Tertiary/Quaternary Level Essential Drug List
Review Document

Medication Name: **Date:** 12 July 2016
Basiliximab

Indication:
Induction therapy for prophylaxis against acute rejection in renal transplant recipients.

Context:
Induction therapy in the transplant setting is an intense prophylactic treatment strategy intended to lower the risk of acute rejection in the early post-transplant period. Current treatment protocols consist of lymphocyte depleting agents, including anti-thymocyte globulin (ATG) and interleukin 2 receptor antagonists (IL2-RAs).

Basiliximab is a monoclonal antibody directed at the interleukin-2 receptor and has a specificity for CD25 on activated lymphocytes. IL2-RAs inhibit the proliferation of T-cells resulting from allograft antigen stimulation but do not affect resting T-lymphocytes. As a result, compared with ATG, IL2-RAs are thought to offer more selective immunosuppression. ATG, on the other hand, when compared with no induction, has been reported to be associated with higher risks of opportunistic infections and lymphoproliferative disorders. Basiliximab is licensed as an induction therapy for the prophylaxis of acute organ rejection in de novo allogenic renal transplantation. The standard total dosage is 40 mg given in two doses of 20 mg each (one dose 2 hours pre-operatively, the second dose 4 days post-operatively).

An application from Groote Schuur's renal unit has motivated for the inclusion of basiliximab on the Tertiary Level Essential Medicines List. Although the original application pertains to solid organ transplant in general, it was agreed to focus specifically on renal transplantation, as this is the therapeutic area associated with the highest utilization and largest volume of evidence.

Out of interest, in 2012, there were 1607 renal transplants carried out in South Africa – 837 (52%) in the public sector and 770 (48%) in the private sector. The transplant rate in South Africa was reported as being 4.7 per million population (pmp). (Davids et. al., 2014)

Quality of evidence:
("basiliximab"[Supplementary Concept] OR "basiliximab"[All Fields]) AND ("kidney transplantation"[MeSH Terms] OR ("kidney"[All Fields] AND "transplantation"[All Fields]) OR "kidney transplantation"[All Fields] OR ("renal"[All Fields] AND "transplantation"[All Fields]) OR "renal transplantation"[All Fields]) = 883 results

("basiliximab"[Supplementary Concept] OR "basiliximab"[All Fields]) AND induction[All Fields] AND renal[All Fields] = 349 results

The services of the Medicines Information Centre, UCT, were also enlisted to further search for updated randmomised controlled trials, systematic reviews and meta-analyses. Relevant documents from 2010 onwards were sought as Webster and colleagues (2010) published an updated Cochrane review of IL2-RAs in renal transplant recipients. However, the search strategies of both the Reviewer and the MIC yielded no further meta-analyses or randomized controlled trials of significance.

Clinical efficacy:
The data in support of IL2-RAs is best summarized in the Cochrane review by Webster, et al (2010):

Webster *et al* (2010) conducted a Cochrane review to identify and summarise the effects of IL2-RAs, as an addition to standard therapy, or as an alternative to another immunosuppressive induction therapy. 71 studies were included (involving 10 520 participants). When compared with placebo (32 studies, 5 854 participants) graft loss, including death with a functioning graft, was reduced by 25% at 6 months (16 studies: RR 0.75, 95% CI 0.58 to 0.98) and at one year (24 studies: RR 0.75, 95% CI 0.62 to 0.90). At one-year, biopsy-proven acute rejection was reduced by 28% (14 studies: RR 0.72, 95% CI 0.64 to 0.81), and there was a 19% reduction in CMV disease (13 studies: RR 0.81, 95% CI 0.68 to 0.97).

When IL2-RAs were compared to ATG (18 studies, 1844 participants), there was no difference in graft loss at any time point, or for acute rejection diagnosed clinically. However, ATG therapy did demonstrate benefit over IL2-RAs for biopsy-proven acute rejection at one year (8 studies: RR 1.30 95% CI 1.01 to 1.67). It was further reported that ATG was associated with a 75% increase in malignancy (7 studies: RR 0.25 95% CI 0.07 to 0.87) and a 32% increase in CMV disease (13 studies: RR 0.68 95% CI 0.50 to 0.93). These aspects are discussed in further detail below. ATG patients experienced significantly more fever, cytokine release syndrome, leucopenia as well as other adverse reactions to drug administration.

The meta-analysis concludes that the Numbers Needed to Treat for IL2-RA was calculated as 9 to prevent one recipient having rejection, 42 to prevent one graft loss, and 38 to prevent one having CMV disease over the first year post-transplantation.

When compared with ATG treatment, ATG may prevent some experiencing acute rejection, but 16 recipients would need IL2-RA to prevent one having CMV, and 58 would need IL2-RA to prevent one having malignancy. The meta-analysis summarises that IL-2RAs are as effective as other antibody therapies and with significantly fewer side effects.

Cancer risk

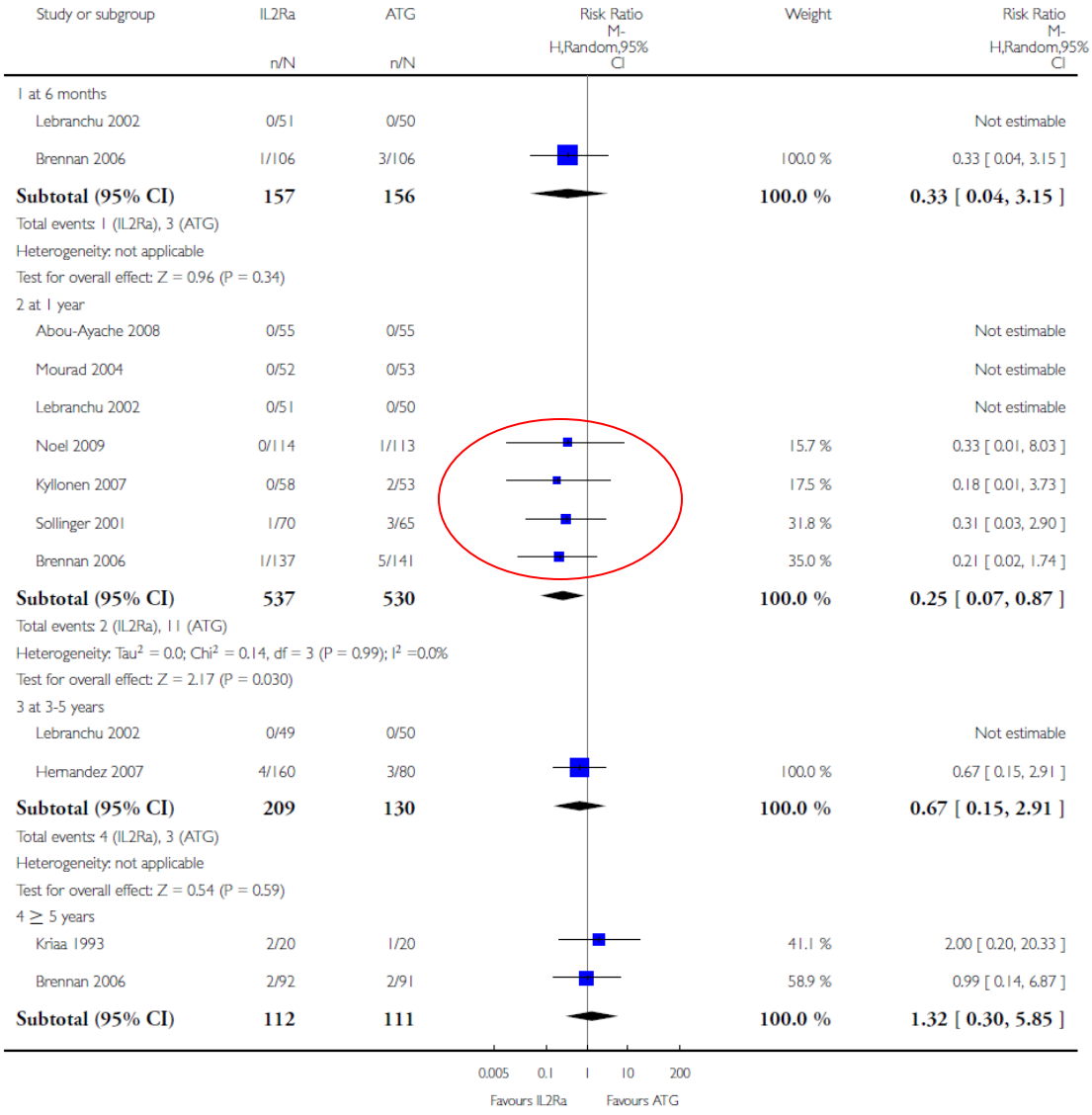
The increased risk of malignancy was further reviewed. Analysis 2.7 (page 185 of Webster et. al.) provides a Forest plot for the outcome of malignancy when IL2-RAs are compared with ATG. Notwithstanding the finding that ATG was associated with a 75% increase in malignancy (7 studies: RR 0.25 95% CI 0.07 to 0.87), of the 4 studies with an estimable risk for malignancy, all the results for this endpoint crossed unity. This trend was also observed at 6 months, 3 – 5 years and ≥ 5 years. It is difficult to understand how, in these circumstances, the authors we able to be as definitive as they were.

Analysis 2.7. Comparison 2 IL2Ra versus ATG, Outcome 7 Malignancy: total.

Review: Interleukin 2 receptor antagonists for kidney transplant recipients

Comparison: 2 IL2Ra versus ATG

Outcome: 7 Malignancy: total



CMV Risk

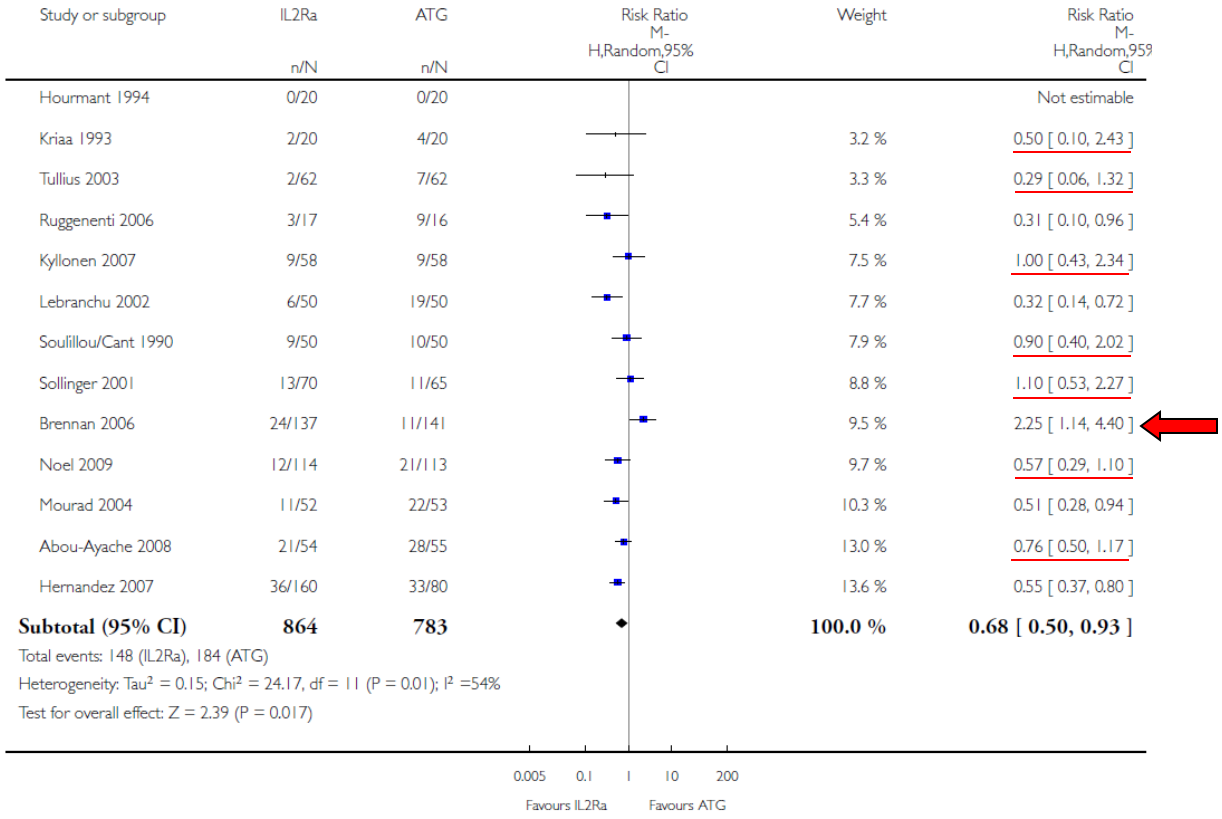
An analysis of CMV risk was documented in Analysis 2.9 (page 187). The assertion that ATG results in a 32% increase in CMV disease (13 studies: RR 0.68 95% CI 0.50 to 0.93) also begs interrogation. The differences in CMV infection were non-significant at 3 months, 6 months, 1 year, 2 years and ≥ 5 years. However, for the parameter, 'Any within the first year', where the 32% increased incidence was noted, 13 studies were included as part of the analysis. The findings of 1 study was not estimable, 7 were non-significant (i.e. they crossed unity), 1 found in *favour* of ATG (i.e. as resulting in a lower risk of CMV infection).

Analysis 2.9. Comparison 2 IL2Ra versus ATG, Outcome 9 Infection: CMV all.

Review: Interleukin 2 receptor antagonists for kidney transplant recipients

Comparison: 2 IL2Ra versus ATG

Outcome: 9 Infection: CMV all



Other

Sun et. al (2015) conducted a meta-analysis comparing the efficacy and safety of basiliximab and daclizumab in kidney transplant patients. It was concluded that these two agents of comparable within this indication.

Guidelines
KDIGO Clinical Practice Guidelines:

1: INDUCTION THERAPY
1.2: We recommend including induction therapy with a biologic agent as part of the initial immunosuppressive regimen in KTRs. (1A)
1.2.1: We recommend that an IL2-RA be the first-line induction therapy. (1B)
1.2.2: We suggest using a lymphocyte-depleting agent, rather than an IL2-RA, for KTRs at high immunologic risk. (2B)

Safety concerns:
Nil

Further considerations:
Costs of basiliximab compared with ATG.

Private sector costing:

Drug	Trade name	Strength	Cost	Dosing regimen	Cost
Basiliximab	Simulect®	20mg/5ml	R13 620.23	20mg pre-op followed by 20mg 4 days post-transplant	R27 240.46
Anti-thymocyte globulin*	Thymoglobuline®	25mg/5ml	R2 496.74	1 – 1.5mg/kg/day for 2 to 9 days post renal transplant	R14 980.44 – R19 973.92@
					R52 431.54 – R69 908#
					R67 411.98 – R89 882.64$

* Calculated for a 70kg patient requiring a total of 3 to 4 vials per day
@ Cost calculated for a two daycourse # Cost calculated for a 7 day course
$ Cost calculated for a 9 day course

Recommendation:
Based on the available evidence, there appears to be a case for including basiliximab as induction therapy for renal transplantation recipients. From an efficacy perspective, ATG and basiliximab are considered equivalent. There are statistically significant increases in CMV infections and malignancy associated with ATG, however, the clinical relevance needs further elucidation.

Consideration for the use of basiliximab as induction therapy in other solid organ transplants should be conducted as separate review processes per transplanted organ.

References:

Ansari D, Lund LH, Stehlik J et. al. Induction with anti-thymocyte globulin in heart transplantation in associated with better long-term survival compared with basiliximab. *J Heart Lung Transplant* 2015; 34: 1283–1291.

Davids MR, Marais N, Jacobs JC. South African Renal Registry Annual Report 2012. South African Renal Society, Cape Town 2014. [online] www.sa-renalsociety.org/Registry/2012/SA-RenalRegistry2012.pdf [accessed 16 May 2016].

Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *American Journal of Transplantation* 2009; 9 (Suppl 3): S1–S157

Sun ZJ, Du X, Su LL et. al. Efficacy and safety of basiliximab versus daclizumab in kidney transplantation: a meta-analysis. *Transplant Proc* 2015; 47 (8): 2439 – 45. DOI: 10.1016/j.transproceed.2015.08.009.

Webster AC, Ruster LP, McGee RG, et.al. Interleukin 2 receptor antagonists for kidney transplant recipients. *Cochrane Database of Systematic Reviews* 2010, Issue 1. Art. No.: CD003897. DOI: 10.1002/14651858.CD003897.pub3.