50**	**30**	
first month post TX			
	IL-2RA	**ATG**	**p-value**
number of patients within one-year follow-up being treated with			
no anti-infective medications N (%)	12 (60%)	12 (60%)	
1 anti-infective medication N (%)	7 (35%)	5 (25%)	*0,804*
2 anti-infective medications N (%)	1 (5%)	3 (15%)	
total anti-infective medications within induction group N	**9**	**11**	
month 2 to 6 post TX			
	IL-2RA	**ATG**	**p-value**
number of patients within one-year follow-up being treated with			
no anti-infective medications N (%)	5 (25%)	14 (70%)	
1 anti-infective medication N (%)	7 (35%)	3 (15%)	***0,005***
2 anti-infective medications N (%)	5 (25%)	3 (15%)	
3 anti-infective medications N (%)	3 (15%)	0	
total anti-infective medications within induction group N	**26**	**9**	
month 7 to 12 post TX			
	IL-2RA	**ATG**	**p-value**
number of patients within one-year follow-up being treated with			
no anti-infective medications N (%)	8 (40%)	12 (60%)	
1 anti-infective medication N (%)	10 (50%)	6 (30%)	*0,266*
2 anti-infective medications N (%)	1 (5%)	2 (10%)	
3 anti-infective medications N (%)	1 (5%)	0	
total anti-infective medications within induction group N	**15**	**10**	

statistical analysis: Man-Whitney-U-test (asymptomatic significance); abbreviations: N = number; TX = transplantation; IL-2RA = interleukin-2 receptor antagonist; ATG = antithymocyte globulin

figure 16: number of complications that led to anti-infective treatment

shown are the number of patients with 0 to 6 infectious complications that were treated with anti-infective agents during the complete follow-up period of one year



abbreviations: IL-2RA = interleukin-2 receptor antagonist; ATG = antithymocyte globulin

3.4.5 Other infectious complications

Other infections were defined as infectious complications that were documented in medical records but did not indicate anti-infective therapy or hospitalisation. All the infections that met criteria of previous infection categories were excluded. Examples for other infectious complications are respiratory infections, urinary tract infections or local herpes infections. Between the induction groups, no significant differences were recorded (p = 1,0; 1,0; 0,317; 0, 553) when compared with the Man-Whitney-U-test. The number of patients suffering from other infections is shown in table 11.

table 11: other infectious complications

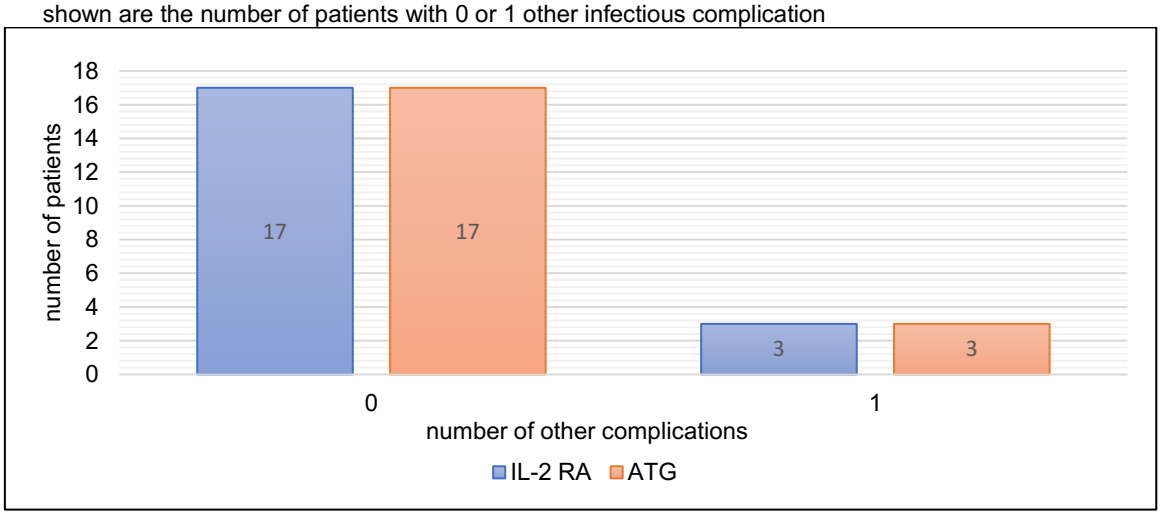
total other infectious complications			
	IL-2RA	**ATG**	**p-value**
number of patients within one-year follow-up showing			
no other infectious complication N (%)	17 (85%)	17 (85%)	*1,000*
1 other infectious complication N (%)	3 (15%)	3 (15%)	
total other infectious complications within induction group N	**3**	**3**	
first month post TX			
	IL-2RA	**ATG**	**p-value**
number of patients within one-year follow-up showing			
no other infectious complication N (%)	19 (95%)	19 (95%)	*1,000*
1 other infectious complication N (%)	1 (5%)	1 (5%)	
total other infectious complications within induction group N	**1**	**1**	
month 2 to 6 post TX			
	IL-2RA	**ATG**	**p-value**
number of patients within one-year follow-up showing			
no other infectious complication N (%)	19 (95%)	20 (100%)	*0,317*
1 other infectious complication N (%)	1 (5%)	0	
total other infectious complications within induction group N	**1**	**0**	
month 7 to 12 post TX			
	IL-2RA	**ATG**	**p-value**
number of patients within one-year follow-up showing			
no other infectious complication N (%)	19 (95%)	18 (90%)	*0,553*
1 other infectious complication N (%)	1 (5%)	2 (10%)	
total other infectious complications within induction group N	**1**	**2**	

statistical analysis: Man-Whitney-U-test (asymptomatic significance); abbreviations: N = number; TX = transplantation; IL-2RA = interleukin-2 receptor antagonist; ATG = antithymocyte globulin

In figure 17, all other infectious complications during the follow-up period of one year are shown in a bar chart.

figure 17: number of other infectious complications

shown are the number of patients with 0 or 1 other infectious complication



abbreviations: IL-2RA = interleukin-2 receptor antagonist; ATG = antithymocyte globulin

3.5 Total infectious complications

For table 12, major and minor infections were summed up and listed. When the severity of infection is left completely unconsidered and only the quantity is regarded, there is no significant difference between IL-2RA induction and ATG induction when the follow-up period is analysed altogether (p =0,323). What stands out, is that there are 4 patients (20%) within the IL-2RA group, that suffered from a total of 8 infections during the one-year follow-up, which is the maximum value, compared to only 1 patient (5%) in ATG group.

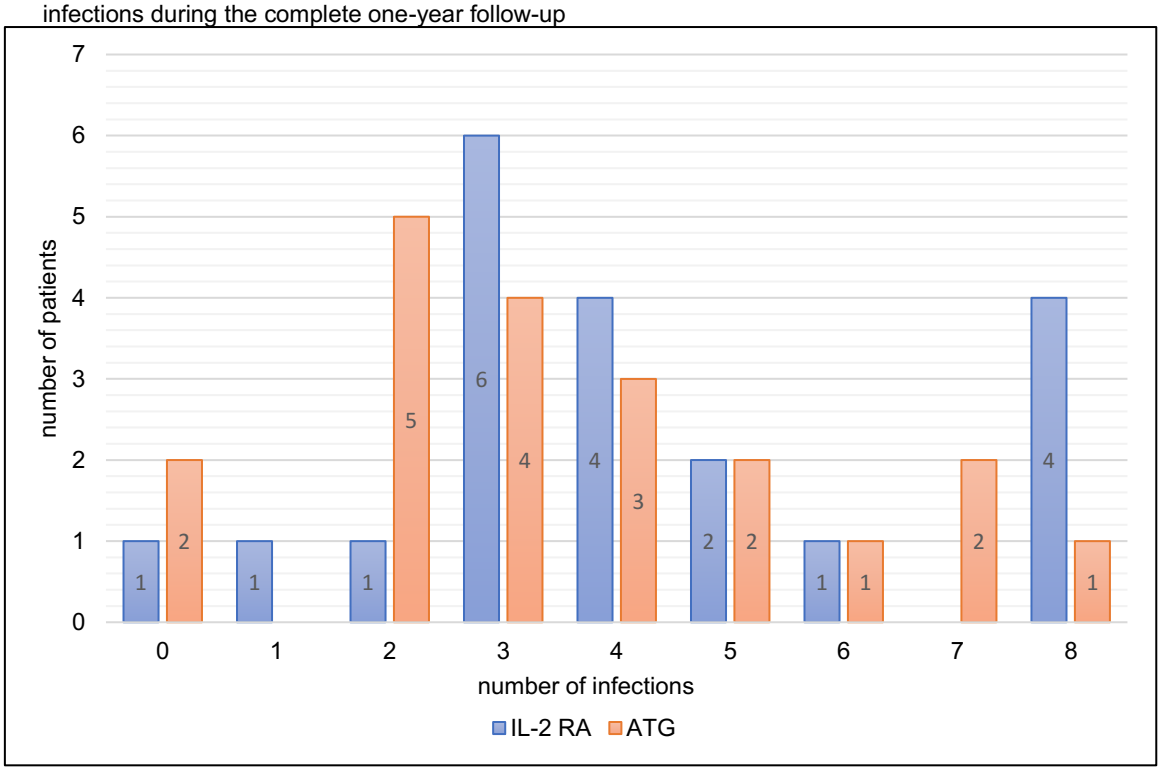
In the first month after transplantation, ATG-induced patients showed a total of 31 infections, while IL-2RA induction caused only 17 infections within the induction group (p = 0,036). In the intermediate post-transplant period on the other hand, IL-2RA caused more infections, with 44 within the induction group facing 25 within the ATG group (p = 0,027). For comparison again, the Man-Whitney-U-test came to use. In figure 18 the number of total infections is displayed.

table 12: total infectious complications
shown is the sum of major and minor infections

major and minor infections			
	IL-2RA	**ATG**	**p-value**
number of patients within one-year follow-up showing			
no infections N (%)	1 (5%)	2 (10%)	
1 infection N (%)	1 (5%)	0	
2 infections N (%)	1 (5%)	5 (25%)	
3 infections N (%)	6 (30%)	4 (20%)	
4 infections N (%)	4 (20%)	3 (15%)	*0,323*
5 infections N (%)	2 (10%)	2 (10%)	
6 infections N (%)	1 (5%)	1 (5%)	
7 infections N (%)	0	2 (10%)	
8 infections N (%)	4 (20%)	1 (5%)	
total infections within induction group N	**85**	**72**	
first month post TX			
	IL-2RA	**ATG**	**p-value**
number of patients within first month post TX showing			
no infections N (%)	11 (55%)	4 (20%)	
1 infection N (%)	5 (25%)	7 (35%)	
2 infections N (%)	1 (5%)	3 (15%)	***0,036***
3 infections N (%)	2 (10%)	6 (30%)	
4 infections N (%)	1 (5%)	0	
total infections within induction group N	**17**	**31**	
month 2 to 6 post TX			
	IL-2RA	**ATG**	**p-value**
number of patients within month 2 - 6 post TX showing			
no infections N (%)	4 (20%)	8 (40%)	
1 infection N (%)	1 (5%)	5 (25%)	
2 infections N (%)	5 (25%)	4 (20%)	
3 infections N (%)	7 (35%)	1 (5%)	***0,027***
4 infections N (%)	3 (15%)	1 (5%)	
5 infections N (%)	0	1 (5%)	
total infections within induction group N	**44**	**25**	
month 7 to 12 post TX			
	IL-2RA	**ATG**	**p-value**
number of patients within month 7 - 12 post TX showing			
no infections N (%)	6 (30%)	10 (50%)	
1 infection N (%)	8 (40%)	5 (25%)	
2 infections N (%)	3 (15%)	4 (20%)	*0,253*
3 infections N (%)	2 (10%)	1 (5%)	
4 infections N (%)	1 (5%)	0	
total infections within induction group N	**24**	**16**	

statistical analysis: Man-Whitney-U-test (asymptomatic significance); abbreviations: N = number; TX = transplantation; IL-2RA = interleukin-2 receptor antagonist; ATG = antithymocyte globulin

figure 18: number of total infectious complications
shown are the number of patients with 0 to 8 infectious complications, summed up from major and minor infections during the complete one-year follow-up



abbreviations: IL-2RA = interleukin-2 receptor antagonist; ATG = antithymocyte globulin

3.6 Side findings

3.6.1 Kidney function

The kidney function of the 40 patients included, was assessed by eGFR CKD-EPI, serum creatinine and serum urea, recorded 1, 8, 26 and 52 weeks after transplantation. The groups show no significant differences, as can be seen in table 13. The median eGFR of the patients receiving IL-2RA as induction therapy was 50,9 with an IQR of 30,6, compared to a MDN of 46,1 and an IQR of 21,2 in ATG recipients.

table 13: kidney function during one-year post-transplant follow-up

kidney function			
	IL-2RA	**ATG**	**p-value**
graft function			
immediate graft function N (%)	10 (50%)	9 (45%)	
delayed graft function N (%)	10 (50%)	11 (55%)	
graft survival after one year			
yes N (%)	19 (95%)	20 (100%)	
no N (%)	1 (5%)	0	
serum creatinine [mg/dl]			
1 week post TX MDN (IQR)	3,8 (4,22)	2,4 (2,9)	0,341
8 weeks post TX MDN (IQR)	1,4 (0,6)	1,5 (0,8)	0,883
26 weeks post TX MDN (IQR)	1,6 (0,6)	1,6 (0,7)	0,738
52 weeks post TX MDN (IQR)	1,5 (0,7)	1,4 (0,75)	0,758
serum urea [mg/dl]			
1 week post TX MDN (IQR)	110 (57)	99,5 (54)	0,659
8 weeks post TX MDN (IQR)	48 (43)	56,5 (35)	0,529
26 weeks post TX MDN (IQR)	60 (42)	58,5 (24)	1,000
52 weeks post TX MDN (IQR)	50 (42)	53,5 (34)	0,857
e GFR CKD-BP			
1 week post TX MDN (IQR)	15,1 (29,6)	24,6 (19,8)	0,698
8 weeks post TX MDN (IQR)	57,2 (29,0)	44,3 (28,8)	0,242
26 weeks post TX MDN (IQR)	48,0 (29,1)	43,3 (16,4)	0,495
52 weeks post TX MDN (IQR)	50,9 (30,6)	46,1 (21,1)	0,414

statistical analysis: Man-Whitney-U-test (exact significance); abbreviations: N = number; TX = transplantation; MDN = median; IQR = interquartile range; eGFR CKD-EPI = estimated glomerular filtration rate (chronic kidney disease epidemiology collaboration); IL-2RA = interleukin-2 receptor antagonist; ATG = antithymocyte globulin

3.6.2 FK 506 levels

The FK 506 levels of the patients were measured on day 3 and 7 after transplantation. There was a significant difference on day 3 with IL-2RA induction leading to a median of 8,9 ng/ml (IQR = 6,3) compared to a median of 6,35 ng/ml (IQR = 4,8) in ATG recipients (p = 0,035). On day 7, there were no significant differences between the groups (p = 0,253). The Man-Whitney-U-test came to use for statistical analysis. The results are shown in table 14.

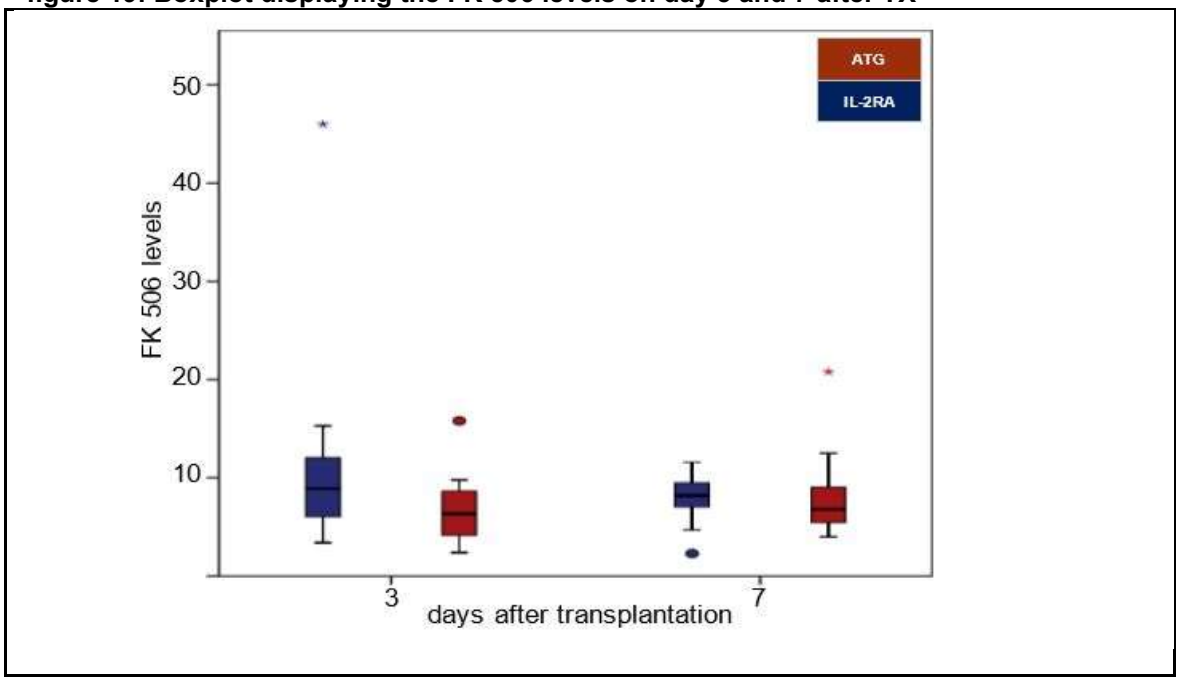
In figure 19, a boxplot displays the FK 506 levels measured on day 3 and 7.

table 14: FK 506 levels on day 3 and 7 after transplantation

FK 506 levels sorted by induction therapy			
	IL-2RA	**ATG**	**p-value**
FK 506 levels [ng/ml]			
3 days post TX MDN (IQR)	8,9 (6,3)	6,35 (4,8)	**0,035**
6 days post TX MDN (IQR)	8,2 (2,6)	6,8 (4)	0,253

statistical analysis: Man-Whitney-U-test (asymptomatic significance); abbreviations: TX = transplantation; MDN = median; IQR = interquartile range; IL-2RA = interleukin-2 receptor antagonist; ATG = antithymocyte globulin

figure 19: Boxplot displaying the FK 506 levels on day 3 and 7 after TX



note: boxplot (°= moderate outsiders >1,5 SDs; * = extreme outsiders > 3 SDs); abbreviations: TX = transplantation; IL-2RA = interleukin-2 receptor antagonist; ATG = antithymocyte globulin; SDs = standard deviations

3.6.3 Leucocytes

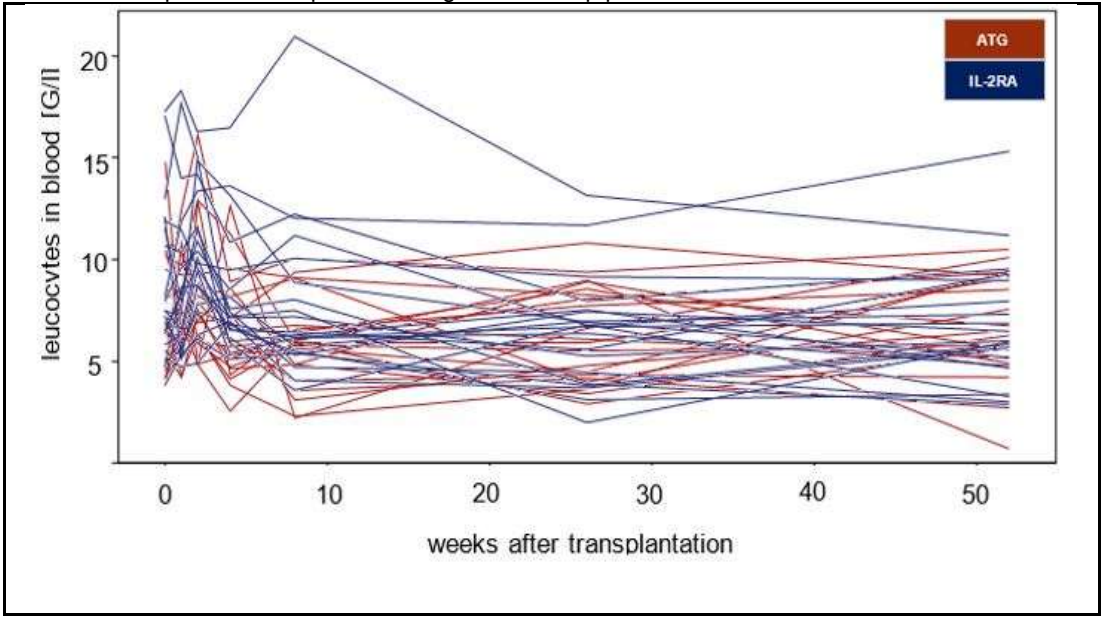
Leucocytes in blood were screened 0, 1, 2, 4, 8, 26 and 52 weeks after transplantation. MDN and IQR, as p-values calculated using the Man-Whitney-U-test can be seen in table 15. A significant difference in leucocytes in blood was observed two weeks after transplantation, when ATG induced patients had a median leucocyte level in blood of 7,44 G/l (IQR = 2,8) compared to 9,95 G/l (IQR =4,9) in IL-2RA group (p = 0,01). In figure 20, a diagram displays how leucocyte levels developed over time within the induction groups.

table 15: leucocytes in blood during follow-up period

leucocytes			
	IL-2RA	**ATG**	**p-value**
leucocytes in blood [G/l]			
day of transplantation MDN (IQR)	7,50 (5,9)	6,59 (4,4)	0,127
1 week after transplantation MDN (IQR)	9,14 (5,7)	6,46 (3,6)	0,242
2 weeks after transplantation MDN (IQR)	9,95 (4,9)	7,44 (2,8)	**0,010**
4 weeks after transplantation MDN (IQR)	7,17 (2,7)	6,00 (3,8)	0,056
8 weeks after transplantation MDN (IQR)	6,35 (4,4)	5,91 (2,5)	0,108
26 weeks after transplantation MDN (IQR)	6,72 (3,5)	5,99 (4,3)	1,000
52 weeks after transplantation MDN (IQR)	5,97 (4,0)	6,64 (4,0)	0,602

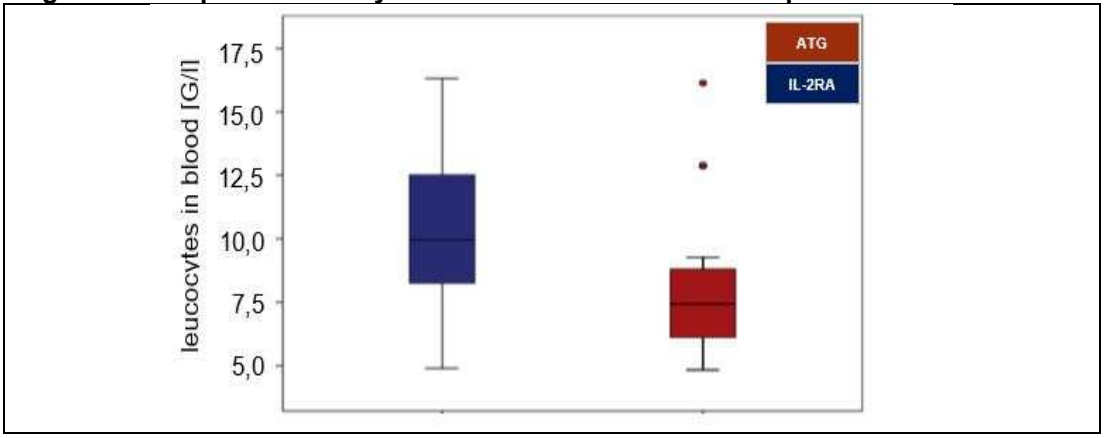
statistical analysis: Man-Whitney-U-test (exact significance); abbreviations: MDN = median; IQR = interquartile range; IL-2RA = interleukin-2 receptor antagonist; ATG = antithymocyte globulin

figure 20: leucocytes process flow during one-year follow-up
each line represents one patient during the follow-up period



abbreviations: IL-2RA = interleukin-2 receptor antagonist; ATG = antithymocyte globulin

figure 21: boxplot of leucocytes in blood 2 weeks after transplantation



note: boxplot (°= moderate outsiders >1,5 SDs); abbreviations: IL-2RA = interleukin-2 receptor antagonist; ATG = antithymocyte globulin; SDs = standard deviations

4 Discussion

This small retrospective study aimed to evaluate the induction therapy of ECD kidney recipients with ATG for reduction of CNI through levels. The main endpoint evaluated was the rate of major infections which required hospitalisation. The present diploma thesis evaluated the one-year post-transplant incidence of infectious complications, while another diploma thesis prepared in parallel evaluated the rejection rates with these two different induction strategies. Therefore, 20 patients receiving ATG as induction therapy while targeting lower CNI through levels were compared to 20 prior patients who received standard immunosuppressive therapy with IL-2RAs and standard FK506 through levels.

We found that there were no significant differences between the two induction groups concerning graft function and major infection rates during the first year after kidney transplantation. There was however a significant difference in FK 506 levels between the two groups on the third day after transplantation. With the firm caveat of the small sample size of this study, these results allow us to cautiously draw two different conclusions – one – that ATG induction therapy is noninferior to IL-2RA induction regarding major infection rates, and – two – that the desired reduction of CNI through levels in ECD kidney recipients can be achieved with ATG induction. Importantly, as far as the limited sample size allows to draw conclusions, these data do not show the desired effect of an improvement in post-transplant graft function compared to patients exposed standard CNI through levels.

Within each group, a relatively low incidence of major (i.e. requiring hospitalisations) infections was recorded. Seven hospitalisations due to infection occurred in each group during the one-year follow-up. On the other hand, with 4 hospitalisations, the greater part of major infections in IL-2RA recipients occurred during the intermediate-post-transplant-period, while 4 ATG recipients – the bulk of major infections within the group – was hospitalised later than 6 months after the transplantation. These results suggest that ATG has prolonged immunosuppressive effects in comparison to IL-2RA. These findings confirm our expectations and are consistent with the findings of a small retrospective study from Spain (81) and a recent meta-analysis of cardiac transplantations (94) also comparing IL-2RAs to ATG. Also, this nicely concurs with what is widely known about the immunomodulatory effects of ATG.

When it comes to minor infections, which for this study were defined as infectious complications that did not lead to hospitalisation, no significant difference was found between the groups during the complete follow-up period. In the first month however, ATG recipients suffered from almost twice as much infectious complications (p = 0,033) as IL-2RAs recipients. Broken down to the individual causes, this is mostly due to EBV infections or reactivations, which were significantly increased in frequency in ATG recipients during this early post-transplant period. This leads to the conclusion that ATG induction may render the recipients more vulnerable to EBV infection/reactivation and that, therefore, special attention should be taken. Pathophysiologically, the long-lasting leucopaenia and especially lymphopaenia may be responsible for this increased risk of EBV replication (72). This observation is potentially of high-relevance, since EBV infection/reactivation (especially in seronegative patients) is associated with a considerable increase in the incidence of PTLD (100). Concern over potentially increased risk of PTLD in ATG is not a novel concern (72) and was addressed in a number of retrospective studies. In 2007 Kirk et al. showed in approximately 60.000 kidney allograft recipients, that PTLD incidence is significantly associated with induction therapy (101), where ATG was significantly associated with a higher incidence compared to alemtuzumab induction and no induction. However, retrospective analysis is inherently prone to bias: despite statistical adjusting the fact that ATG recipients are likely to be rejecting or at higher immunological risk and thus be receiving higher maintenance immunosuppressive therapy renders any causal inference problematic. Accordingly, both Kirk and Brennan et al (79) noted that PTLD is more strongly associated with maintenance rather than induction therapy.

In terms of CMV infections, the results of this study show no significant differences between the induction groups. However, during the later post-transplant-period, 4 CMV infections occurred in IL-2RA group compared to none in ATG group (p = 0,037). These findings are not completely consistent with current literature, as recent studies suggest that CMV infections and reactivations are more common in the ATG induction group than in IL-2RA recipients (81,96,98), the reasons most likely being the same as outlined above for increased EBV reactivation. The limited

number of cases and the lack of data on donor and receptor status for this comparison are possible explanations for the deviation from the current literature.

In comparison, BK polyomavirus was more frequent in IL-2RA recipients than in patients receiving ATG, although this remained without statistical significance. In recent publications, Cyclosporin A-treated showed a lower risk of polyomavirus BK viraemia than tacrolimus-treated patients, probably because of lower overall immunosuppressive loads (102,103).

Our study showed a significant difference in the number of anti-infective medications prescribed between the two induction groups ($p = 0,031$), especially during the period between month two and six after transplantation ($p = 0,005$). Due to this difference, the number of total infectious complications was higher in the IL-2RA group, although not significantly but in the intermediate-posttransplant-period. These findings did not really meet our expectations, as current literature suggests infections rates to be either comparable (94) or higher in ATG induction group (95,96).

There were significantly lower early FK 506 levels in ATG recipients compared to IL-2RA recipients on day three after transplantation in our study ($p = 0,035$). This leads to the conclusion that the lower through levels, which are aimed for in ECD kidney recipients, are actually reached three days after transplantation. This makes ATG induction an effective strategy to reduce CNI exposure. The underlying purpose of the ATG induction protocol is to spare ECD kidneys, which might be more vulnerable to CNI cytotoxicity and thus reduce delayed graft function and improve long-term graft function.

Yet, no significant differences in kidney functions were found in this study. Our results show that graft function is not affected by changing induction therapy to ATG, yet there was also no decrease in delayed graft function with this reduced CNI exposure. In this context it is important to note that there was no significant difference in patients' and donors' characteristics. Two weeks after transplantation, leucocyte levels were significantly lower in the ATG group ($p = 0,01$). This early

occurrence of leucopaenia due to ATG-induced leucocyte depletion was to be expected.

This study has several limitations. The most important of which is the number of cases. With only 40 patients – 20 of each induction group – the findings of our study can only cautiously be generalised for larger groups of ECD recipients. The data collected for this study stretch over a relatively large period of time. Importantly, the extent of electronic medical record keeping was rather limited during the period of time in which ECD recipients received standard induction compared to when ATG was used.
Another prominent limiting factor is that only quantity, but not quality of infections was assessed. Although major infections were distinguished from other infectious complications, there was no assessment of severity within the categories of infection, which limits comparability. A prospective study with increased case numbers and targeted assessment of infection rates could confirm the results of this study.

This small retrospective cohort analysis shows that when comparing recipients of ECD renal allografts who were induced using IL-2RA compared to ATG there was no difference in the rate of major infections. Importantly, while early CNI through levels were significantly lower in ATG-induced patients, there was no difference in rates of delayed graft function or long-term graft function. To make any firm recommendations these data would have to be expanded and more patients would have to be included in the analysis.

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