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Nuria Montero, María José Pérez-Sáez, Julio Pascual

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IMMUNOSUPPRESSION IN THE ELDERLY RENAL ALLOGRAFT RECIPIENT: A

SYSTEMATIC REVIEW

Nuria Montero MD^a; María José Pérez-Sáez MD^{b,c,d} and Julio Pascual MD, PhD^{b,c,d,e} on behalf of the DESCARTES Working Group*

^aDepartment of Nephrology, Hospital Universitari Bellvitge, Barcelona, Spain.

^bRed de Investigación Renal (Redinren) Instituto Carlos III, Madrid, Spain.

^cDepartment of Nephrology, Hospital del Mar, Barcelona, Spain

^dUniversitat Autònoma de Barcelona, Barcelona, Spain

^eCorresponding author. Department of Nephrology, Hospital del Mar. Passeig Marítim 25-29, 08003 Barcelona, Spain. Phone: +34932483162, e-mail: julpascual@gmail.com.

*DESCARTES ERA-EDTA Working Group [alphabetical order]: Daniel Abramowicz (*Department of Nephrology, Antwerp University Hospital, Antwerp*), Belgium, Klemens Budde (*Department of Nephrology Campus Charité Mitte, Berlin, Germany*); Chris Dudley (*Richard Bright Renal Unit, Bristol, UK*); Mark Hazzan (*Service de Néphrologie, Univ Lille Nord de France, Lille, France*); Marian Klinger (*Department of Nephrology and Transplantation Medicine, Wrocław Medical University, Poland*); Umberto Maggiore (*Department of Nephrology, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy*); Rainer Oberbauer (*Department of Nephrology, Medical University of Vienna, Vienna, Austria*); Julio Pascual (*Department of Nephrology, Hospital del Mar, Barcelona, Spain*). Søren S. Sørensen (*Department of Nephrology P, Rigshospitalet, University Hospital of Copenhagen, Copenhagen, Denmark*); Ondřej Viklický (*Department of Nephrology, Transplant Centre, Prague, Czech Republic*);

AUTHORS' CONTRIBUTIONS

1. Draft the protocol: NM, MJPS, JP
2. Study selection: NM, MJPS
3. Extract data from studies: NM, MJPS
4. Disagreement resolution: JP
5. Carry out the analysis: NM
6. Interpret the analysis: All authors
7. Draft the final review: NM
8. Correct and approve the final manuscript: All authors

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CONFLICT OF INTEREST

None.

ABBREVIATIONS

CI	confidence intervals
CNI	calcineurin inhibitors
CsA	cyclosporine
GFR	glomerular filtration rate
IL2r	interleukin-2 receptor
IL2RA	interleukin 2 receptor alpha
KT	kidney transplantation
MD	mean difference
MMF	mycophenolate mofetil
mTOR	mammalian target of rapamycin
OKT3	mouse monoclonal CD3 antibody
OPTN	Organ Procurement and Transplantation Network
OR	odds ratios
PTDM	post-transplant diabetes mellitus
rATG	rabbit antithymocyte globulin
RCT	randomized controlled trials
SCr	serum creatinine
SRL	sirolimus
TAC	tacrolimus
UNOS	United Network for Organ Sharing data
USA	United States of America
USRDS	United States Renal Data System

ABSTRACT

Background: Elderly are the fastest growing part of kidney transplant recipients. The best immunosuppressive strategy is unknown.

Methods: We performed a systematic search of randomized controlled trials and observational studies focused on safety and efficacy of different immunosuppression strategies in elderly kidney recipients. Data extraction and risk of bias evaluation was systematically performed.

Results: Ten studies were included: 2 randomized clinical trials and 8 observational. A marginal benefit was found for early renal function with delayed tacrolimus or complete tacrolimus avoidance using Mycophenolate Mofetil (MMF). Observational cohort studies looked at different antibody induction strategies, calcineurin-inhibitors based maintenance immunosuppression, calcineurin-inhibitors-free sirolimus-based therapy and use of MMF versus azathioprine. Treatment with interleukin-2 receptor antibody induction, calcineurin-inhibitor minimization with MMF and steroid minimization is advisable in the low immunologic risk elderly recipient, considering the increased risk of toxicities, infection and malignancies. In the high immunologic risk elderly recipient, taking into account the morbid consequences of acute rejection in the elderly, observational studies support antibody induction with depletive antibodies, calcineurin-inhibitor, MMF and steroids; calcineurin-inhibitor-minimization is not recommended.

Conclusions: There is very limited evidence for the benefits and harms of different immunosuppression strategies in the elderly. Most of the published literature are observational studies, and randomized controlled trials are urgently needed.

KEYWORDS: Elderly, Immunology, Immunosuppression, Kidney transplantation, Meta-analysis

1. INTRODUCTION

The majority of the incident end-stage renal disease patients and the fastest growing subgroup of kidney transplantation (KT) candidates are elderly [1,2,3,4]. Data from European Renal Registry shows that there are approximately 17000 listed patients of more than 65 years old (around 20% of the overall waiting list) [5]. The United States Renal Data System (USRDS), shows that transplant counts for those over 65 years old increased but remained stable at close to 800 per year from 2010 to 2012 and those patients of more than 65 years old on the waiting list are around 15% of overall [6].

KT is the best choice of renal replacement therapy in terms of patient survival, even using expanded criteria donors [7,8,9]. The elderly recipient usually receives an old kidney, and this does not seem to affect death-censored graft survival [3]. Graft losses are caused by different etiologies depending on the recipient age: rejection is the most frequent cause in the young population, and death with a functioning graft in the elderly [10].

Older KT recipients have a higher mortality, more medication side effects and lower rejection rates. There are frequent adverse effects related to certain immunosuppression medications: gastrointestinal effects or leucopenia related to mycophenolate mofetil (MMF), cosmetic effects and tremors with calcineurin inhibitors (CNI) cyclosporine (CsA) or tacrolimus, and hypertension, hyperglycemia, hyperlipidemia, increase risk of infection, obesity, cataracts, myopathy, bone metabolism alterations, dermatologic problems and cushingoid appearance with steroids. In this frail population, cardiovascular mortality is the limiting factor in graft survival rather than immunological factors [11], so it seems logical to apply a personalized immunosuppression strategy for them. A big problem is that most of trials evaluating the safety and efficacy of immunosuppressive treatments contain only a small part of

these subset of recipients, and there are a limited number of studies that have focused on this age group [12,13,14,15].

In addition, age per se changes drug metabolism, making the elderly vulnerable to immunosuppressive medications. Changes such as reduced gastric emptying, impaired gastrointestinal motor function, decreased splanchnic blood flow, decreased renal clearance, changes in cytochrome IIIA isoenzymes and P-glycoprotein, decreased protein binding and decreased hepatic blood flow are of particular importance [16].

Several factors explain that in older patients there is a spontaneous tapered immune response: natural immunosenescence [17,18,19], less active P450 microsomal system [20], and more vulnerability to a wide variety of adverse events including death [21-24]. Immunosuppressive drug reduction may led to a reduction in cardiovascular risk, reduced drug side effects, cost savings and improved patient and graft survival. KT recipients over the age of 60 years are more likely to have an increased risk of chronic allograft dysfunction because of increased susceptibility to oxidative stress and CNI toxicity which exacerbate the renal damage caused by aging [25-27]. Moreover, these recipients have a greater likelihood of receiving a worse kidney, the majority of them will receive an expanded criteria donor organ, or from a donor after cardiac death or with a long cold ischemic time. That implies an amplification of senescence changes of the kidney allograft and also exaggerate the negative impact of episodes of acute rejection [16]. The Eurotransplant Senior Program was designed to allocate old donors to old recipients using local transplant candidates to decrease ischemia time, resulted in poorer HLA (human leukocyte antigen) matching, and that encouraged physicians to use induction therapy [28].

Despite these arguments, little is known on the best immunosuppressive regimen to prevent rejection, assure stable graft function and favor good outcomes in the elderly. The objective of this systematic review is to assess the published literature on the different immunosuppression strategies in elderly patients receiving a KT.

2. MATERIALS AND METHODS

2.1. Study design

We searched MEDLINE (via OVID), CENTRAL, related journals and proceedings of international scientific conferences, International Clinical Trials Register Search Portal and ClinicalTrials.gov. In addition, references cited in review articles were searched to identify any publications that were overlooked. We also sent emails seeking information about unpublished or incomplete studies to investigators involved in previous studies. See Appendix 1 for search terms used.

2.2. Selection criteria for studies

The obtained titles and abstracts of studies potentially relevant to the review were screened independently by two reviewers (N.M. and MJ.P). We included all randomised controlled trials (RCTs) looking at immunosuppression in elderly recipients. We also sought observational cohort studies assessing the outcome of KT in adult patients. Those studies whose authors did not present the results specifying the age of the participants or type of immunosuppression were excluded. Observational studies were analysed separately. The inclusion criteria were kidney recipients >60 years old and the exclusion criteria were patients receiving multiorgan transplantations.

2.3. Data extraction, outcomes and quality assessment

Data extraction was carried out by two reviewers (N.M and MJ.P.) independently by using standard data extraction forms. We extracted data on donor and recipient demographics and clinical characteristics, all-cause mortality, graft loss, acute rejection, graft function (serum creatinine (SCr) or measured or calculated glomerular filtration rate [GFR]) and delayed graft function. In addition, we tried to extract data on possible clinical effects of different immunosuppression strategies: infections, cardiovascular events, malignant neoplasia and treatment-related adverse reactions.

2.4. Risk of bias assessment

Risk of bias was collected from each included study in duplicate by two reviewers (N.M. and MJ.P.) independently from each other using a standardized form. For RCT, the Cochrane Collaboration specific tool for assessing risk of bias in each included study was used. This comprises a judgement and a support for the judgement for specific features of the study including 5 domains: sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting. The judgement for each entry involves assessing the risk of bias as 'low risk', as 'high risk, or as 'unclear risk', with the last category indicating either lack of information or uncertainty over the potential for bias. For observational studies, the Newcastle Ottawa scale for Cohort and Case-control studies was used [29].

2.5. Data synthesis and analysis

For dichotomous outcomes (acute rejection, graft loss, mortality) results were expressed as odds ratios (OR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment (function measured by serum creatinine) the mean difference (MD) was used. Because of heterogeneity of

immunosuppression strategies evaluated in the different RCTs, we have not been able to pool data pooled using the random-effects model [30]. All statistical analyses were performed using Review Manager Software [31].

3. RESULTS

We have followed the PRISMA statements to report this systematic review [32] and MOOSE Guidelines for observational studies [33].

3.1. Search strategy and selection criteria

A total of 6188 reports were found by using the defined search strategy. Of these, 5828 were excluded because they evaluated wrong interventions (no immunosuppression strategies), were wrong population studies (young participants), were reviews or commentaries or were duplicates. Full-text assessment of 360 potentially eligible reports identified 10 studies which met our inclusion criteria: 2 RCT and 8 observational studies [34-44]. Three hundred and fourteen excluded studies (349 reports) were not disaggregated by age (n=215), were not randomised (n=6), investigated the wrong intervention (n=45), assessed young participants (n=48), or the results were referred to a wrong population (n=3). We found one ongoing study potentially relevant to this review in recruitment phase [49]. The combined search results are presented in Figure 1.

3.2. Characteristics of included studies

Both RCTs included were parallel design [34-35], one was multicenter and one monocenter (Table 1). Andres et al. (252 participants) compared delayed tacrolimus

(started on day 7), basiliximab and early steroid discontinuation on day 8 versus standard tacrolimus and steroids until day 91 [34]. Meiers' trial (90 participants) compared tacrolimus plus MMF until 6 weeks versus tacrolimus until 6 weeks plus MMF [35]. Duration of follow-up was from 6 to 12 months.

Moreover, we included 8 observational studies. They looked at different interventions: CNI based maintenance immunosuppression (1 study) [36], CNI-free with MMF-SRL-based therapy (3 studies) [37-40], use of MMF versus azathioprine (2 studies) [41-42] and different induction strategies (2 studies) [43,44].

3.3. Risk of bias

The included RCT had an overall moderate risk of bias (Table 2, Figure 2). They had high risk of performance and detection bias because all were open-label. In one study [34] there was a clear random sequence generation method (computer-generated randomized list) although the allocation concealment was unclear (they used sealed randomization envelopes without specifying if they were opaque or sequentially numbered) and no report if the patients that dropped out the study were included in the main analysis (unclear attrition bias). Meier's et al study [35] specified patients lost for follow-up. All the observational studies included had an overall high risk of bias (Figure 3). Funnel plots to detect publication bias were not feasible because of the small number of studies included in this review.

3.4. Systematic review

Because of the absence of similar comparisons in the RCTs and in the observational studies, the results have not been meta-analysed or grouped. The description of the characteristics of included studies and the main results are in Tables 3 and 4. The forest

plots of all the RCTs considering the main outcomes are in the Supplementary Material (Appendix 2).

We analysed the results depending on the immunosuppressive strategy used and especially considering outcomes related to: patient and graft survival, graft function, complications after KT and treatment related adverse effects. Most of the published studies are observational, so consequently we reviewed separately their results.

3.4.1. Use or avoidance of calcineurin inhibitors

Five studies compared CNI based immunosuppression strategies: 2 RCT and 3 cohort studies.

In terms of *mortality*, Andres et al [34] (254 patients) estimated that patient survival rate (calculated using Kaplan-Meier) in the delayed tacrolimus introduction group was slightly lower (96.1%) compared to the 99.2% patient survival in the standard tacrolimus group, without a statistically significant difference. In the other RCT comparing tacrolimus versus MMF as a maintenance immunosuppression [35] the authors also found an uncertain direction of effect on patient survival with no events in each comparison group, perhaps because of the large exclusion criteria list for selecting their participants. No significant differences between CNI-based and CNI-free strategies were found in 5 additional observational studies. One study compared lower versus higher target tacrolimus levels [36] and three studies used a CNI-free strategy using MMF-based [39] or sirolimus-MMF-based immunosuppression [37,38,40]. Most of these observational studies had a short-term follow-up. In only one out of the 8 observational studies, the author demonstrated that less intense immunosuppression (minimized levels of MMF and tacrolimus) had an impact on lowering the risk of death [36].

In terms of *graft loss* and *graft function*, the only RCT that reported statistically significant differences was the multicenter trial within the Eurotransplant Senior Program with only 52 patients [35]. It compared KT recipients receiving MMF (without tacrolimus at 3 months post-transplantation) and those treated with low-dose tacrolimus. A higher creatinine clearance was observed in MMF group compared to low-dose of tacrolimus after 6 months (44 ± 6 vs. 31 ± 4 ml/min respectively, $p<0.05$) and 12 months (45 ± 4 vs. 32 ± 6 ml/min, $p<0.002$). In their comparison of delayed versus immediated tacrolimus initiation after KT, Andrés et al [34] reported a similar incidence of graft loss and graft function at 6 months. None of the three included observational cohort studies found a worse graft survival after 1 to 4 years of follow-up.

Focusing on treatment related adverse effects, all the included RCT analysed the incidence of infections, cardiovascular events and malignant neoplasia. Neither the immunosuppression based on delayed tacrolimus [34], nor tacrolimus versus MMF maintenance treatment [35] assessed differences in complications after KT outcomes. Andrés et al [34] described fewer requirements of antidiabetic treatment when the introduction of tacrolimus was delayed than in the standard group (8.4% vs 16.9% respectively). No differences were seen in the incidence of hypertension or lipid values. The other study assessing impaired glucose metabolism was the one comparing MMF/tacrolimus after a randomization at 3 months postransplant, without any meaningful difference [35]. Similar infection rates were detected with different immunosuppression strategies in observational studies. The studies using mammalian target of rapamycin inhibitor (mTORi) strategies showed low incidence of CMV infections [37-40]. Cruzado et al in their dual-KT series, described a numerically higher incidence of lymphocele in sirolimus vs cyclosporine-based therapy (36% vs 11% respectively).

3.4.2. Mycophenolate mofetil or azathioprine

Less adverse effects and improvement of graft and patient survival is found with the use of MMF than azathioprine, and it is generalized not only for young recipients but also for elderly [41-42].

3.4.3. Induction with depleting or non-depleting agents

In a study comparing basiliximab versus the mouse monoclonal CD3 antibody OKT3, no significantly different was observed in patient (98% vs 96%, $p=0.62$) or graft survival (98% vs 96%, $p=0.58$) [43].

The multicenter registry using OPTN/UNOS (Organ Procurement and Transplantation Network/United Network for Organ Sharing data) [44] showed a higher risk of acute rejection within the first year and after with IL2RA (interleukin 2 receptor alpha) than in rATG or alemtuzumab groups. Tacrolimus use was less frequent in the IL2RA group. They also reported a greater death rate at 1-year with alemtuzumab than rATG (adjusted HR 1.32; 95%CI 1.14-1.53) in high-risk donors (expanded criteria donors, donors after cardiac death or prolonged cold ischemia time). They concluded that no matter that elderly have a decreased immunogenicity, the risk of acute rejection is significantly higher with IL2RA than in young recipients. Complications associated to the use of depleting agents were evaluated only in one study (basiliximab versus OKT3) [43]. Basiliximab-treated patients experienced a more rapid clinical recovery than OKT3-treated ones, as reflected by a 40% decrease in the initial hospital length of stay and experienced fewer post-operative infections and general hospital readmissions.

Although in other included studies the comparisons were not focused on different induction strategies, they did use distinct induction agents. For example, Diekmann [39,40] found a higher acute rejection rate in the MMF group (45%) compared to the 15% in the sirolimus group ($p<0.01$), probably because of the use of basiliximab or

ATG in the second one. Kode et al [43], in their analysis on different outcomes according to different induction agents, did not disaggregate data for older recipients.

3.4.4. Steroids

Based on previous systematic reviews, it seems logical that steroid withdrawal or minimization might be safe for older patients [46-49]. None study was found evaluating this strategy in older recipients.

4. DISCUSSION

Elderly patients are usually excluded from clinical trials evaluating immunosuppressive agents. That is why there are very few number of available studies about drug protocol in this population [12]. In a recent report, the authors focused the "future research directions" on immunosuppression with particular questions summarised in three points: the critical immune mechanisms that change with age and influence patient management, specific factors that could influence the clinical management and the impact on elderly patients of chronic immune suppression in other organ systems [50]. Making an evidence-based decision is difficult, however, with the limited evidence available, and until new trials are developed, it seems reasonable to use a triple therapy regimen based on steroids, mycophenolate and a CNI. This is the regimen currently used in most units, with the three drugs usually prescribed at low doses.

The need of induction therapy with anti-IL2RA or ATG in this particular population is unclear. Acute rejection is associated with graft loss, and consequences may be even stronger in the elderly [16]. Although the use of IL2RA seems to be the safest option in old recipients with low or intermediate immunological risk, our systematic review shows that rATG may be preferable in high-risk recipients transplanted with kidneys

from high-risk donors and possibly low-risk recipients with high-risk donors. It is important to highlight that complications derived of the use of depleting agents were evaluated in only study comparing basiliximab versus OKT3, confirming lower rates of infections and readmissions in basiliximab-treated patients.

During the initial phase, steroid sparing strategies have become popular, especially in the US. Whether or not this is of particular benefit in the elderly remains unknown. Another widely used approach to the initial therapy is the delayed introduction of CNI, but the only RCT designed to test its benefit concluded that outcomes were not significantly different in comparison with immediate tacrolimus initiation. Also it would be an interesting alternative in these aged patients the use of belatacept instead of CNI because it is non-nephrotoxic drug with a less cardiovascular risk. The BENEFIT-EXT study [51] was designed to evaluate the use of this drug in patients receiving a kidney donor >60 years old, but unfortunately no subgroup analysis was done by age. Consequently, results of better kidney function graft, less death and graft loss and better cardiovascular profile with belatacept compared to cyclosporine cannot be extrapolated to older recipients. The same results were found in the recently published Cochrane meta-analysis but without subgroup analysis of the outcomes in elderly [52].

Although the risk of acute rejection may be lower in elderly, the morbid consequences of rejection may be greater [16], so cautious follow-up is required [53].

Our main conclusion is that evidence level is very low to decide a particular immunosuppressive drug regimen in the elderly. Careful review of the data suggest that in the low immunologic risk elderly recipient, considering the increased risk of toxicities, infection and malignancy, treatment with IL2RA induction, CNI minimization with MMF and steroid minimization is advisable. In the high immunologic risk elderly recipient, and taking into account the morbid consequences of

acute rejection in the elderly, minimization is not recommended. In these cases, observational studies support antibody induction with depletive antibodies, steroids, CNI and MMF.

The main limitation of this review is that there are only four RCT available. Most of the studies in this topic do not consider this age-stratum recipients, and when they are included, the results are presented altogether without stratifying for age. It is also remarkable that none of these trials consider making a quantitative evaluation of frailty as a better stratification for aging, and this fact is not possible to assess retrospectively.

In summary, it is advisable to have a sufficiently powerful immunosuppressive regimen without excessively increasing the risk of infection in these patients and with low nephrotoxicity. Ours is the first systematic review focused on this topic. The absence of high-level of evidence is very important. Specific well-designed controlled trials of immunosuppressive strategies are urgently needed in elderly KT to define the optimal drug regimen they need.

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FIGURES

Figure 1. Flow of the studies reviewed

Figure 2. Bias of included RCT studies

Figure 3. Bias of included observational studies

ACCEPTED MANUSCRIPT

Figure 1. Flow of the studies reviewed

Figure 2. Bias of included RCT studies

Figure 3. Bias of included observational studies

Author year	Representative exposed cohort	Non exposed cohort drawn from same community	Adequate ascertainment of exposure	Demonstration outcome of interest not present at start of study	Adequate control for most crucial confounders	Adequate control for additional confounders	Adequate assessment of outcome	Follow up long enough for outcomes to occur	Adequate cohort follow-up
Badowski [36]	*	*	*	*	*	?	*	--	?
Diekmann [37,38]	*	*	*	*	?	?	*	--	?
Furian [39]	*	*	?	*	*	*	?	--	?
Cruzado [40]	*	*	*	*	*	?	*	--	?
Meier-Kriesche [41]	*	*	*	*	*	--	--	--	?
Meier-Kriesche [42]	*	*	?	*	*	?	?	--	?
Kode [43]	*	*	?	*	--	--	*	--	?
Gill [44]	*	*	*	*	--	--	--	--	?

Legend: *A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability (adequate control for the most important factor and adequate control for any additional factor)

Table 1. Characteristics of included randomized controlled trials.

Author and type of study	n	Donor demographics	Recipient demographics	Duration	Interventions			Cointervention
Andres 2009 [34]	252	Age: 63.2 (±13.3) Donation type: 97% deceased	Inclusion criteria: <ul style="list-style-type: none">• age = or > 60 years• primary kidney transplantation or retransplantation• deceased or living donor with compatible ABO blood type Exclusion criteria: <ul style="list-style-type: none">• PRA > 50%• cold ischemia time >30 hr• continuous corticosteroid use• use T-cell depleting antibody preparations;• HIV• history of cancer (except skin cancers or successfully treated)• previous non-kidney transplant• presence of severe secondary illness	6 months	d- TAC	delayed TAC (started on day 7)+ basiliximab + early steroid discontinuation on day 8	132	MMF First-line treatment of rejection was with corticosteroids administered according to local practice. Corticosteroid refractory rejection was treated with OKT3 or polyclonal antibodies according to local practice.
					s-TAC	standard TAC + steroids until day 91	122	
					Initial TAC dose was 0.15 mg/kg twice daily (orally) for both groups. Same TAC levels in all groups: <ul style="list-style-type: none">• days 0 or 7 to 14: 10 to 15ng/mL,• days 15 to 42: 8 to 12ng/mL• day 43 to end of study: 5 to 10ng/mL			
Meier 2011 [35]	90, 52 randomized	Deceased donor	Inclusion criteria: <ul style="list-style-type: none">• age > 65 years• single kidney transplant Exclusion criteria: <ul style="list-style-type: none">• non heart beating donor grafts• gastrointestinal disorder that might interfere with the ability to absorb oral medication, active peptic ulcer• history of cancer (except successfully treated); localized nonmelanocytic skin cancer;• evidence of active liver disease• anemia, leukopenia, or thrombocytopenia.	12 months	TAC	TAC (levels 5-8 ng/ml) + MMF until 6 weeks (25% dose reduction every 2 weeks) +	29	Daclizumab (2 doses) + Steroids (according to the local center protocol) CMV prophylaxis with ganciclovir in seronegative recipients with donor positive grafts for three months
					MMF	TAC until 6 weeks + MMF (1-2g/day)	23	

CMV: cytomegalovirus ; CNI: calcineurin inhibitors; CsA: cyclosporine; EVE: everolimus; IL2rA: Interleukin 2 receptor antibody; MMF: mycophenolate mofetil; MPA: mycophenolate acid agent; OPTN/UNOS: Organ Procurement Transplantation Network/United Network of Organ Sharing; PRA: panel reactive antibodies; rATG: rabbit antithymocyte globulin; TAC: tacrolimus

Table 2. Risk of bias assessment of randomized clinical trials

Study reference	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Andres 2009 [34]	LOW computer-generated randomized list of variable permuted blocks was used for a 1:1 stratification by study center.	UNCLEAR Allocation to treatment was performed locally using sealed randomization envelopes supplied by the study sponsor.	HIGH Treatment allocation was concealed from the investigators	UNCLEAR	LOW
Meier 2011 [35]	LOW computer-generated randomized list	UNCLEAR No specified	HIGH Treatment allocation was concealed from the investigators	UNCLEAR	HIGH Lost of follow-up

Table 3. Randomised controlled trials of immunosuppression strategies in kidney transplantation in elderly.

First author (Ref)	Year published	Country	Groups	Regimen	N	Donor Age (y)	Recipient age (y)	Follow-up	Efficacy				Safety	
						mean ±SD	mean ±SD		DGF	AR	SCr (μmol/L)	Survival		
Delayed vs standard introduction of CNi														
Andres [34]	2009	multicenter European	Delayed	TAC started on day 7+ basiliximab + early steroid discontinuation on day 8	132	63.2 ±13.3	66.4 ±4.0	6 m	17.4±28 d 30.3%	18.9%	148.4±53	PS: 96.1% GS: 90.0%	Infections: 65.2% CMV infection: 10.6% Malignancies: 0	
			Standard	TAC + steroids until day 91	122	63.2 ±13.7	65.5 ±3.8		21.3±39 d 23.8%	18%	169±89.7	PS: 99.2% GS: 87.6%	Infections: 61.5% CMV infection: 6.6% Malignancies: 0.02%	
Maintenance with TAC vs MMF														
Meier [35]	2011	multicenter (Germany+ USA)	TAC	Daclizumab + steroids (according to the local center protocol) + <i>after 3 months</i> : TAC (levels 5-8 ng/ml) + MMF until 6 weeks (25% dose reduction every 2 weeks)	29	≥65	65 ±2	1 y	31%	1 y 41.37%	6m: 170±71	PS: 100% GS: 86.2%	Infections: 37.9% CMV infection: 13.8%	
			MMF	Daclizumab + steroids (according to the local center protocol) + <i>after 3 months</i> :: TAC until 6 weeks + MMF (1-2g/day)	23		67 ±2		39%	1 y 21.73%	6m: 127 ±38	PS: 100% GS: 86.9%	CMV infection: 17.4% Sepsis: 13%	

ATG: antithymocyte globulin; AZA: azathioprine; AR: acute rejection; CMV: cytomegalovirus; CNi: calcineurin inhibitor; CsA: ciclosporin; D: donor; d: days; DGF: delayed graft function; DM: diabetes mellitus; GS: graft survival; m: month/s; MMF: mycophenolate mofetil; N: number of patients; PS: patient survival; SRL: sirolimus, SCr: serum creatinine; TAC: tacrolimus; y: year

Table 4. Observational studies of immunosuppression strategies in kidney transplantation in elderly.

First author (Ref)	Year published	Country	CNI	Regimen	N	Recipient age (y)	Follow-up (mean)	Efficacy		Safety			
								DGF	AR	SCr (μmol/L)	Survival	Other	
CNI based													
Badowski [36]	2009	USA	yes	MMF 2 g/d + TAC (target level 10–12 ng/mL)	101	67.2 ± 5.8	23.8 ± 14.2 m	51.5%	15.8%	6 m: 160.9±97.2; 12m: 151.2 ±79.6	2 y PS: 81,2% GS: 73,3%	CMV viremia: 4 cases	
				MMF 1 g/d + TAC (target level 8–10 ng/mL)	88	66.7 ± 4.8	21.3 ± 11.8 m	46.1%	20.5%	6 m: 164.4±106.08 12m: 162.7±114.9	2 y PS: 91,2% GS: 90,9%	CMV viremia: 6 cases	
CNI-free with SRL-MMF-based therapy													
Diekmann [37-38]	2007	Spain**	Free	MMF (2-6 um/l) + steroids +/- Basiliximab (2 d)	75	67.3± 4	12 m Inclusion from Dec 1996 to Nov 2002	-	45%	1 y 185.7±106	1y PS 88% death censored GS 83%	Conversion to CNI 15%	
				Basiliximab(2d)/ATG (7 d) + MMF (2-6 um/l) + steroids + SRL from day 5 th	33	65.7± 6.4	Inclusion from Dec 2002-2004	21% (66% if DCD)	15%	1 y 159.2±53	1 y PS 94% death censored GS 94%	SRL withdrawn 24%	
Furian [39]	2007	Italy***	Free	ATG (2d) + SRL + MMF + steroids	31	>60	10.1±7.6 m	16%	19%	1y 115±31	1y PS 100%; GS 96%	De novo DM 32% CMV infection 3%	
			CNI-based	CsA + MMF + steroids	25		48.2 ± 17.4 m	48%	16%	1y 135±55	1y PS 100%; GS 87%	De novo DM 24% CMV infection 48%	

Cruzado [40]	2007	Spain***	Free	ATG (2d) + SRL + MMF + steroids	42	>60	5 y	40%	8%	1y: 115±53; 2y: 136±90	1,3,5 y PS 88,76,76; GS 95,90,90	Lymphocele 36% CMV infection 9.5%
			Historical	CsA + MMF + steroids	36			44%	40%	1y: 124±27; 2y: 123±29	1,3,5 y: PS 92,89,86; GS 94,94,94	Lymphocele 11% CMV infection 14%
Maintenance with MMF vs AZA												
Meier-Kriesche [41]	1999	USA	MMF	MMF + CsA/TAC + steroids	45	> 60	21.9 ± 9.1 m	-	15.6%	1, 6, 12m: 136.1±53; 145.9±61; 140.6± 65	1y: PS 84% GS 81%	Infection 33% Opportunistic infections: 22%
			AZA	AZA + CsA + steroids	46			61.1 ± 17.4 m	-	10.9%	1, 6, 12m: 161.7±88; 152.9±63; 138.8±65	1y: PS 92% GS 89%
Meier-Kriesche [42]	2004	USA	MMF	MMF	2493	>65	4 y	-	1y 24% 4y 2.3%	-	4y: PS 73% GS 68.9%	-
			AZA	AZA	2576			-	1y 28.2% 4y 12.6%	-	4y: PS 69.2% GS 63.2%	-
Depending on induction strategy												
Kode	2003	USA	Basil	Basiliximab + CsA + reduced steroids + MMF	63	>60	100 d	-	9.5%	200±150	100d PS 88.9%	-

[43]			OKT3	OKT3 + CsA + high-dose steroids + MMF	4			-	-	-	100d PS 100%	-
Gill [44]	2011	Multicenter OPTN/UNOS	rATG	Maintenance: 94% CNI; 85% MMF; 68% steroids	7140	≥ 60	6 y	-	73%	-	-	-
			Alentuzu mab	Maintenance: 91% CNI; 78% MMF; 30% steroids	1465			-	11.4%	-	-	-
			IL2RA	Maintenance: 92% CNI; 85% MMF; 89% steroids	6215			-	0.5%	-	-	-

ALG: antilymphocyte globulin; ALE: alemtuzumab; AR: acute rejection; ATG: antithymocyte globulin; rATG: rabbit antithymocyte globulin; AZA: azathioprine; CMV: cytomegalovirus; CNI: calcineurin inhibitor; CsA: ciclosporin; D: donor; d: days; DGF: delayed graft function; DM: diabetes mellitus; ECD: expanded criteria donor; GS: graft survival; M: month/s; MMF: mycophenolate mofetil; n: number of patients; OPTN/UNOS: organ procurement transplantation network/united network of organ sharing; PS: patient survival; R: recipient; SRL: sirolimus. SRTR: scientific renal transplant registry, SCr: serum creatinine; TAC: tacrolimus; Y: year

* considering only those transplanted after January 1, 2000 (because they had an uniform immunosuppression protocol) **consecutive series ***dual KT series.