Appendix 7 ADVERSE EVENTS Immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85)

ERRATA

This document outlines errata to the report dated March 25th 2015: Immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85). In order to establish the impact of removing the non-Thymoglobulin studies and also add the direction of effect to analyses, we have repeated the meta-analysis and updated the results. The errata replaces the Appendix 7 (pages 682-713).

Appendix 7 Adverse events

Adverse events; meta-analyses at 1-year follow-up

Where data permitted, the 1–year follow-up results of individual studies were pooled using meta-analyses; new onset diabetes (NODAT), post-transplant lymphoproliferative disorder (PTLD), malignancy (including PTLD), any infections, and cytomegalovirus (CMV) were considered. The DerSimonian–Laird random effects method was used for pooling. Odd ratio (OR) was used as a measure of treatment effect. All analyses were performed in Stata 13 and excel (if the number of events was zero in one of the studies arms, a value of 0.5 was added to all study arms to allow for statistical analyses).

All studies were polled irrespective of concomitant treatments used in the individual studies. For example, to compare CSA and TAC therapies, results of a study comparing a triple regimen of CSA +AZA+CCS with a triple regimen of TAC+AZA+CCS were pooled with results of a study comparing the following two regimens BAS+CCS+MMF+S and BAS+ TAC +MMF+CCS; studies were pooled irrespective of induction and concomitant therapies used in the studies, as long as the same therapies were used in the two comparative arms.

The number of studies included in the individual meta-analyses was between two and eight, therefore we did not investigate publication bias; tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (Cochrane handbook, 2008).[196] In addition, no corrections for multiple comparisons were executed. Therefore any meta-analyses results presented in this section must be interpreted with caution.

Induction regimens

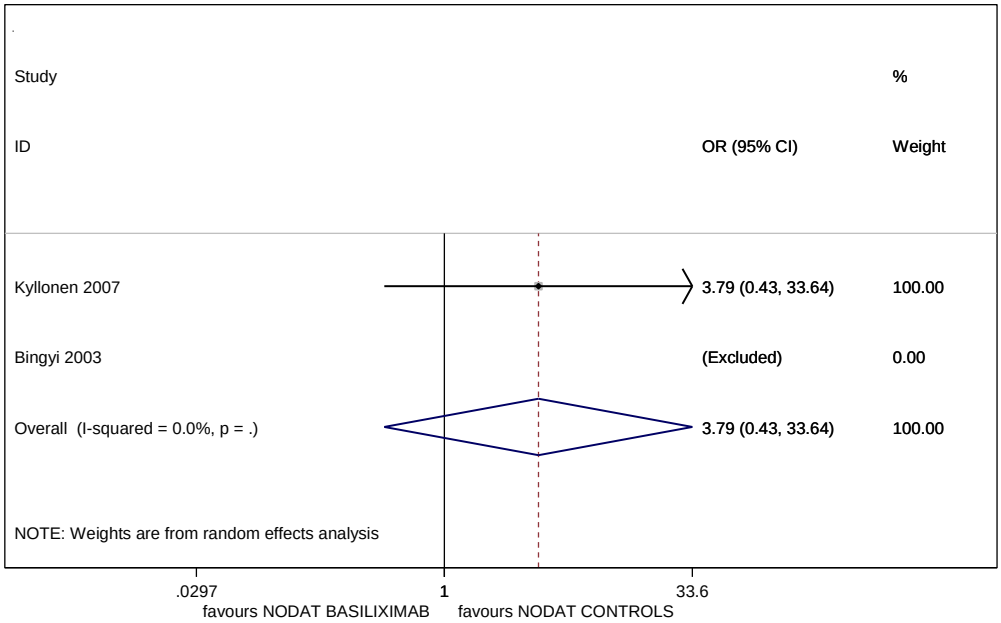
Nine studies reported some AE at 1–year follow-up: four studies compared Basiliximab with placebo or no induction (Bingyi et al. 2003, Kahan et al. 1999, Nashan et al. 1997, Lawen et al. 2003),[66 67 69 81] three studies compared Basiliximab and rATG (Brennan et al. 2006, Mourad et al. 2004, Lebranchu et al. 2002);[89 90 91] one study compared rATG with no induction (Charpentier et al .2001),[82] and one study compared basiliximab, ATG-Fresenius and no induction (Kyllonen et al. 2007; only the comparison of basiliximab and no induction was considered in the analyses).[86]

All AE are summarised in the sections below according to induction therapy used. Similarly to the clinical effectiveness outcomes studies comparing Basiliximab with placebo, and Basiliximab with no induction were combined

Basiliximab versus placebo and no induction

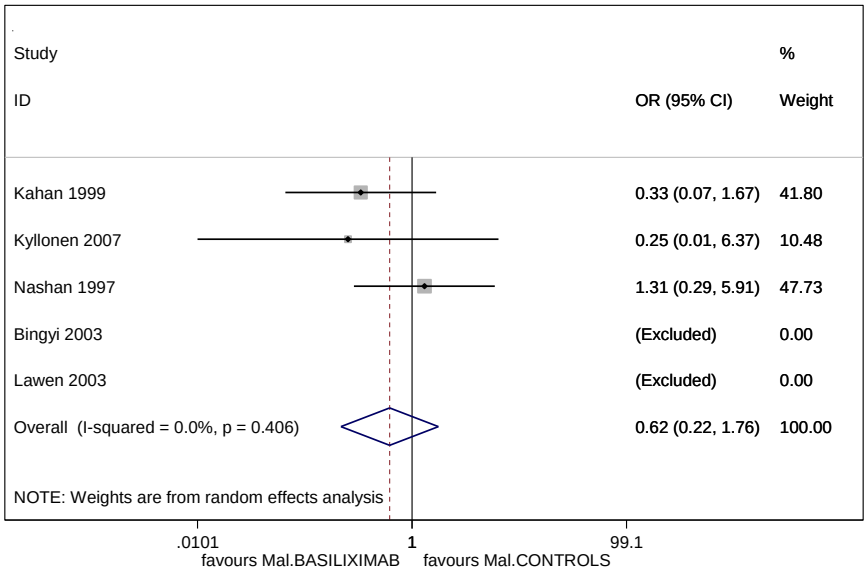
NODAT, PTLD, malignancy, infections and CMV infections were reported in studies comparing Basiliximab versus placebo and Basiliximab versus no induction (results from studies comparing Basiliximab with placebo, and Basiliximab with no induction were combined). No differences between Basiliximab and control arms were identified for any AE. The NODAT (**Figure 121**), malignancy (**Figure 122**) PTLD (**Figure 123**), Infections (**Figure 124**) and CMV results (**Figure 125**) are presented below. In summary, no difference in NODAT, PTLD, malignancy, infections and CMV infections were found between Basiliximab and control arms.

Figure 121 NODAT; Basiliximab versus placebo and no induction



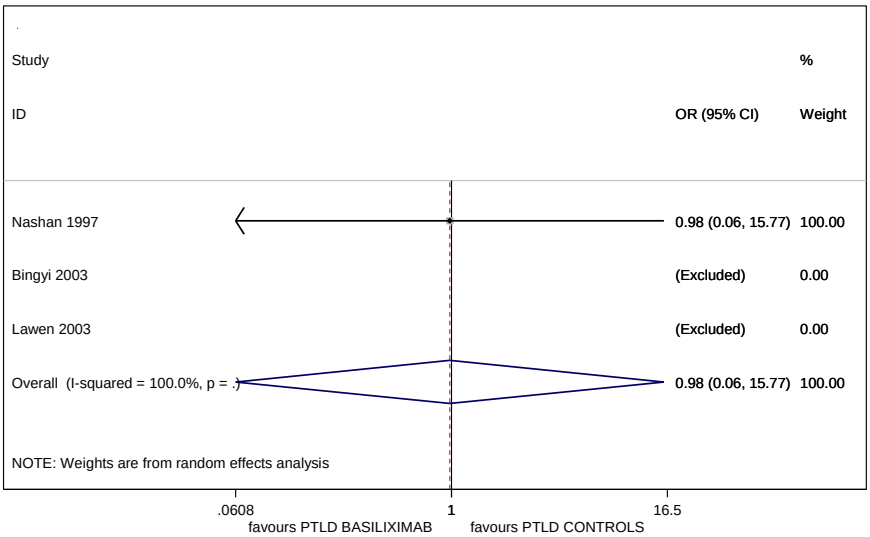
Key: OR, odds ratio; ID, identification; NODAT, new onset diabetes. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; studies with no events in both arms were excluded from the analysis. Bingyi et al. 2003 reported 0/6 and 0/6 NODAT cases in BAS and no induction arms respectively.

Figure 122 Malignancy; Basiliximab versus placebo and no induction



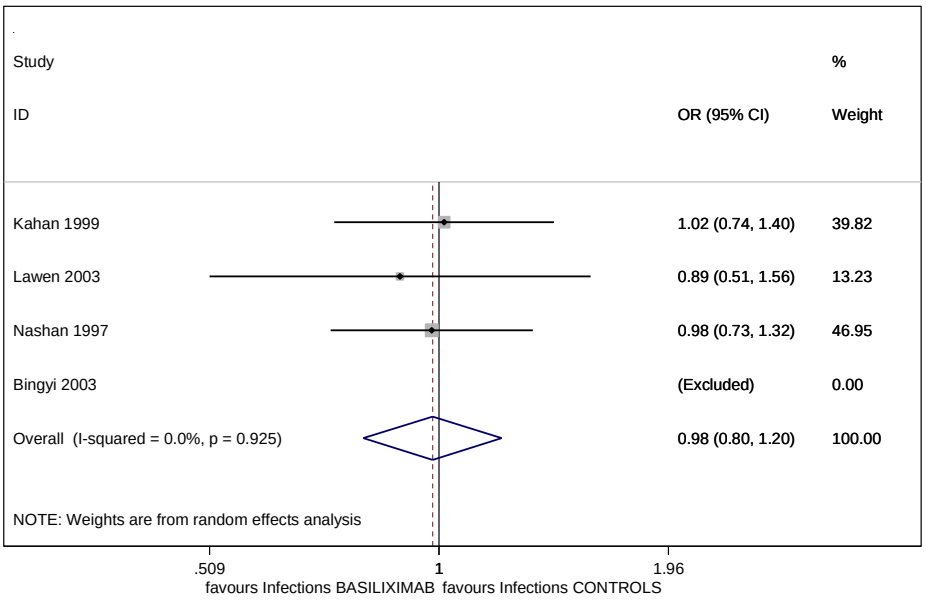
Key: OR, odds ratio; ID, identification. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; studies with no events in both arms were excluded from the analysis.Bingyi et al. 2003 reported 0/6 and 0/6 malignancy cases in BAS and no induction arms respectively. Lawen et al. 2003 reported 0/59 and 0/64 malignancy cases in BAS and no induction arms respectively.

Figure 123 PTLD; Basiliximab versus placebo and no induction



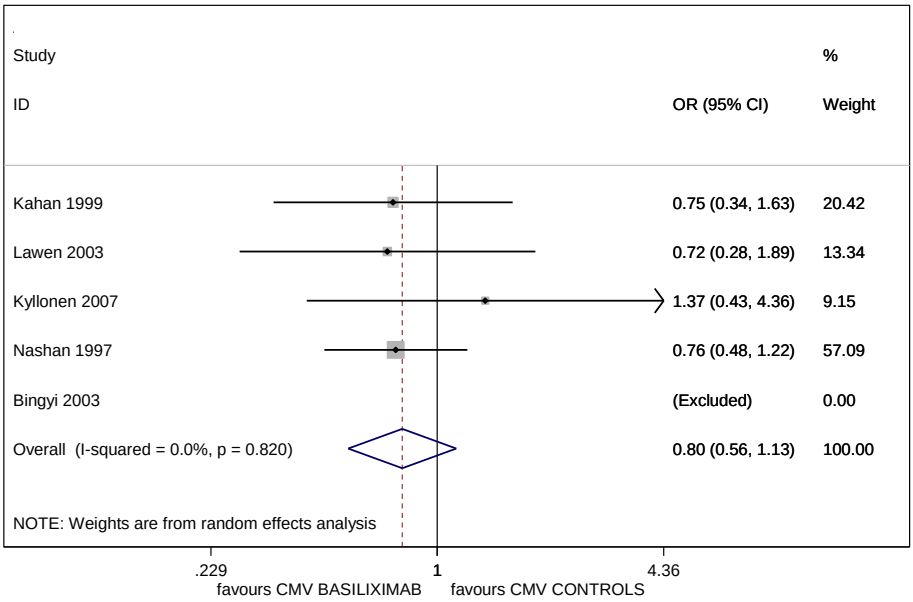
Key: OR, odds ratio; ID, identification; PTLD, post-transplant lymphoproliferative disorder. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; studies with no events in both arms were excluded from the analysis. Bingyi et al. 2003 reported 0/6 and 0/6 PTLD cases in BAS and no induction arms respectively. Lawen et al. 2003 reported 0/59 and 0/64 PTLD cases in BAS and no induction arms respectively.

Figure 124 Infections; Basiliximab versus placebo and no induction



Key: OR, odds ratio; ID, identification. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; studies with no events in both arms were excluded from the analysis; the estimate of between-study variance Tau-squared was 0.000. Bingyi et al. 2003 reported 0/6 and 0/6 infections in BAS and no induction arms respectively.

Figure 125 CMV; Basiliximab versus placebo and no induction



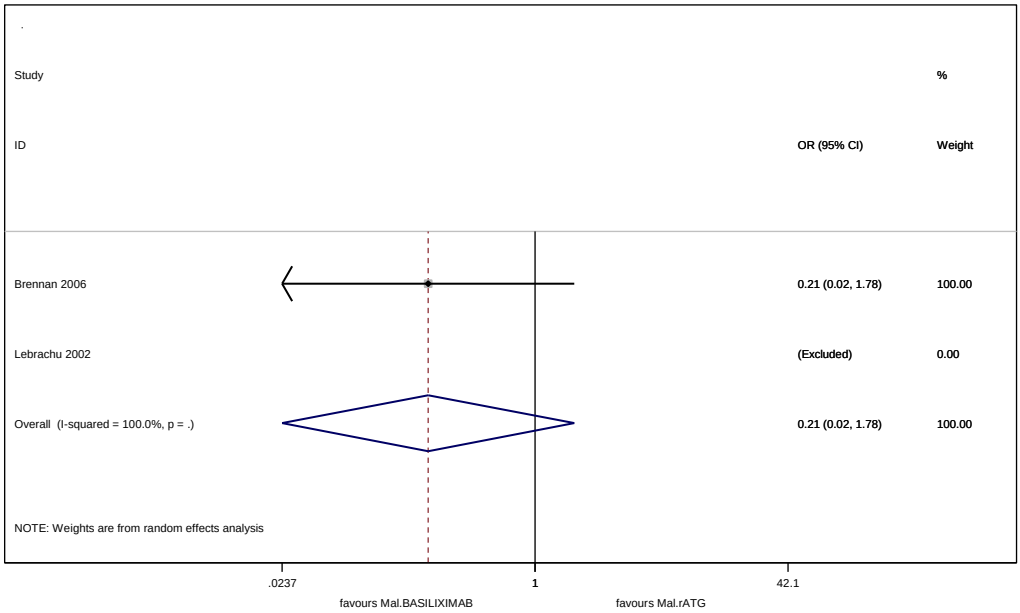
Key: OR, odds ratio; ID, identification; CMV, cytomegalovirus. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; studies with no events in both arms were excluded from the analysis; the estimate of between-study variance Tau-squared was 0.000. Bingyi et al. 2003 reported 0/6 and 0/6 CMV infections in BAS and no induction arms respectively.

Basiliximab versus rATG

NODAT, PTLD, malignancy, infections and CMV infections were reported in studies comparing Basiliximab versus rATG. No difference in NODAT was found in one study (Lebrachu et al. 2007): OR 0.98 (favours BAS, 95%CI 0.06; 16.11). Malignancy (**Figure 127**), PTLD (**Figure 128**), infections (**Figure 129**) and CMV results (**Figure 130**) are presented below.

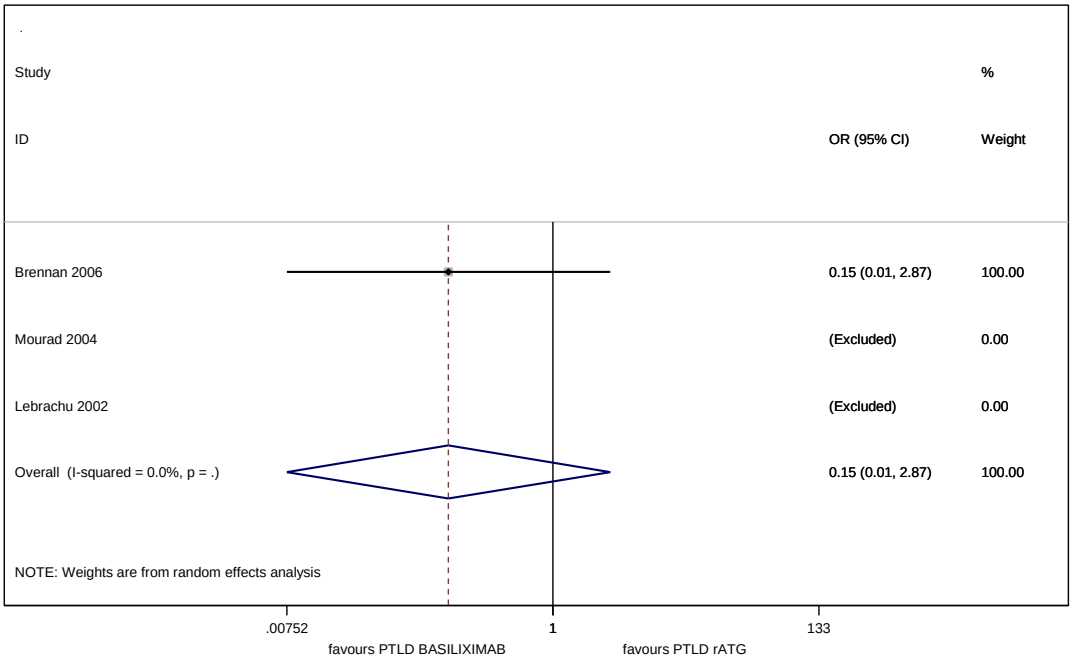
In summary, no difference in NODAT, PTLD, malignancy and infections were found between the two induction regimens, rATG and BAS. One study suggested more CMV infections in rATG regimens compared with BAS regimens (Brennan et al. 2006;[89] **OR 2.25**, favours rATG **95% CI 1.06; 4.76**).

Figure 127 Malignancy; Basiliximab versus rATG



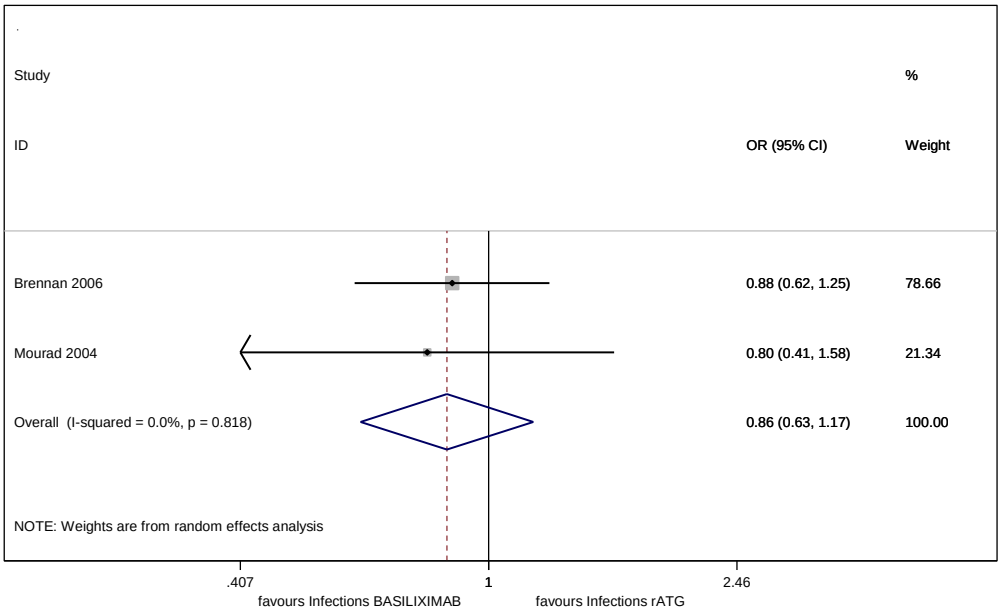
Key: OR, odds ratio; ID, identification; Mal., malignancy. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; studies with no events in both arms were excluded from the analysis; the estimate of between-study variance Tau-squared was 0.000. Lebrachu et al. 2003 reported 0/51 and 0/50 malignancy cases in BAS and rATG arms respectively.

Figure 128 PTLD; Basiliximab versus rATG



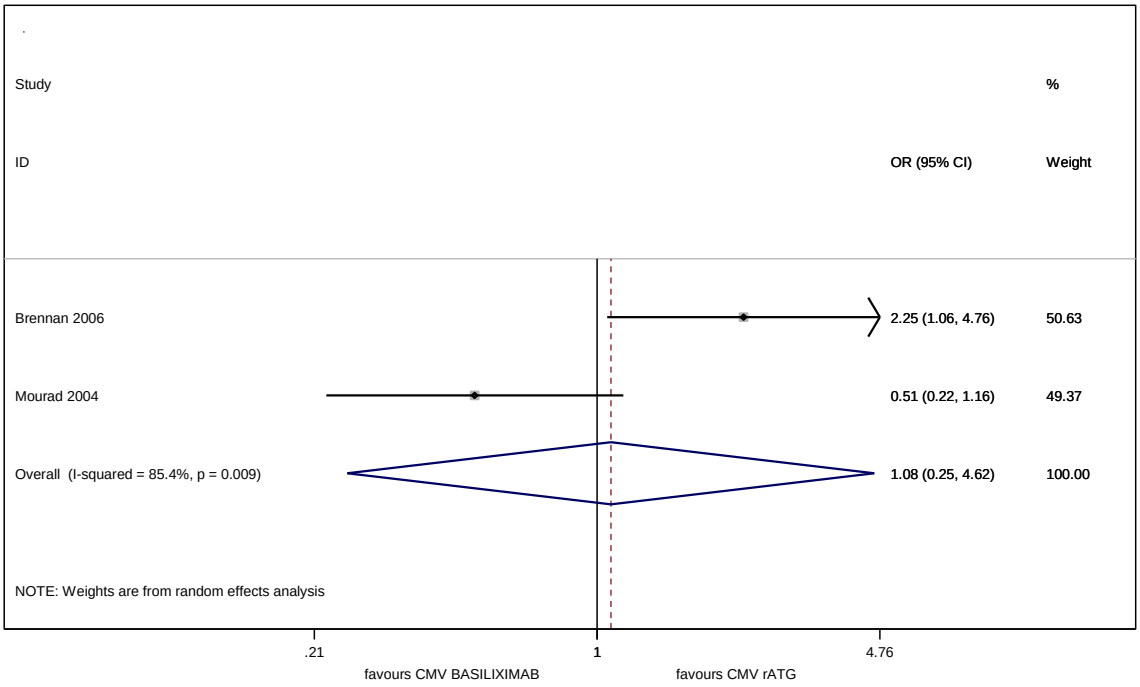
Key: OR, odds ratio; ID, identification; PTLD, post-transplant lymphoproliferative disorder. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; studies with no events in both arms were excluded from the analysis. Lebrachu et al. 2003 reported 0/51 and 0/50 PTLDcases in BAS and rATG arms respectively. Mourad et al. 2004 reported 0/51 and 0/50 PTLD cases in BAS and rATG arms respectively.

Figure 129 Infections; Basiliximab versus rATG



Key: OR, odds ratio; ID, identification. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Figure 130 CMV; Basiliximab versus rATG



Key: OR, odds ratio; ID, identification; CMV, cytomegalovirus. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.251.

rATG versus no induction

NODAT and CMV were reported in one study comparing rATG versus no induction (Charpentier et al. 2001)[82]. More CMV infections were reported in the rATG arm compared with controls: **OR 2.11** (favours no induction; **95% 1.26; 3.52**), and no difference in NODAT between rATG and no induction was found (OR 0.75 favours rATG; 95%CI 0.23; 2.42).

In summary, one study suggested more CMV infections in rATG regimens compared with no induction (Charpentier et al. 2001)[82].

Maintenance regimens

Thirty nine studies (of the 76 maintenance studies) reported some AE at 1–year follow-up. Twenty nine studies reported NODAT, 22 studies reported malignancy, nine studies reported PTLD, 15 studies reported infections and 28 studies reported CMV infections.

Ferguson et al. 2011 compared three regimens BEL+MMF and TAC+MMF and BEL+SIR, however only BEL+MMF and TAC+MMF results were used in meta-analyses.[138] Similarly, a one study by Chadban et al. 2013 compared EVL+CSA and MPS+CSA and EVL, however only results of EVL+CSA and MPS+CSA arms were used in meta-analyses [144] Finally, SYMPHONY trial compared low CSA+MMF, low TAC +MMF, SRL+MMF, and CSA+MMF, however only results of low CSA+MMF, low TAC +MMF and SRL+MMF were used in meta-analyses. [420] In addition, one study reported AE at 1-year follow-up, but the study did not use comparable concomitant rtherapies and therefore the results of this study could not be included in meta-analyses (Vacher-Coponat et al. 2012).[119]

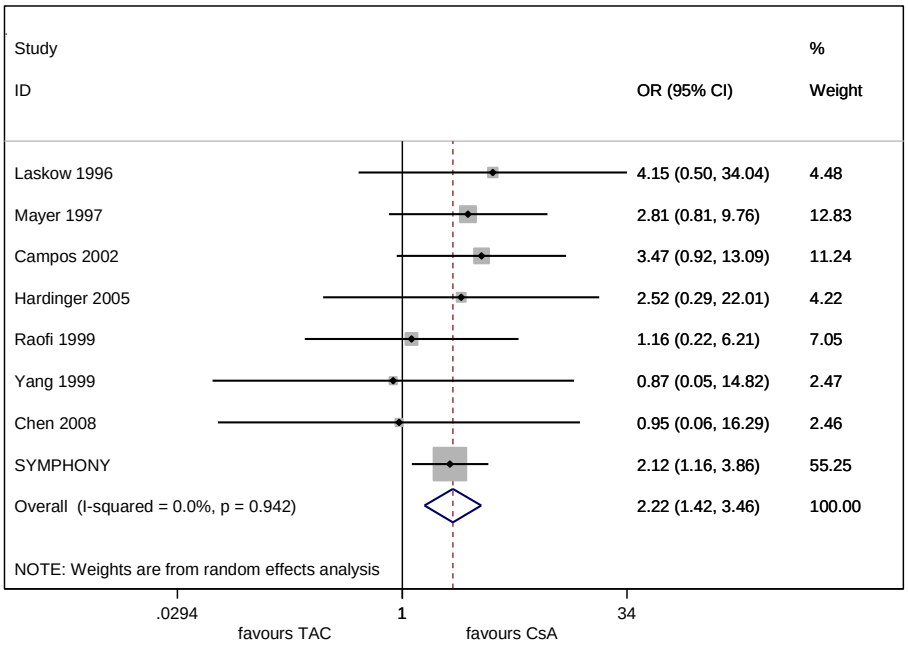
Tacrolimus versus Cyclosporine

Ten studies comparing TAC with CSA reported AE; six studies used TAC + AZA + CS and CSA+ AZA + CS regimens (Laskow et al. 1996, Mayer et al. 1997, Raofi et al. 199 [Jarzembowski et al. 200], Campos et al. 2002, Hardinger et al. 2005, Baboolal at al. 2002), two studies compared TAC+MMF+CCS and CSA+MMF+CCS regimens (Yang et al. 1999,Weimer at al 2006), one study compared TAC+SRL+CCS and CSA+SRL+CCS regimens (Chen et al. 2008) and one study comparing four regimens

also compared low TAC +MMF+CCS and low CSA+MMF +CCS regimens (SYMPHONY)[420].

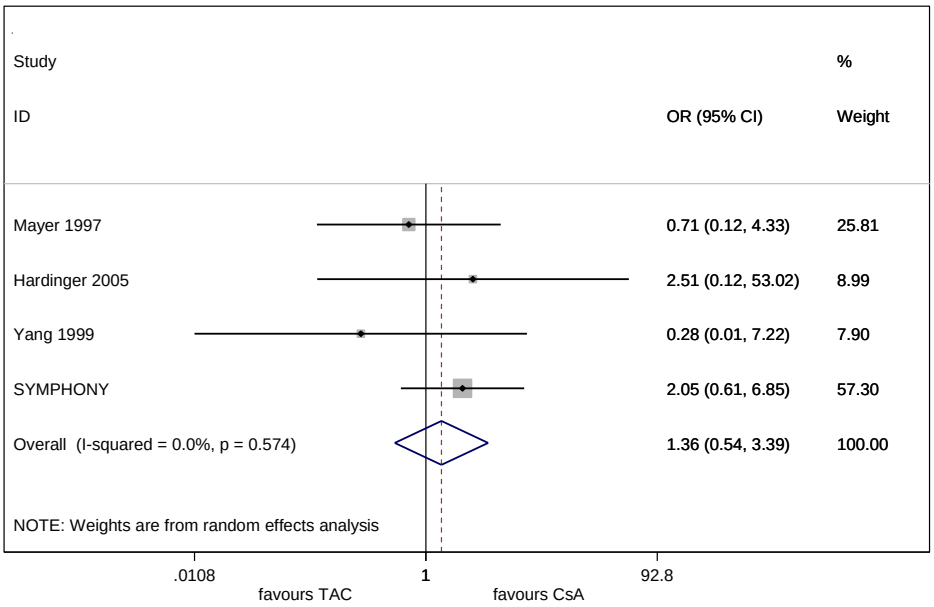
The meta-analyses suggested more cases of NODAT in TAC regimens compared with CSA (**Figure 134**), no difference for malignancy (**Figure 135**), no difference for infections (**Figure 136**) and no difference for CMV infections (**Figure 137**). Three studies reported no PTLD cases in both arms. [108 245 420] In summary, no difference in PTLD, malignancy, infections and CMV infection were found between TAC and CSA regimens at 1–year -follow-up. The meta-analysis (including 8 studies) suggested more cases of NODAT in TAC regimens compared with CSA.

Figure 134 NODAT; Tacrolimus versus Cyclosporine



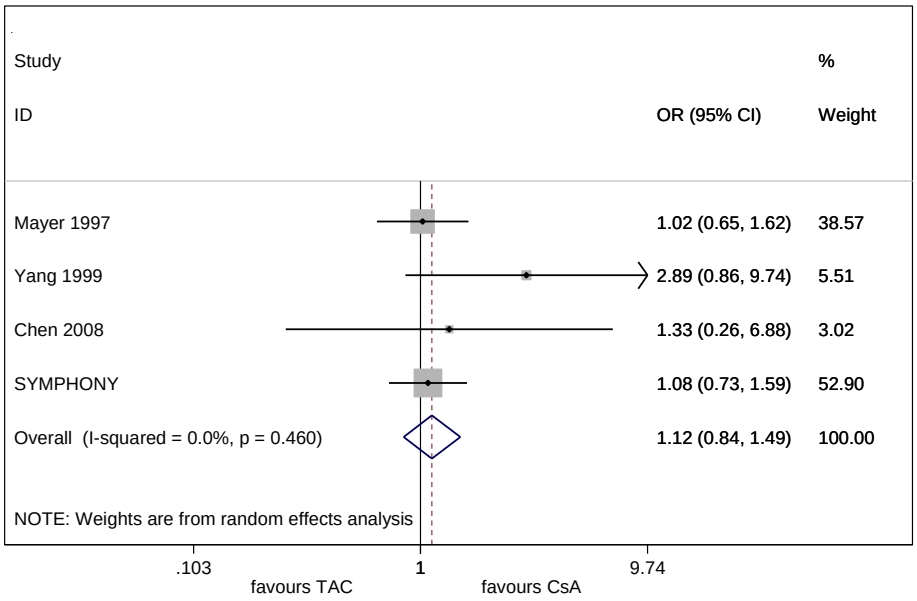
Key: OR, odds ratio; ID, identification; NODAT, new onset diabetes; TAC, Tacrolimus; CSA, cyclosporine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Figure 135 Malignancy; Tacrolimus versus Cyclosporine



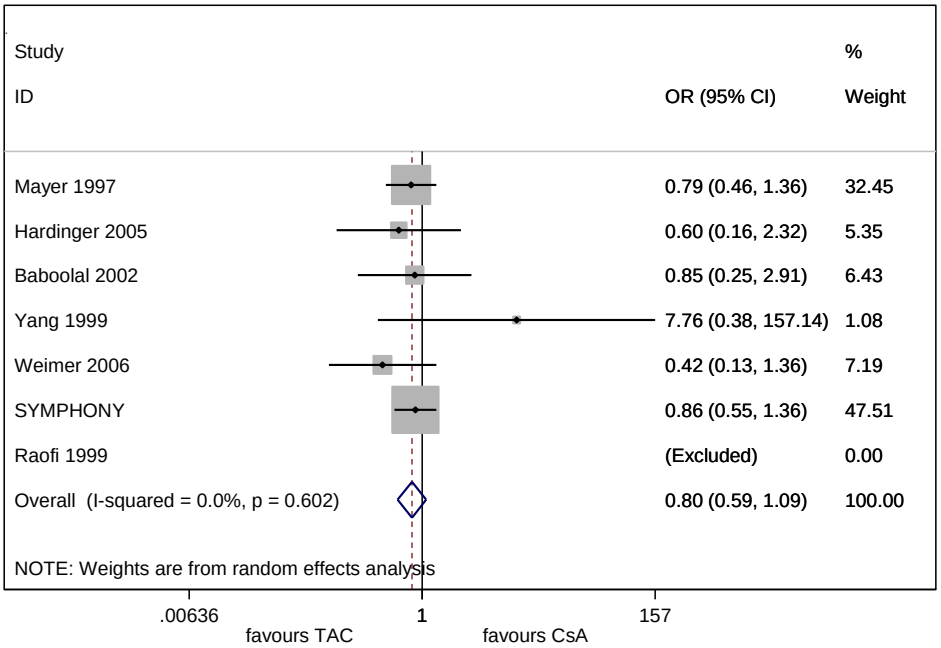
Key: OR, odds ratio; ID, identification; TAC, Tacrolimus; CSA, cyclosporine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Figure 136 Infections; Tacrolimus versus Cyclosporine



Key: OR, odds ratio; ID, identification; TAC, Tacrolimus; CSA, cyclosporine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; ; the estimate of between-study variance Tau-squared was 0.000.

Figure 137 CMV; Tacrolimus versus Cyclosporine



Key: OR, odds ratio; ID, identification; CMV, cytomegalovirus; TAC, Tacrolimus; CSA, cyclosporine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; studies with no events in both arms were excluded from the analysis; the estimate of between-study variance Tau-squared was 0.000. Raofi et al. 1999 reported 0/14 and 0/24 CMV infections in TAC and CSA arms respectively.

Mycophenolate Mofetil versus Cyclosporine

One three-arm study comparing MMF with CSA reported AE; this study used the following regimens MMF+AZA+CCS and CSA+AZA+CCS (Sadek et al. 2002)[113]. No difference was found between the two arms for infections, OR=0.86 (favours CSA; 95% CI 0.56-1.30). No other AE were reported in this study.

In summary, no difference in infections was found between MMF and CSA regimens at 1–year follow-up. However, only one study reported infection.

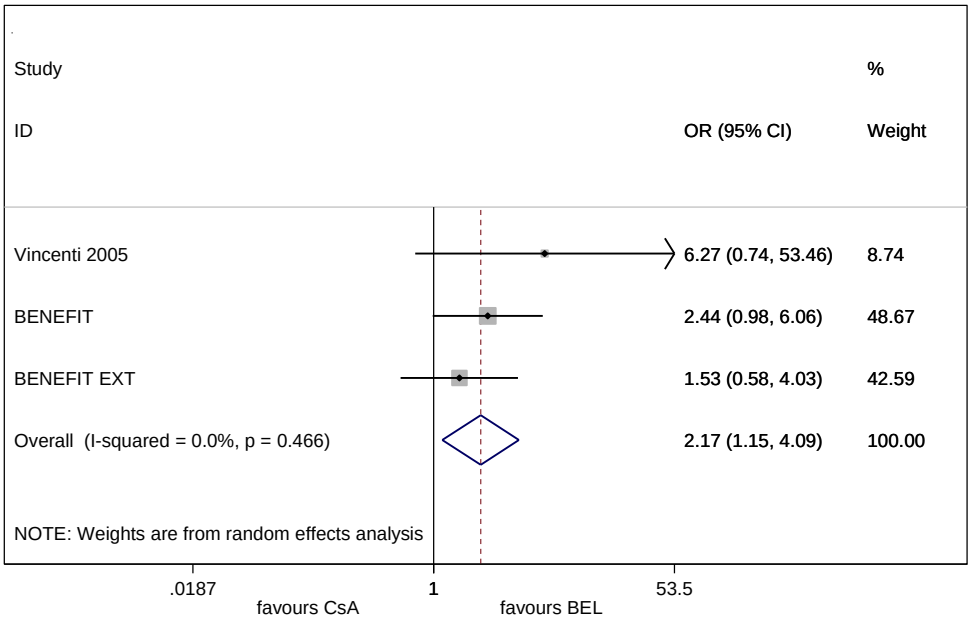
Belatacept versus Cyclosporine

Three studies comparing BEL with CSA reported AE; three studies used BEL+MMF+CCS and CSA+MMF+CCS regimens (Vincenti et al.2005, BENEFIT, BENEFIT-EXT)[71 135 421]. Two studies BENEFIT, BENEFIT-EXT)[135 421] had two BEL

regimens, using low and high BEL doses. Only the results of the low BEL arms (closer to the licence dose) were used in the analyses.

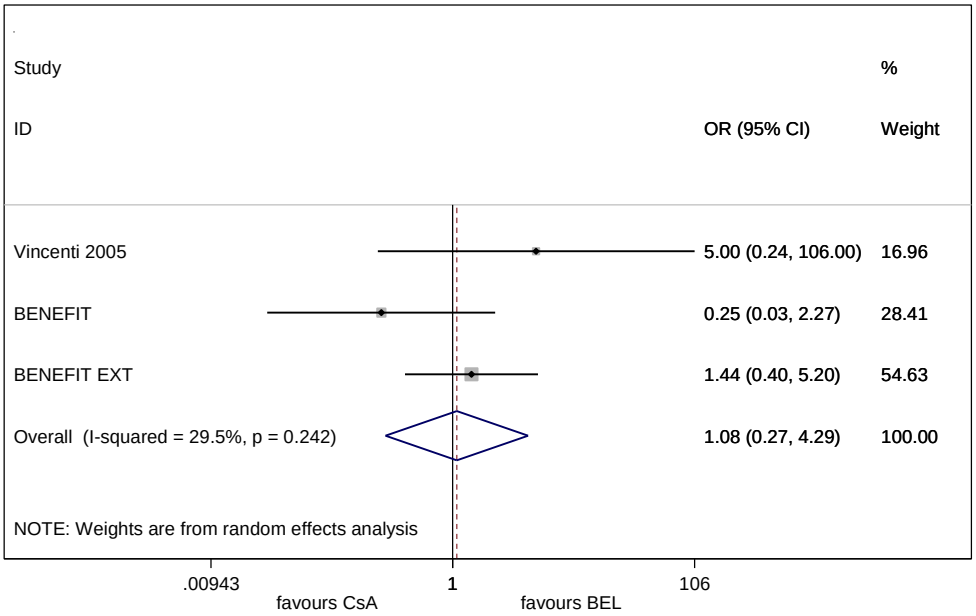
The meta-analyses suggested more cases of NODAT in CSA regimens compared with BEL regimens (**Figure 138**), no difference for malignancy (**Figure 139**), no difference for PTLD (**Figure 140**), no difference for infections (**Figure 141**) and CMV infections (**Figure 142**) between BEL and CSA regimens were identified. In summary, no difference in malignancy, PTLD, infections, and CMV infection were found between BEL and CSA regimens at 1–year -follow-up. The meta-analysis (including 3 studies) suggested more cases of NODAT in CSA regimens compared with BEL regimens.

Figure 138 NODAT; Belatacept versus Cyclosporine



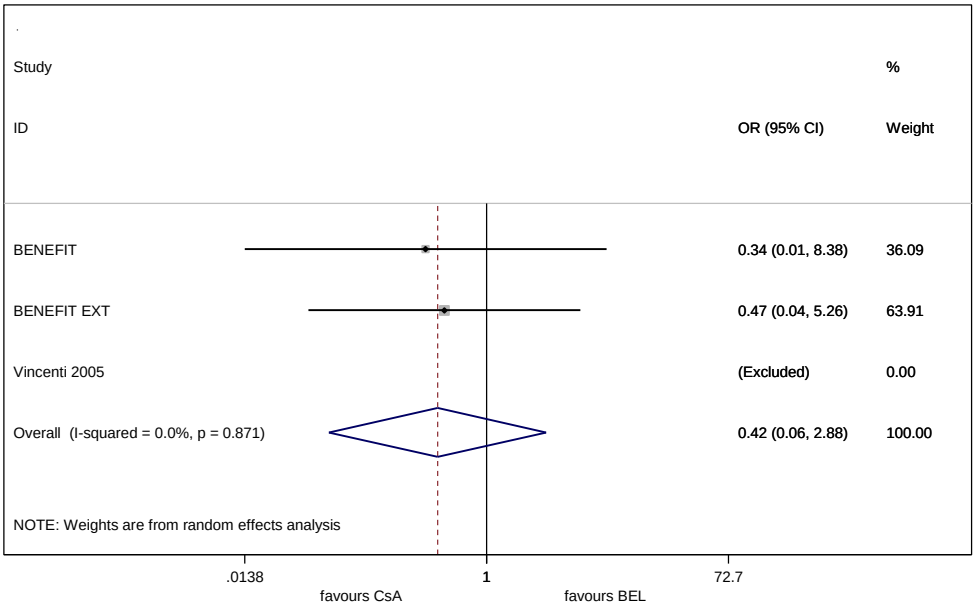
Key: OR, odds ratio; ID, identification; NODAT, new onset diabetes; BEL, Belatacept; CSA, cyclosporine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Figure 139 Malignancy; Belatacept versus Cyclosporine



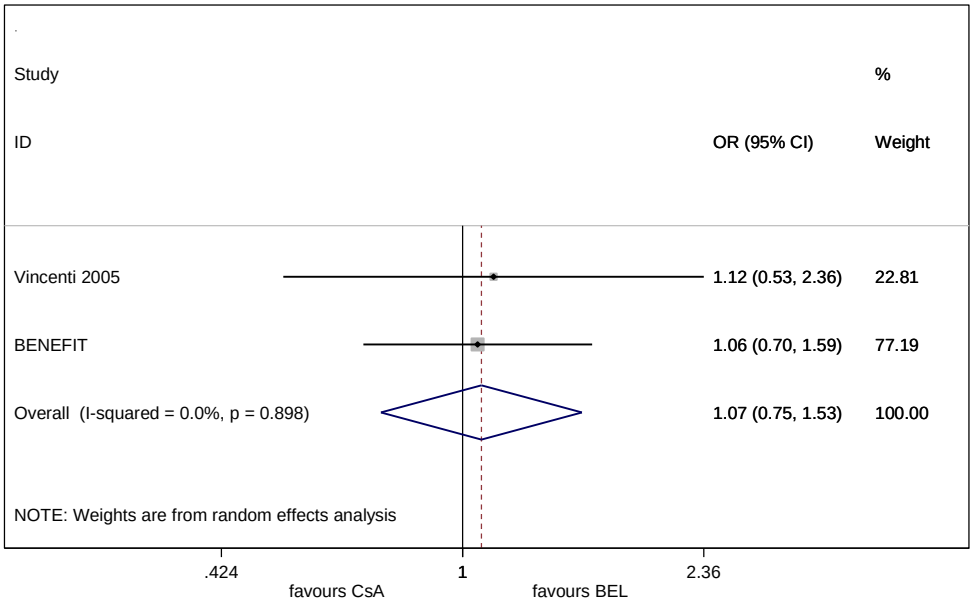
Key: OR, odds ratio; ID, identification; BEL, Belatacept; CSA, cyclosporine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.472.

Figure 140 PTLD; Belatacept versus Cyclosporine



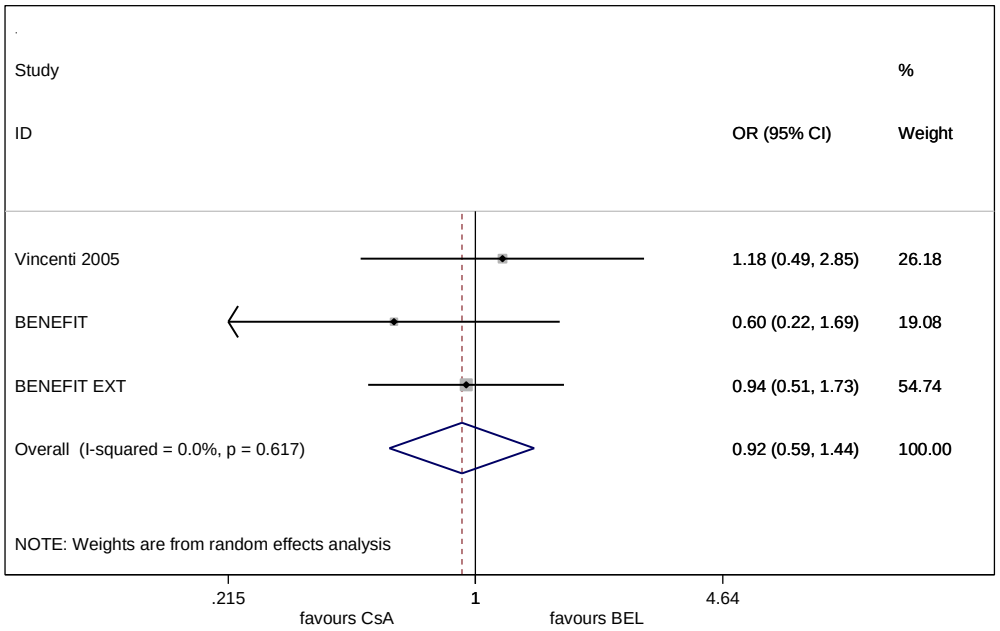
Key: OR, odds ratio; ID, identification PTLD, post-transplant lymphoproliferative disorder; BEL, Belatacept; CSA, cyclosporine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000. Vincenti et al. 2005 reported 0/71 and 0/73 PTLDcases in BEL and CSA arms respectively.

Figure 141 Infections; Belatacept versus Cyclosporine



Key: OR, odds ratio; ID, identification; BEL, Belatacept; CSA, cyclosporine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Figure 142 CMV; Belatacept versus Cyclosporine



Key: OR, odds ratio; ID, identification; CMV, cytomegalovirus; BEL, Belatacept; CSA, cyclosporine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Everolimus versus Cyclosporine

One study comparing EVL with CSA reported AE; this study used the following regimens EVL+MPS+CCS and CSA+MPS+CCS (Mjornstedt et al. 2012)[150]. No difference was found between the two arms for malignancy, OR= 1.02 (favours EVL; 95% CI 0.14-7.39), for infections, OR= 0.79 (favours CSA; 95% CI 0.47-1.32) and for CMV infections, OR= 1.54 (favours EVL; 95% CI 0.63-3.78). PTLD and NODAT were not reported in this study.

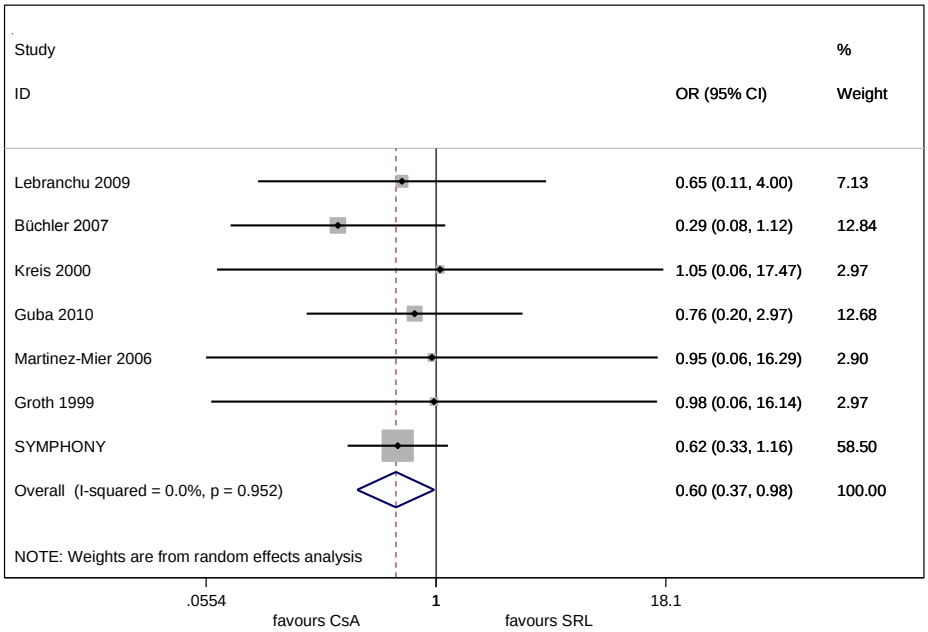
In summary, no difference in malignancy, infections and CMV infection were found between EVL and CSA regimens at 1–year -follow-up. However, only one study reported malignancy, infections and CMV infection.

Sirolimus versus Cyclosporine

Eight studies comparing SRL with CSA reported AE; six studies used SRL+MMF+CCS and CSA+MMF+CCS regimens (Lebranchu et al. 2009, Büchler et al. 2007, Kreis et al. 2000, Guba et al. 2010, Martinez-Mier et al. 2006 and Flechner et al. 2002)[163 167 173 174 205 206], one study used SRL+AZA+CCS and CSA+AZA+CCS regimens (Groth et al. 1999[Charpentier 2003])[185], and one study comparing four regimens also compared SRL+MMF+CCS and CSA+MMF+CCS regimens (SYMPHONY)[420].

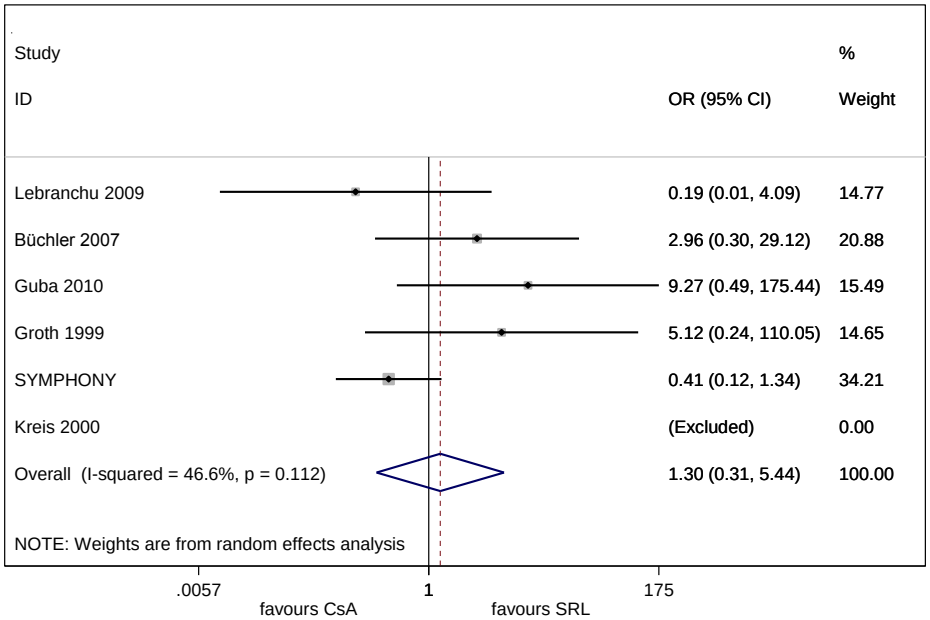
The meta-analyses suggested more cases of NODAT in SRL regimens compared with CSA (**Figure 143**), no difference in malignancy (**Figure 144**), no difference in PTLD (**Figure 145**), no difference for infections (**Figure 146**) and more cases of no difference for infections CMV in CSA compared with SRL regimen (**Figure 147**). In summary, no difference in malignancy, PTLD, infections, and CMV infection were found between SRL and CSA regimens at 1–year -follow-up. The meta-analysis (including 7 studies) suggested more cases of NODAT in CSA regimens compared with SRL.

Figure 143 NODAT; Sirolimus versus Cyclosporine



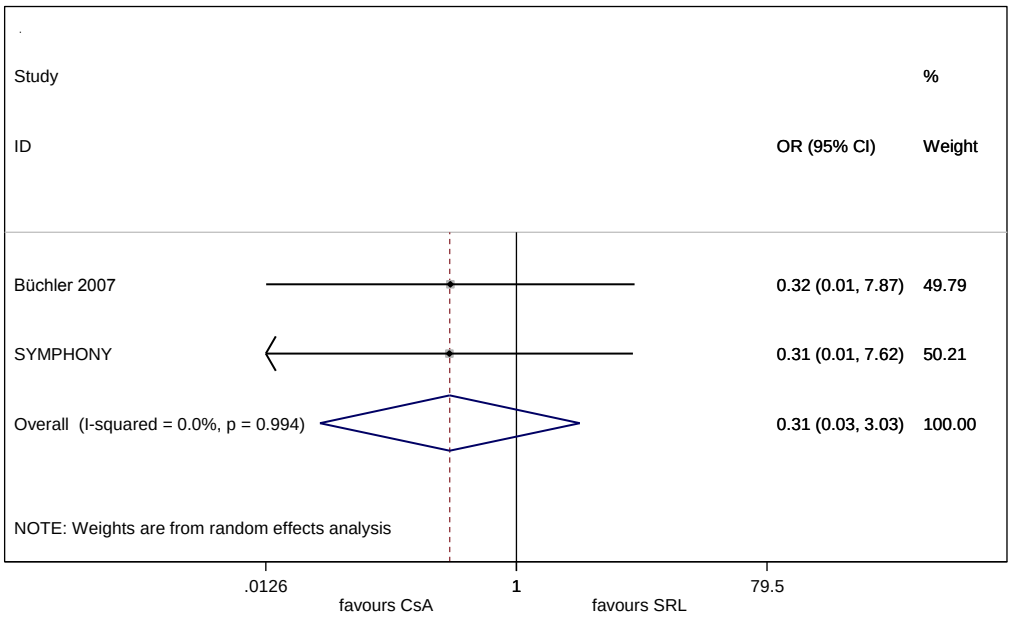
Key: OR, odds ratio; ID, identification; NODAT, new onset diabetes; SRL, sirolimus; CSA, cyclosporine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Figure 144 Malignancy; Sirolimus versus Cyclosporine



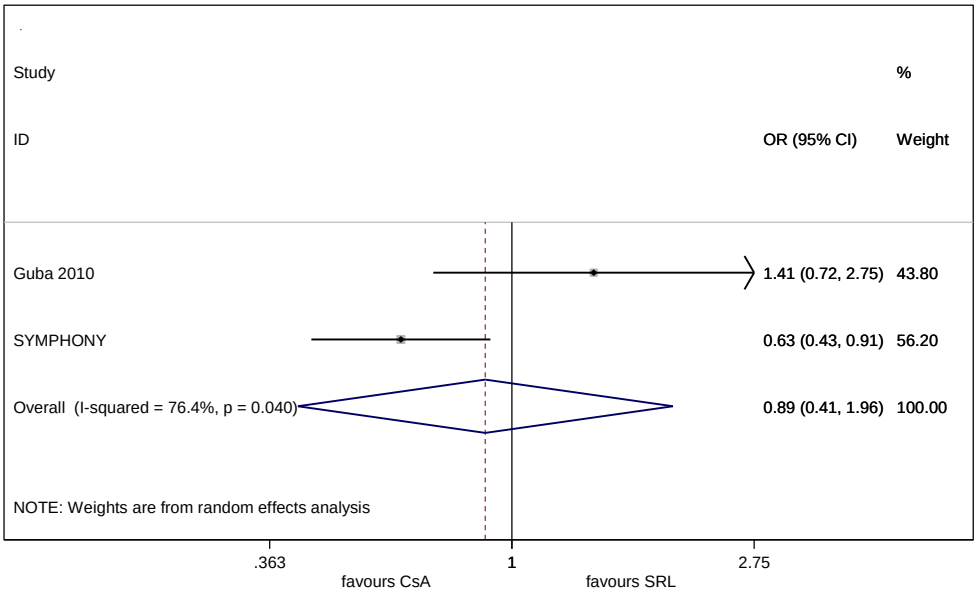
Key: OR, odds ratio; ID, identification; SRL, sirolimus; CSA, cyclosporine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; studies with no events in both arms were excluded from the analysis; the estimate of between-study variance Tau-squared was 0.000. Kreis et al. 2000 reported 0/40 and 0/38 malignancy cases in SRL and CSA arms respectively.

Figure 145 PTLD; Sirolimus versus Cyclosporine



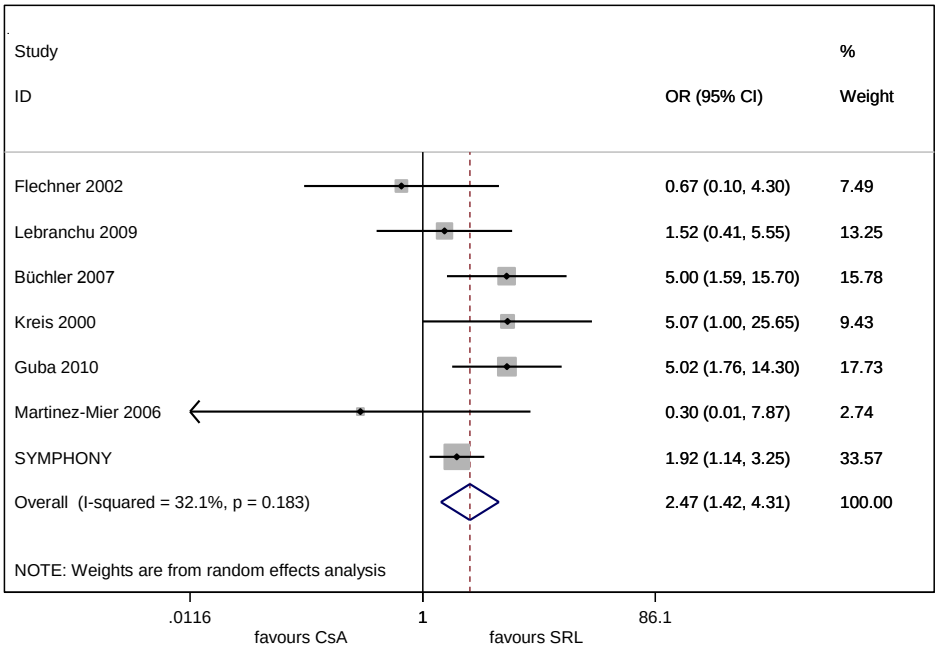
Key: OR, odds ratio; ID, identification; PTLD, post-transplant lymphoproliferative disorder; SRL, sirolimus; CSA, cyclosporine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Figure 146 Infections; Sirolimus versus Cyclosporine



Key: OR, odds ratio; ID, identification; SRL, Sirolimus; CSA, cyclosporine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.248.

Figure 147 CMV; Sirolimus versus Cyclosporine



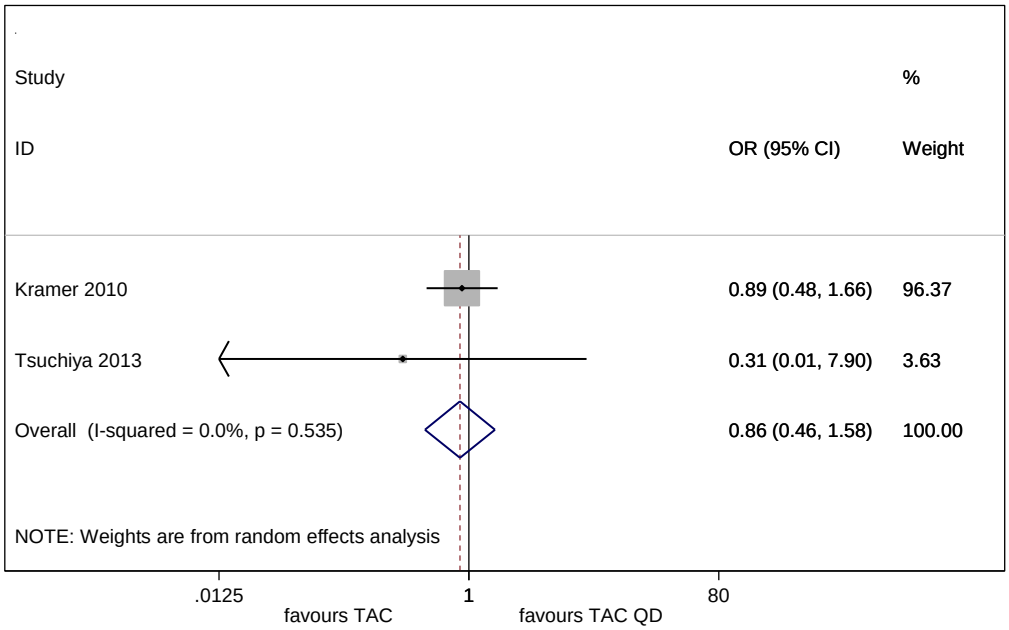
Key: OR, odds ratio; ID, identification; CMV, cytomegalovirus; SRL, Sirolimus; CSA, cyclosporine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Tacrolimus (short release) versus Prolong Release Tacrolimus

Two studies comparing TAC with TAC-PR reported AE; both studies used TAC+MMF+CCS and TAC PR+MMF+CCS regimens (Kramer et al. 2010 and Tsuchiya et al. 2013)[72 128].

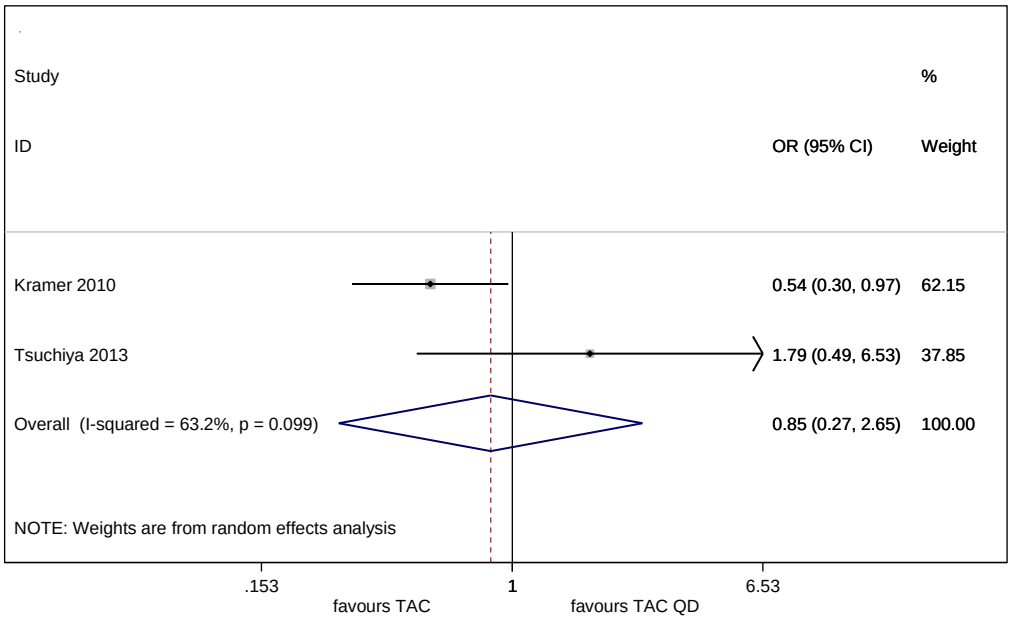
The meta-analyses suggested no differences for NODAT (**Figure 148**) and no differences for CMV (**Figure 149**). In addition, no difference was found between the two arms (Kramer et al. 2010) for malignancy, OR=1.32 (favours TAC-PR; 95% CI 0.45-3.85). No results for PTLD were reported. In summary, no difference in NODATs and CMV infection were found between TAC and TAC-PR regimens at 1–year -follow-up. However, only two studies reported NODATs and CMV infection.

Figure 148 NODAT; Tacrolimus versus Prolong Release Tacrolimus



Key: OR, odds ratio; ID, identification; NODAT, new onset diabetes; TAC, Tacrolimus; TAC QD, Tacrolimus Prolong Release. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Figure 149 CMV; Tacrolimus versus Prolong Release Tacrolimus



Key: OR, odds ratio; ID, identification; CMV, cytomegalovirus; TAC, Tacrolimus; TAC QD, Prolong Release Tacrolimus. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.452.

Mycophenolate Mofetil versus Tacrolimus

One study comparing MMF with TAC reported AE; this study used the following regimens MMF+SRL+CCS and TAC+SRL+CCS (Hamdy et al. 2005)[181]. No difference was found between the two arms for NODAT, OR= 1.59 (favours MMF; 95% CI 0.72-3.53). No other AE were reported in this study.

In summary, no difference in NODAT was found between MMF and TAC regimens at 1–year -follow-up. However, only one study reported NODAT.

Belatacept versus Tacrolimus

One three-arm study comparing BEL with TAC reported AE; this study used the following regimens BEL+MMF+CCS and TAC+MMF+CCS (Fergusson et al. 2011).[138] No difference was found between the two arms for NODAT, OR=3.42 (favours BEL; 95% CI 0.13-87.10), for malignancy, OR=3.42 (favours BEL; 95% CI 0.13-87.10), and for CMV infections, OR=2.29 (favours BEL; 95% CI 0.20-26.47). PTLD and infections were not reported in this study.

In summary, no difference in NODAT, malignancy, infections and CMV infection were found between BEL and TAC regimens at 1–year -follow-up. However, only one study reported NODAT, malignancy, infections and CMV infection.

Sirolimus versus Tacrolimus

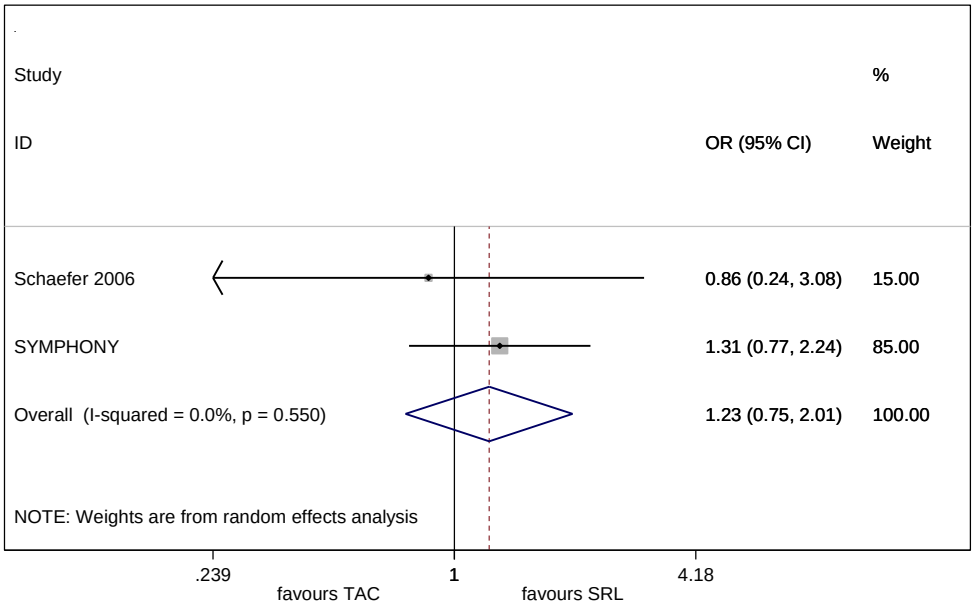
Two studies comparing SRL with TAC reported AE; one study used SRL+MMF+CCS and TAC+MMF+CCS regimens (Schaefer et al. 2006)[78], and one study comparing four regimens also compared SRL+MMF+CCS and TAC+MMF+CCS regimens (SYMPHONY)[420].

The meta-analysis suggested no difference for NODAT (**Figure 150**). However publication bias was not explored and the number of pooled studies is small, therefore the result must be interpreted with caution. No difference was found between the two

arms (SYMPHONY[420]) for malignancy: OR=0.83 (favours TAC; 95% CI 0.32-2.19), for PTLD: OR=0.31 (favours TAC; 95% CI 0.01-7.72), and for CMV infections: OR=1.66 (favours SRL; 95% CI 0.97-2.84). More infections were found in the SRL arm compared with the TAC arm for infections: **OR=0.68 (favours TAC; 95% CI 0.47-0.98).**

In summary, no difference in NODAT, PTLD, malignancy, CMV infection was found between SRL and TAC regimens at 1–year -follow-up. One study found statistically significantly more infections in SRL compared with TAC arm (SYMPHONY[420]). However, only two studies reported NODATs, and only one study reported PTLD, malignancy, infections and CMV infection.

Figure 150 NODAT; Sirolimus versus Tacrolimus



Key: OR, odds ratio; ID, identification; NODAT, new onset diabetes; TAC, Tacrolimus; SRL, Sirolimus. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

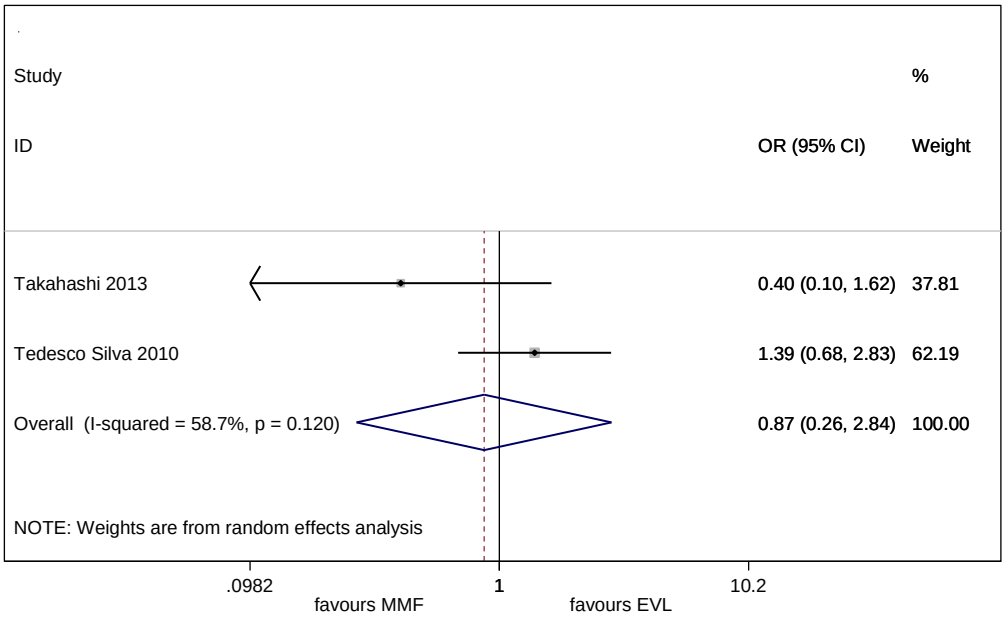
Everolimus versus Mycophenolate Mofetil

Three studies comparing EVL with MMF reported AE; all studies used EVL+CSA+CCS and MMF+CSA+CCS regimens (Vitko et al. 2005, Tedesco Silva et al. 2010 and Takahashi et al. 2013)[142 143 145]. Tedesco Silva et al. 2010[145] reported using MPA; it was assumed that MMF was used.

The meta-analyses suggested no differences for NODAT (**Figure 151** and infections (**Figure 152**), conversely a significant difference was found for CMV infections (**Figure 153**); more

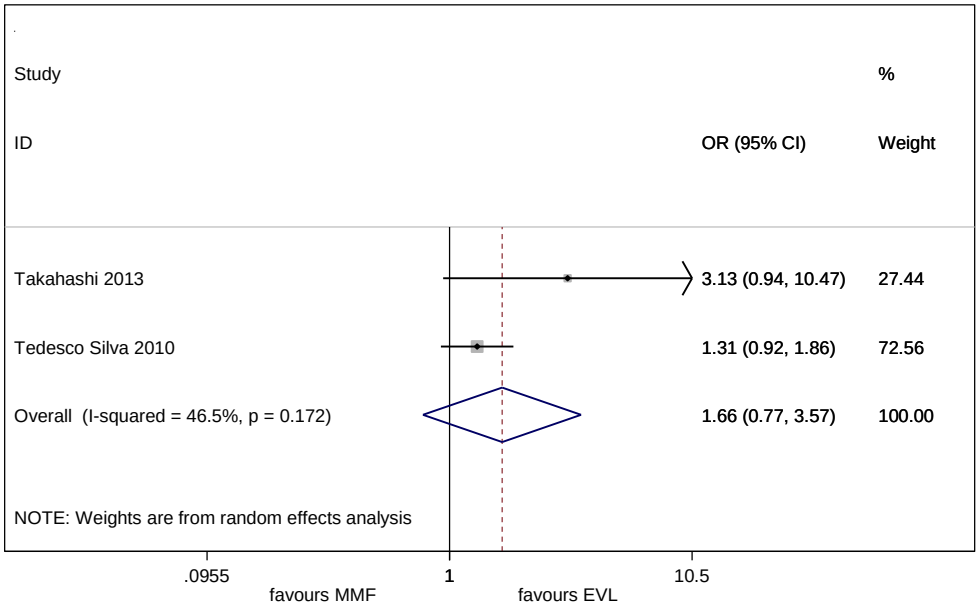
CMV infections were found in MMF compared with EVL. No difference was found between the two arms (Takahashi et al. 2013) for malignancy OR= 0.19 (favours MMF; 95% CI 0.01-4.11). PTLD was not reported in these studies. In summary, no difference in NODAT, PTLD, malignancy and infection were found between EVL and MMF regimens at 1–year -follow-up. The meta-analysis (including 3 studies) suggested more cases of CMV infections in MMF regimens compared with EVL.

Figure 151 NODAT; Everolimus versus Mycophenolate mofetil



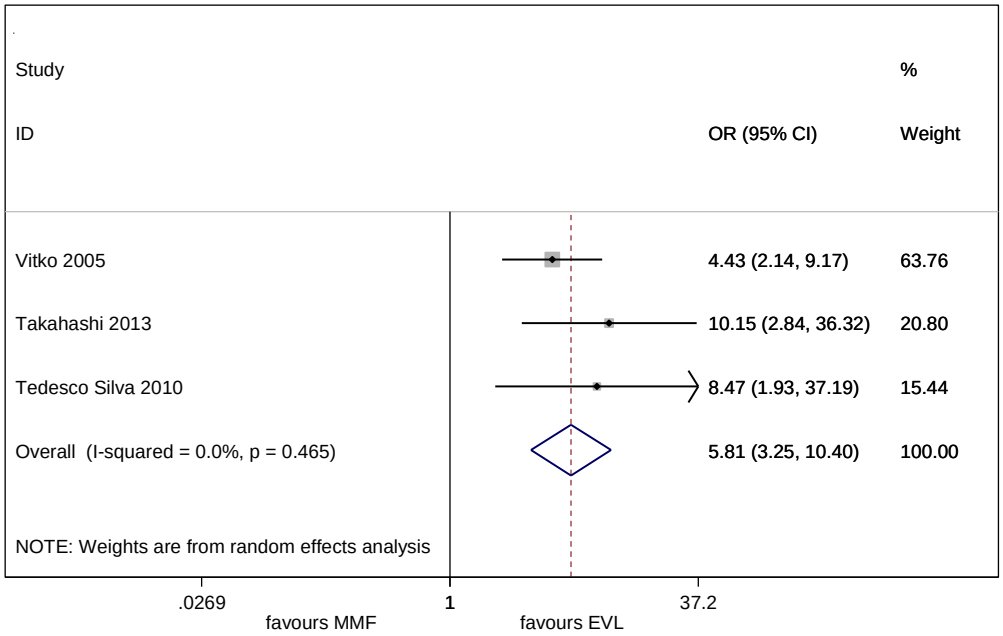
Key: OR, odds ratio; ID, identification; NODAT, new onset diabetes; EVL, Everolimus; MMF, Mycophenolate mofetil. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.456.

Figure 152 Infection; Everolimus versus Mycophenolate mofetil



Key: OR, odds ratio; ID, identification; EVL, Everolimus; MMF, Mycophenolate mofetil. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.178.

Figure 153 CMV; Everolimus versus Mycophenolate mofetil



Key: OR, odds ratio; ID, identification; CMV, cytomegalovirus; EVL, Everolimus; MMF, Mycophenolate mofetil. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

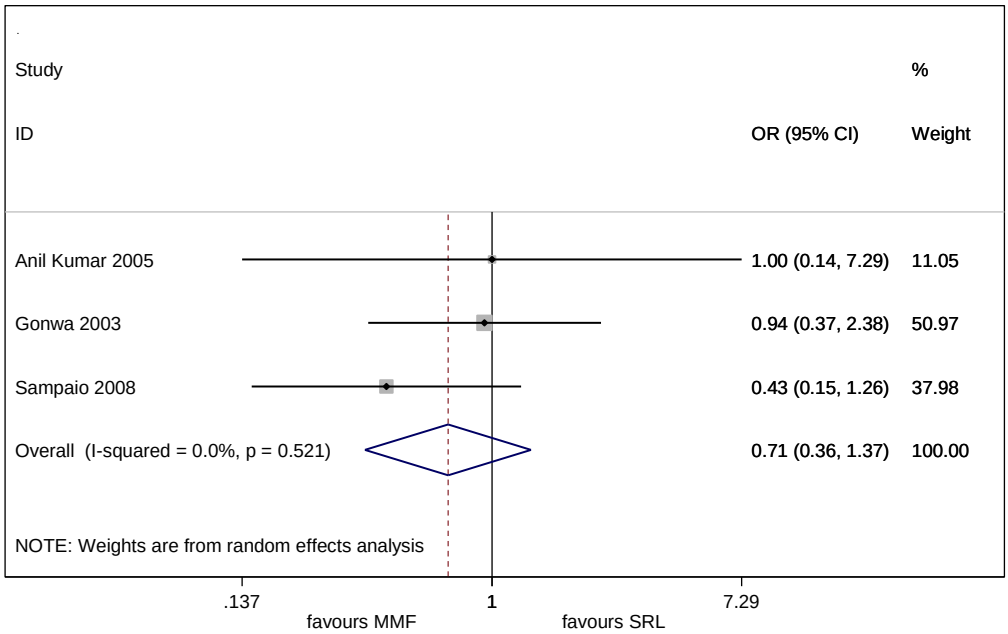
Sirolimus versus Mycophenolate Mofetil

Three studies comparing SRL with MMF reported AE; all studies used SRL+TAC+CCS and MMF+TAC+CCS regimens (Mendez et al. 2005, Anil Kumar et al. 2005 and Sampaio et al. 2008).[153 154 156]

The meta-analyses suggested no differences for NODAT (**Figure 154**), malignancy (**Figure 155**), and PTLD (**Figure 156**). However publication bias was not explored and the number of pooled studies is small, therefore all results must be interpreted with caution. No difference was found between the two arms (Sampaio et al. 2008) for CMV infections; 6/50 (12%) and 6/50 (12%) respectively. Infections were not reported in these studies.

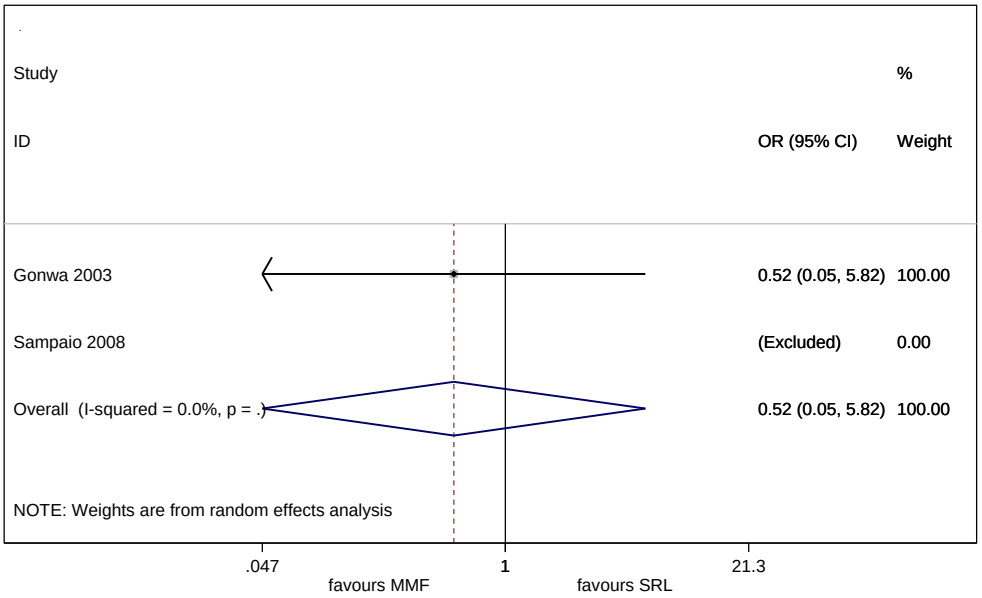
In summary, no difference in NODAT, PTLD, malignancy, and CMV infection were found between SRL and MMF regimens at 1–year -follow-up. However, only three studies reported NODAT and PTLD; two studies reported malignancy; and only one study reported CMV infections.

Figure 154 NODAT; Sirolimus versus Mycophenolate mofetil



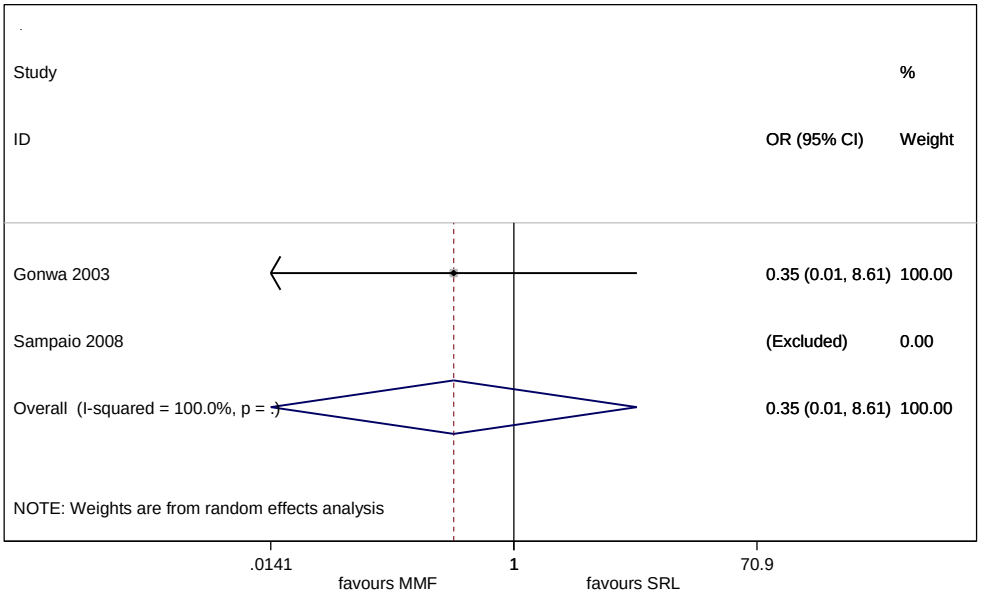
Key: OR, odds ratio; ID, identification; NODAT, new onset diabetes; SRL, Sirolimus; MMF, Mycophenolate mofetil. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Figure 155 Malignancy; Sirolimus versus Mycophenolate mofetil



Key: OR, odds ratio; ID, identification; SRL, Sirolimus; MMF, Mycophenolate mofetil. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; studies with no events in both arms were excluded from the analysis. Sampaio et al. 2008 reported 0/0 and 0/50 malignancy cases in SRL and MMF arms respectively.

Figure 156 PTLD; Sirolimus versus Mycophenolate mofetil



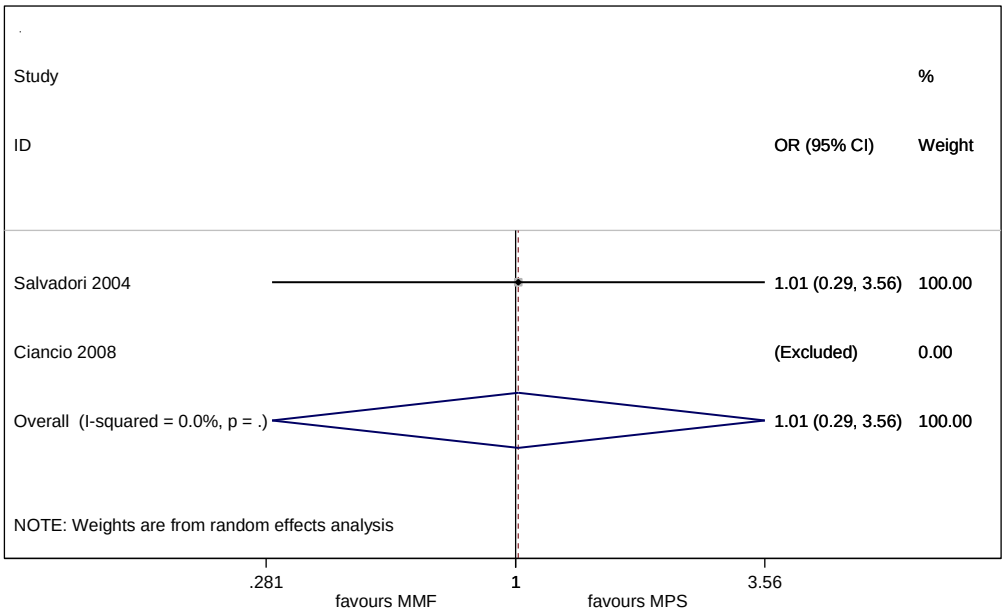
Key: OR, odds ratio; ID, identification; PTLD, post-transplant lymphoproliferative disorder; SRL, Sirolimus; MMF, Mycophenolate mofetil. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data. Sampaio et al. 2008 reported 0/50 and 0/50 PTLD cases in SRL and MMF arms respectively

Mycophenolate Mofetil versus Mycophenolate Sodium

Two studies comparing MMF with MPS reported AE; one study used MMF+TAC+CCS and MPS+TAC+CCS regimens (Cianco et al. 2008)[130] and one study used MMF+CSA+CCS and MPS+CSA+CCS regimens (Salvadori et al. 2004).[132]

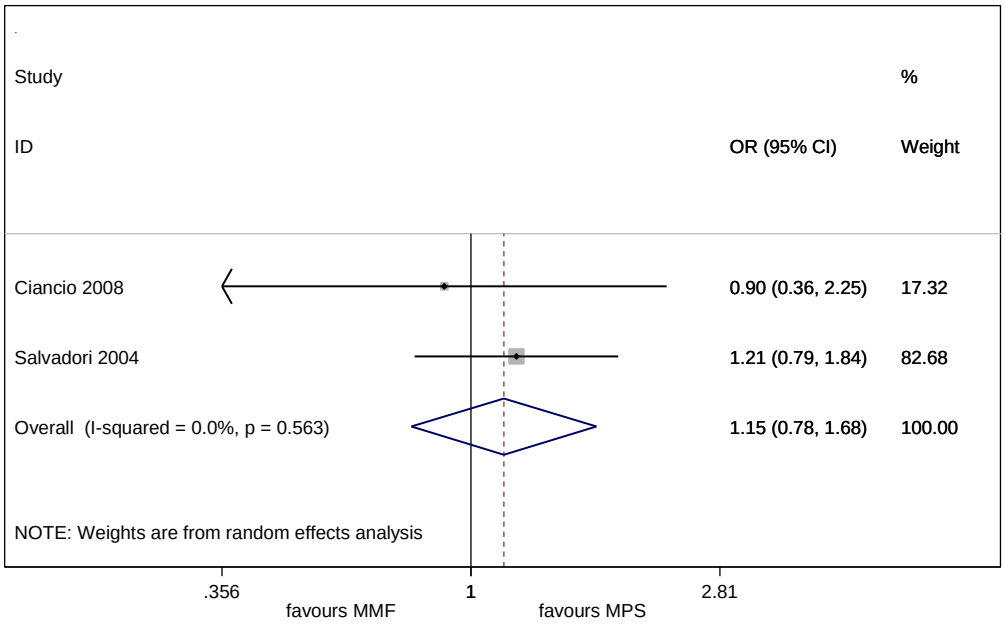
The meta-analyses suggested no differences for malignancy (**Figure 157**) and infections (**Figure 158**) and CMV infections (**Figure 159**). However publication bias was not explored and the number of pooled studies is small, therefore all results must be interpreted with caution. No difference was found between the two arms (Cianco et al. 2008[130]) for NODAT, OR= 1.06 (favours MPS; 95% CI 0.33-3.36). In summary, no difference in NODAT, malignancy, infections and CMV infections were found between MMF and MPS regimens at 1–year -follow-up. However, only two studies reported malignancy, infections and CMV infections, and only one study reported NODAT.

Figure 157 Malignancy; Mycophenolate mofetil versus Mycophenolate sodium



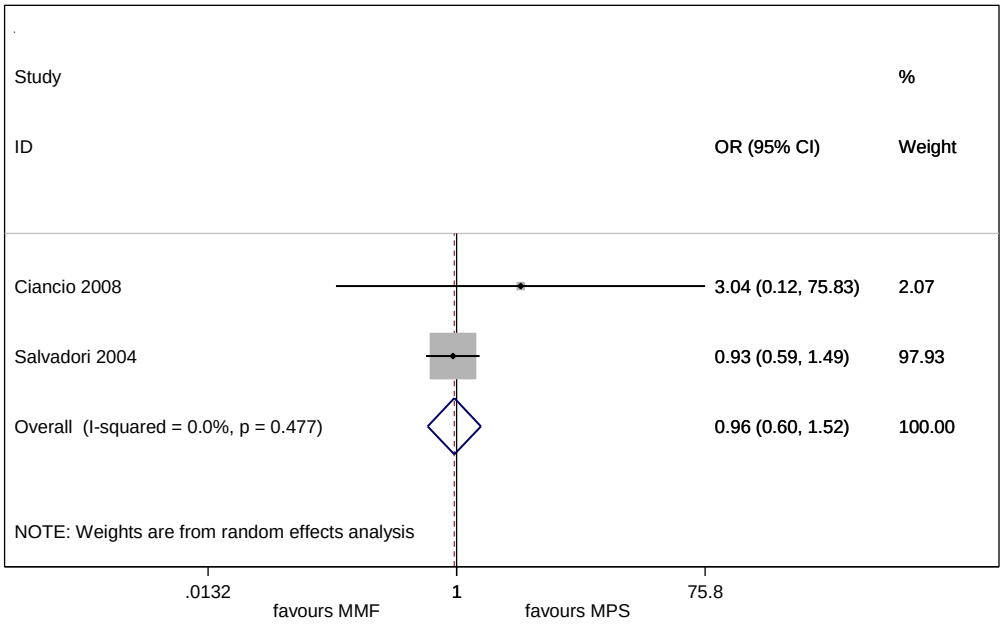
Key: OR, odds ratio; ID, identification; MMF, Mycophenolate mofetil; MPS, Mycophenolate sodium. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; studies with no events in both arms were excluded from the analysis. Ciancio et al. 2008 reported 0/61 and 0/55 malignancy cases in MMF and MPS arms respectively

Figure 158 Infections; Mycophenolate mofetil versus Mycophenolate sodium



Key: OR, odds ratio; ID, identification; MMF, Mycophenolate mofetil; MPS, Mycophenolate sodium. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Figure 159 CMV: Mycophenolate mofetil versus Mycophenolate sodium



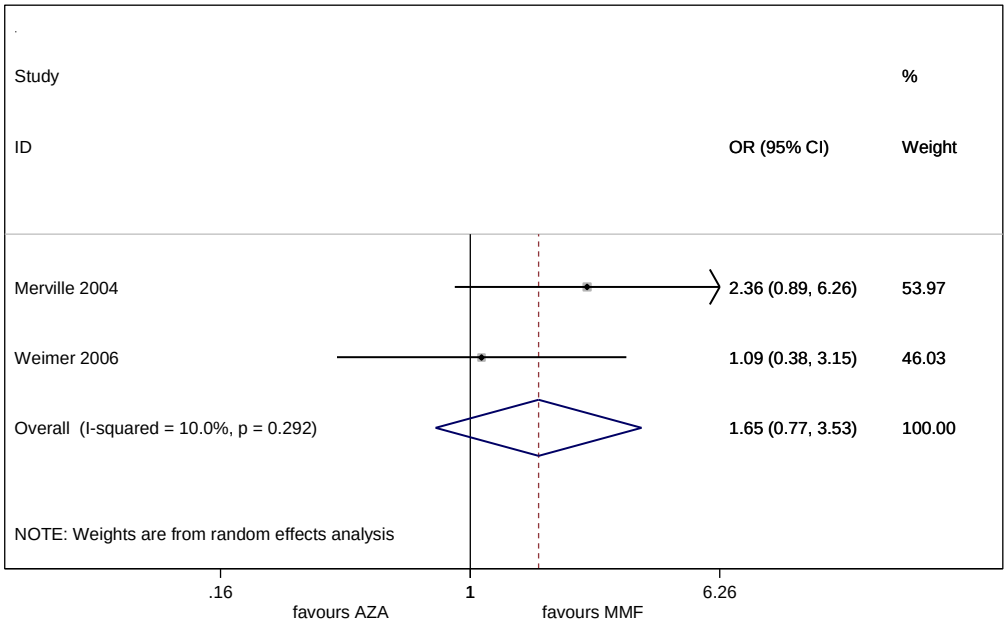
Key: OR, odds ratio; ID, identification; CMV, cytomegalovirus; MMF, Mycophenolate mofetil; MPS, Mycophenolate sodium. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Mycophenolate Mofetil versus Azathioprine

Three studies comparing MMF with AZA reported AE; one study used MMF+CSA+CCS and AZA+CSA+CCS regimens (Merville et al. 2004)[114] and two three-arm studies also used MMF+CSA+CCS and AZA+CSA+CCS regimens (Sadek et al. 2002 and Weimer et al. 2006).[113 125]

The meta-analyses suggested no differences for CMV infections (**Figure 160**). However publication bias was not explored and the number of pooled studies is small, therefore all results must be interpreted with caution. No difference was found between the two arms for infections in one study (Sadek et al. 2002), OR= 1.60 (favours MMF, 95% CI 0.98-2.60). NODAT, malignancy, and PTLD were not reported in these studies. In summary, no difference in infections and CMV infection were found between MMF and AZA regimens at 1–year -follow-up. However, only three studies reported CMV infection, and only one study reported infections.

Figure 160 CMV; Mycophenolate mofetil versus Azathioprine



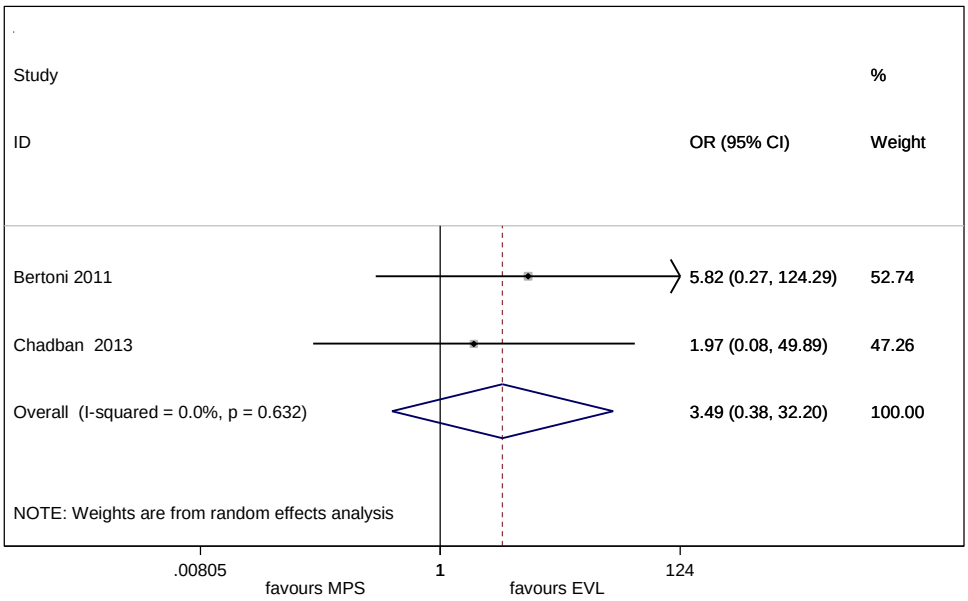
Key: OR, odds ratio; ID, identification; CMV, cytomegalovirus; MMF, Mycophenolate mofetil; AZA, Azathioprine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.030.

Everolimus versus Mycophenolate Sodium

Two studies comparing EVL with MPS reported AE; one study used EVL+CSA+CCS and MPS+CSA+CCS regimens (Bertoni et al. 2011)[146] and one three-arm study also used EVL+CSA+CCS and MPS+CSA+CCS regimens (Chadban et al. 2013).[144]

The meta-analyses suggested no differences for malignancy (**Figure 161**). However publication bias was not explored and the number of pooled studies is small, therefore all results must be interpreted with caution. No difference was found between the two arms (Chadban et al. 2013) for NODAT, OR=0.45 (favours MPS; 95% CI 0.17-1.20), infections, OR= 1.74 (favours MMF; 95% CI 0.72-4.20), and CMV infections, OR=0.29 (favours MPS; 95% CI 0.05-1.71). PTLD was not reported in the two studies. In summary, no difference in NODAT, malignancy, infections and CMV infections were found between EVL and MPS regimens at 1–year -follow-up. However, only two studies reported malignancy, and only one study reported NODAT, infections and CMV infections.

Figure 161 Malignancy; Everolimus versus Mycophenolate sodium



Key: OR, odds ratio; ID, identification; MMF, Mycophenolate mofetil; EVL, Everolimus. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Summary

Induction regimens

No difference in NODAT, PTLD, malignancy and infections were found between the two induction regimens, rATG and BAS when compared with each other or with no induction (and/or placebo) regimens at 1–year follow-up. One study suggested more CMV infections in rATG regimens compared with no induction (Charpentier et al. 2001).[88] One study suggested more CMV infections in rATG regimens compared with BAS regimens (Brennan at al. 2006),[89] but the results were not confirmed by other study (Mourad at al. 2004).[91] In addition, publication bias was not explored and the number of pooled studies is small, therefore all results must be interpreted with caution.

Maintenance regimens

The meta-analyses of AE at 1–year follow-up suggested significant differences in AE for the following regimens. The meta-analysis comparing TAC and CSA regimens (including 8 studies) suggested more cases of NODAT in TAC regimens compared with CSA regimens. The meta-analyses comparing BEL with CSA regimens (including 3 studies) suggested more cases of NODAT in CSA regimens compared with BEL regimens (including 3 studies). The meta-analyses comparing SRL and CSA regimens suggested more cases of NODAT in SRL compared with CSA (including 7 studies), and more CMV infections in CSA compared with SRL (including 7 studies). The meta-analysis comparing MMF and EVL (including 3 studies) suggested more cases of CMV infections in MMF regimens compared with EVL. However, publication bias was not explored and the number of pooled studies is small, therefore all results must be interpreted with caution.