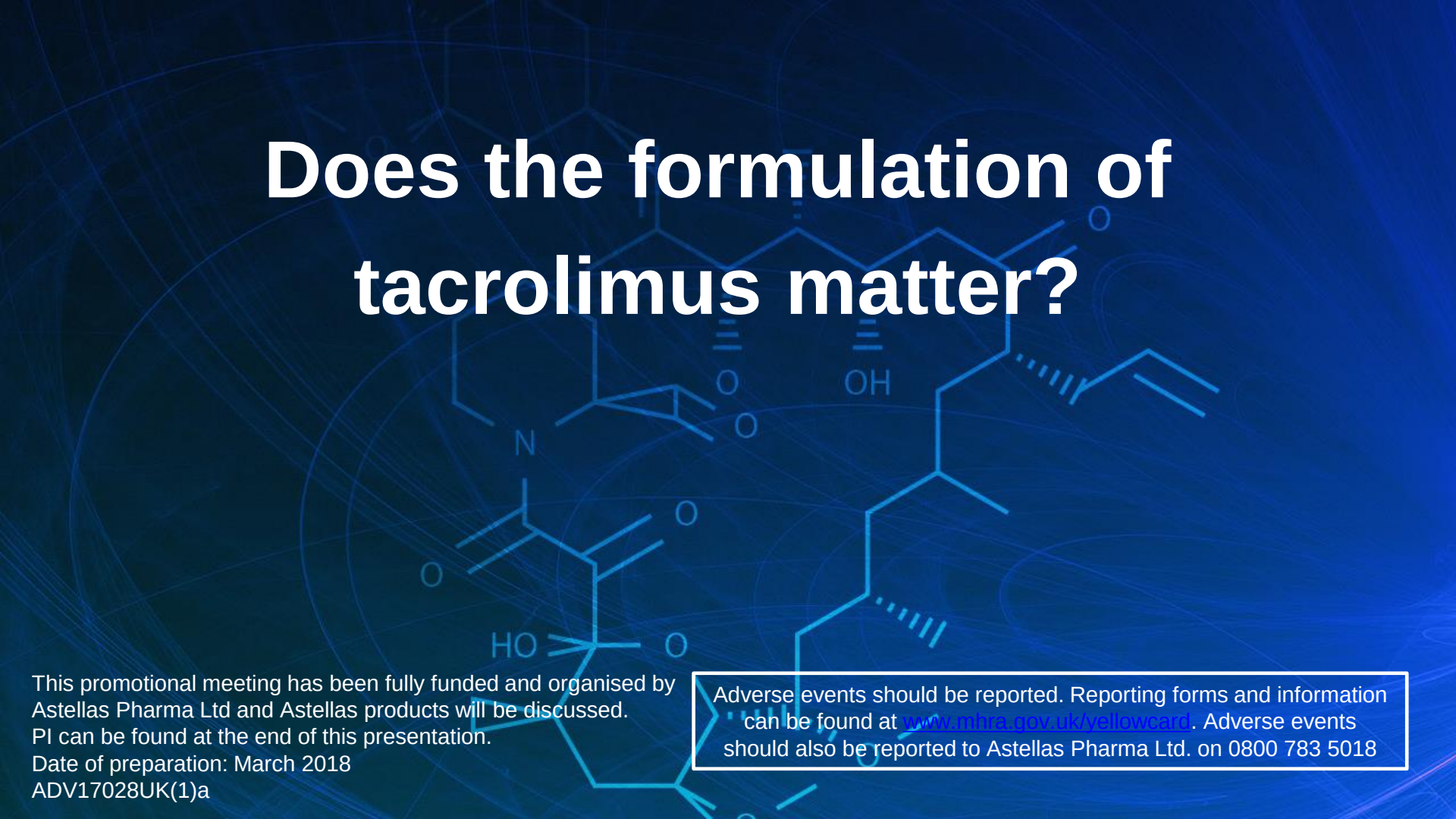
Does the formulation of tacrolimus matter?



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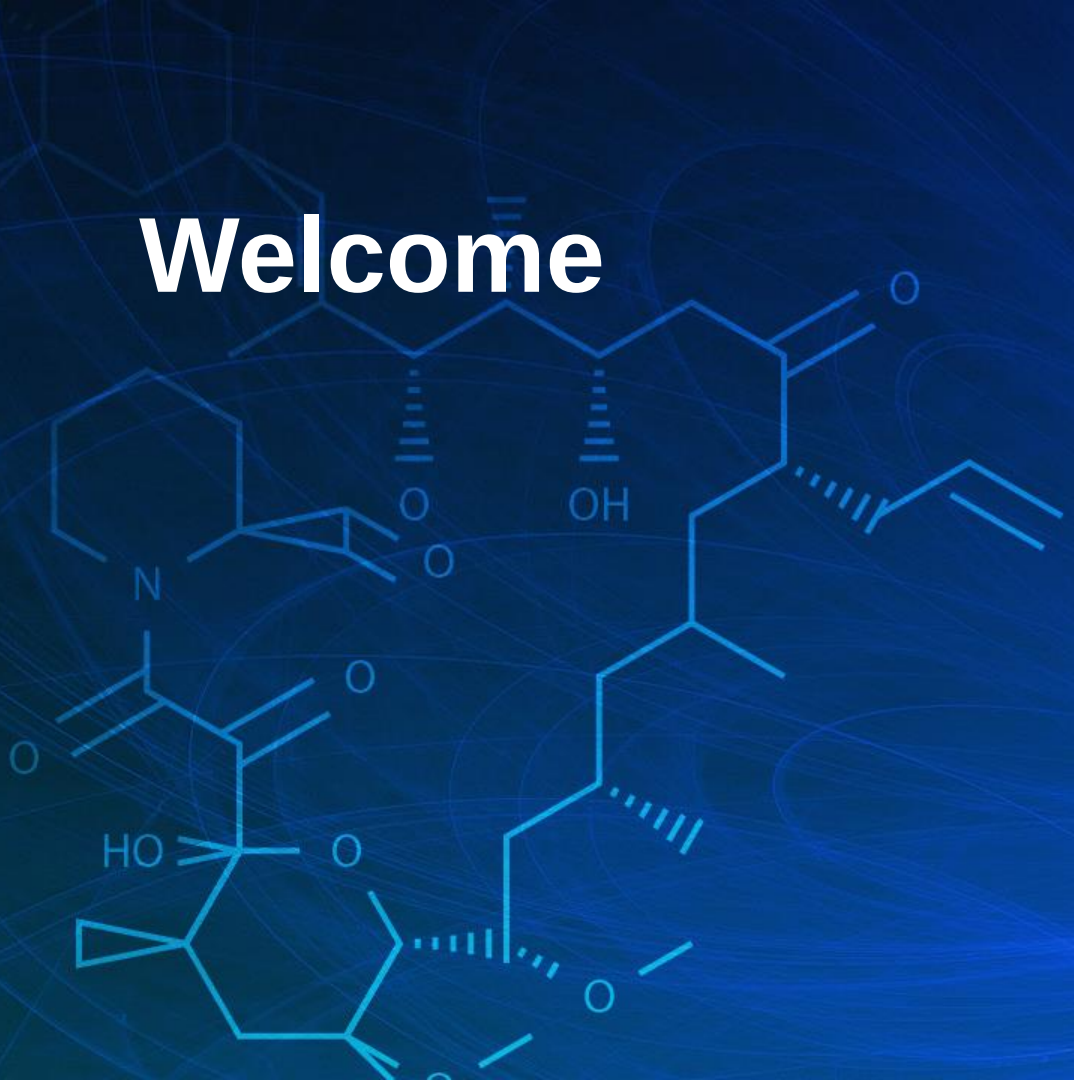
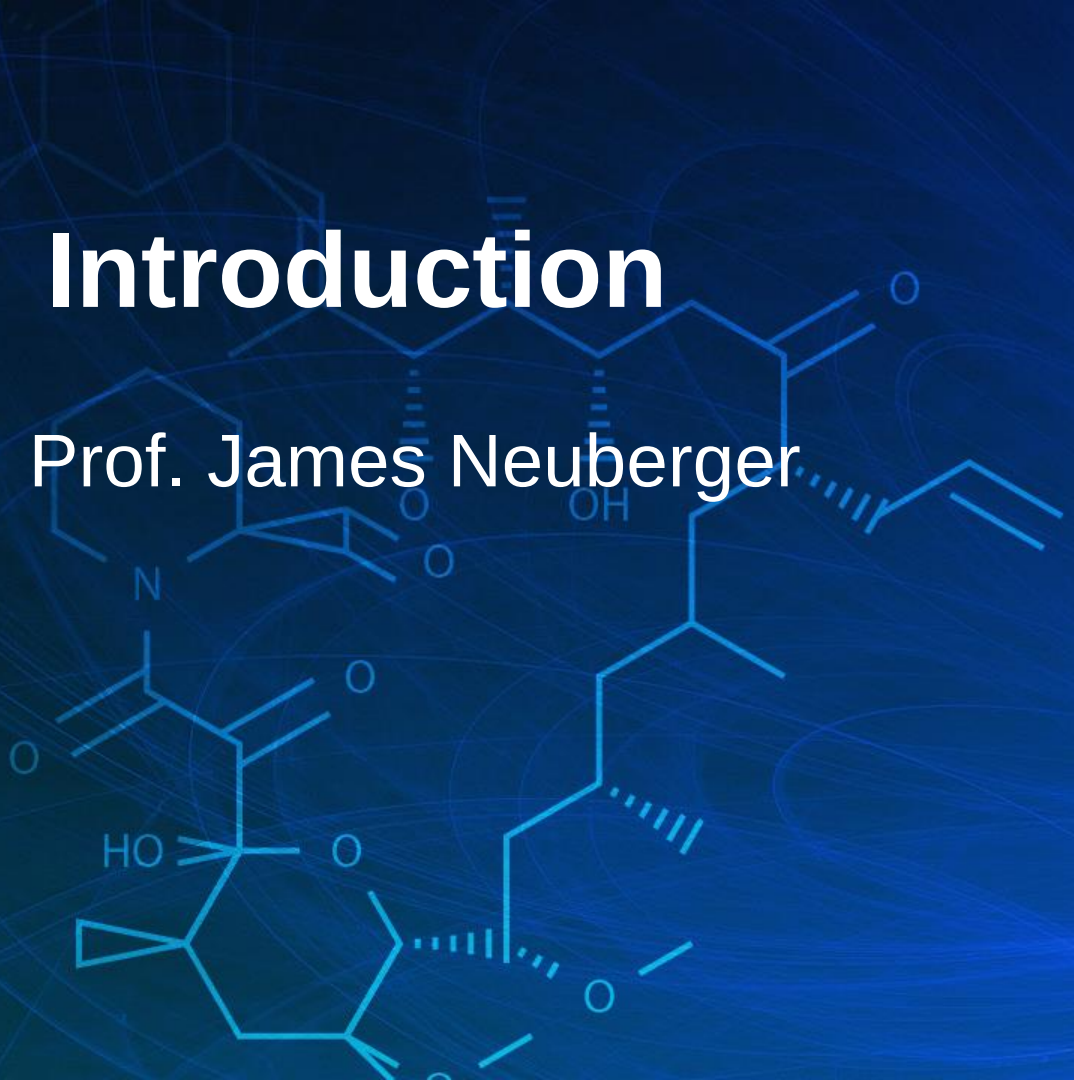
Welcome



Introduction

Prof. James Neuberger



Professor James Neuberger

Disclosures:

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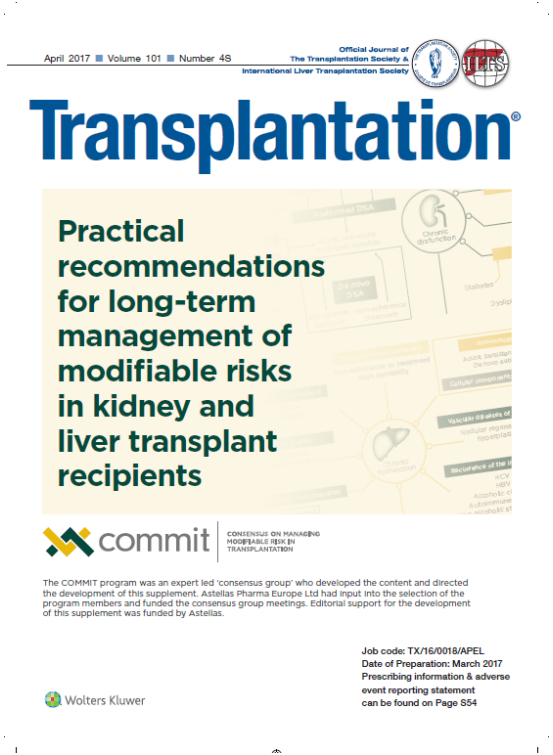
Outcomes after transplantation

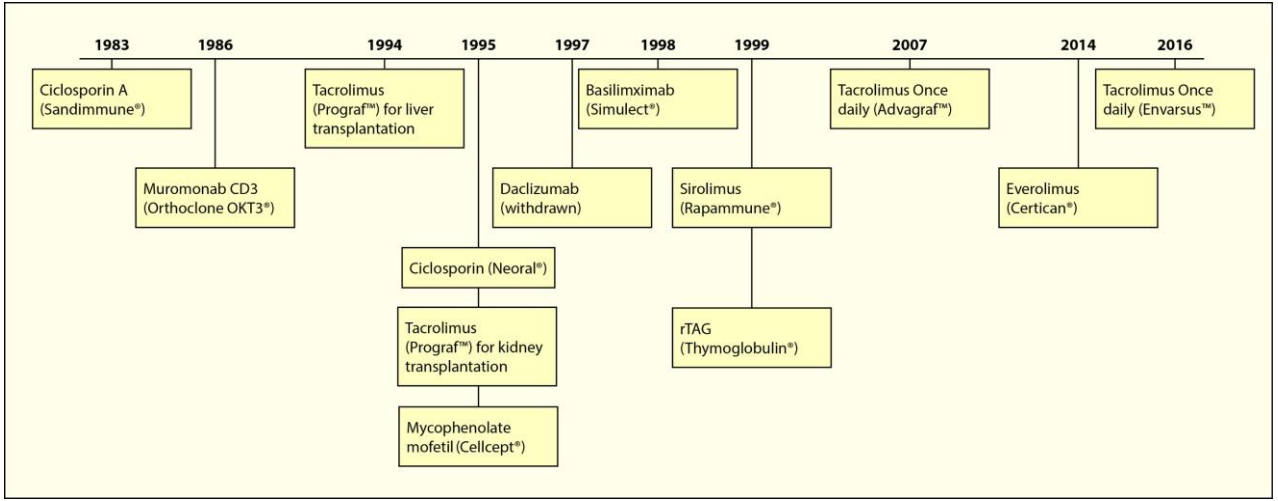
- Outcomes after solid organ transplant are improving, mainly due to a reduction in early death
- Premature death and graft loss in the allograft recipient is due mainly to:
  - Recurrent disease
  - Infection
  - Cardiovascular disease
  - De novo malignancy
  - Immune-mediated damage



Neuberger J et al. Transplantation 2017;101: S1–S56

Role of immunosuppression

- Many of the causes of premature death and graft loss are related, at least in part, to immunosuppression (IMS)[1]
- For most solid organ recipients, long term immunosuppression is required [1]
- We have an increasing number of IMS agents and formulations available[2]
- How can we best use these to maximise outcome after transplant?



Adapted from Meier-Kriesche H-U and Lodhi S. https://www.medscape.org/viewarticle/726494_9

1. Neuberger J et al. Transplantation 2017;101: S1–S56
2. Meier-Kriesche H-U and Lodhi S. https://www.medscape.org/viewarticle/726494_9 2010:1-34 (accessed March 2018)

Advagraf tacrolimus formulation - what does it offer?

Prof. David Holt

ASI
Bioanalytics at St Georges
Forensic Toxicology at St Georges

ADVAGRAF™ TACROLIMUS FORMULATION
What Does It Offer?

David W Holt

Emeritus Professor of Bioanalytics
ASI Ltd

St George's – University of London

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Disclosures

ASI
Bioanalytics at St Georges
Forensic Toxicology at St Georges

- I have been a speaker for and a consultant to a variety of Pharma and Diagnostics companies including: Novartis, Astellas, Pfizer, Sanofi, Roche, Abbott, Applied Biosystems, Siemens, Thermofisher and Waters.
- I am not on the payroll of any of these companies nor do I hold shares in any of them.
- The content of the slides is mine.

Introduction

Bioanalytics at St Georges
Forensic Toxicology at St Georges

- **Critical-dose drugs (NTI) difficult to administer.[1]**
- **Impact of intra-patient exposure to tacrolimus.[1]**
- **Rationale for a tacrolimus extended-release formulation.[1]**

NTI: narrow therapeutic index.

1. Shuker N et al. Transplant International 2016; 29: 1158–1167.

Intra-patient Variability

Bioanalytics at St Georges
Forensic Toxicology at St Georges

J Am Soc Nephrol 11: 1122–1131, 2000

Low Intraindividual Variability of Cyclosporin A Exposure Reduces Chronic Rejection Incidence and Health Care Costs

BARRY D. KAHAN,* MARIA WELSH,* DIANA L. URBAUER,†
MELINDA B. MOSHEIM,* KATHLEEN M. BEUSTERIEN,‡ MARTHA R. WOOD,‡
LINDA P. SCHOENBERG,* JOSEPH DICESARE,§ STEPHEN M. KATZ,* and
CHARLES T. VAN BUREN*

**Division of Immunology and Organ Transplantation, Department of Surgery, University of Texas Houston Health Science Center - Medical School and †Biometrics Consulting, Houston, Texas; ‡Covance Health Economics and Outcomes Services, Inc., Washington, DC; and §Novartis Pharmaceuticals Corporation, East Hanover, New Jersey.*

Intra-patient Variability

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Forensic Toxicology at St Georges

- **Intra-patient variability**
  - **Same dose gives rise to fluctuating exposure in the same patient.**
- **Assessed by**
  - **calculating the SD of sequential AUC or C_{min} expressed as CV%.**
  - **calculating the mean absolute difference from the mean $C_{min,}$ expressed as a percentage.**

AUC: area under the concentration-time curve; C_{min}: minimum concentration; CV: coefficient of variation; SD: standard deviation.
Kahan B et al. J Am Soc Nephrol 11: 1122-1131 2000.

Intra-patient Variability

Bioanalytics at St Georges
Forensic Toxicology at St Georges

Kidney Tx patients
n = 808
6 – 12 months post Tx
3 – 11 C_{min} samples

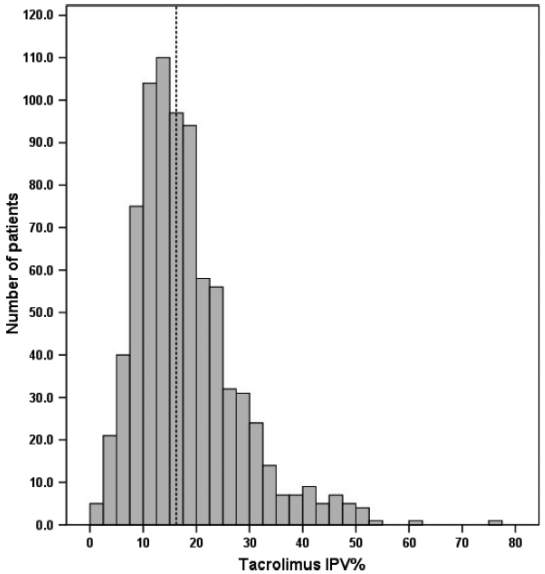


Figure 1 Distribution of Tac IPV in the studied cohort (n = 808). The mean Tac IPV was 18.1% (±9.7); the median (shown by dotted line) Tac IPV was 16.2% (1.1–76.0%).

Shuker N et al. Transplant International 2016; 29: 1158–1167.

Intra-patient Variability

Bioanalytics at St Georges
Forensic Toxicology at St Georges

- **Factors influencing intra-patient variability[1,2]**
  - **Metabolism by CYP3A4/5**
  - **Drug efflux by ABCB1 (P-glycoprotein)**
  - **Drug interactions**
  - **Diurnal variation**
  - **Dose adherence**

1. Tsunashima D et al. Clin Ther. 2014; 36:748-59.
2. Shuker N et al. Transplant International 2016; 29:1158–1167.

Formulation Differences

Bioanalytics at St Georges
Forensic Toxicology at St Georges

- Tacrolimus absorbed along the length of the gut.[1]
- Elimination half-life suitable for once daily dosing.

- Prograf™ (tacrolimus immediate-release capsules) - ~90% released in 1.5h[2]
- Advagraf™ (tacrolimus prolonged-release capsules) - ~90% released in 4 – 6h[3]
- Formulations differ by replacing croscarmellose cellulose with ethyl cellulose in prolonged-release formulation.[4,5]

- Envarsus™ (tacrolimus prolonged-release tablets) – t_{max} 6h[6]

1. Tsunashima D et al. Clin Ther. 2014;36:748-59. 2. Petan JA, Undre N, First MR, et. al. Transplant Proc. 2008;40:1439-42. 3. Tsunashima D, Yamashita K, Ogawara K, Sako K, Higaki K. J Pharm Pharmacol. 2016;68:316-23. 4. Prograf SmPC. 5. Advagraf SmPC. 6. Envarsus SmPC. https://www.medicines.org.uk/emc/medicine/29850. Accessed March 2018.

Prograf™ and Advagraf™

Bioanalytics at St Georges
Forensic Toxicology at St Georges

Lower Variability in 24-Hour Exposure During Once-Daily Compared to Twice-Daily Tacrolimus Formulation in Kidney Transplantation

Frank Stifft,[1] Leo M.L. Stolk,[2] Nasrullah Undre,[3] Johannes P. van Hooff,[1] and Maarten H.L. Christiaans[1,4]

Introduction. Tacrolimus has originally been registered as a twice-daily formulation (Prograf, Tac BID), although a once-daily formulation (Advagraf, Tac QD) is also available. A reduced intrapatient variability of Tac C_{min}, a surrogate marker for 24-hour drug exposure (AUC_{0-24}), has been suggested. The variability of AUC_{0-24} has never been studied prospectively yet. The purpose of this study was to investigate the change in intrapatient variability of Tac AUC_{0-24} after converting from Tac BID to Tac QD.

Methods. Forty renal transplant patients on Tac BID were converted on a 1:1 (mg/mg) basis to Tac QD in an investigator-driven comparative pharmacokinetic (PK) study. AUC_{0-24} was determined five times before and after conversion. Duplicate samples were collected by the patients themselves using the dried blood spot method. The main outcome measure is the change in intrapatient variability of AUC_{0-24} expressed as coefficient of variation (CV). Moreover, the influence of Cyp3A5 genotype polymorphism on the change in CV was studied.

Results. In total, 400 AUC_{0-24} profiles were available for analysis. Conversion to Tac QD resulted in a significant improvement in intra-patient CV from 14.1% to 10.9% (P=0.012). Patients with the Cyp3A5*1/*3 genotype (n=11) had a numerically larger improvement in CV than patients with the CYP3A5*3/*3 genotype.

Conclusion. Intrapatient CV of Tac AUC_{0-24} improved after converting from Tac BID to Tac QD in stable renal transplant patients, especially in patients with the CYP3A5*1/3 genotype. Given the very strict protocol of this PK study, this improvement is most likely due to the different intrinsic PK properties of Tac QD and Tac BID.

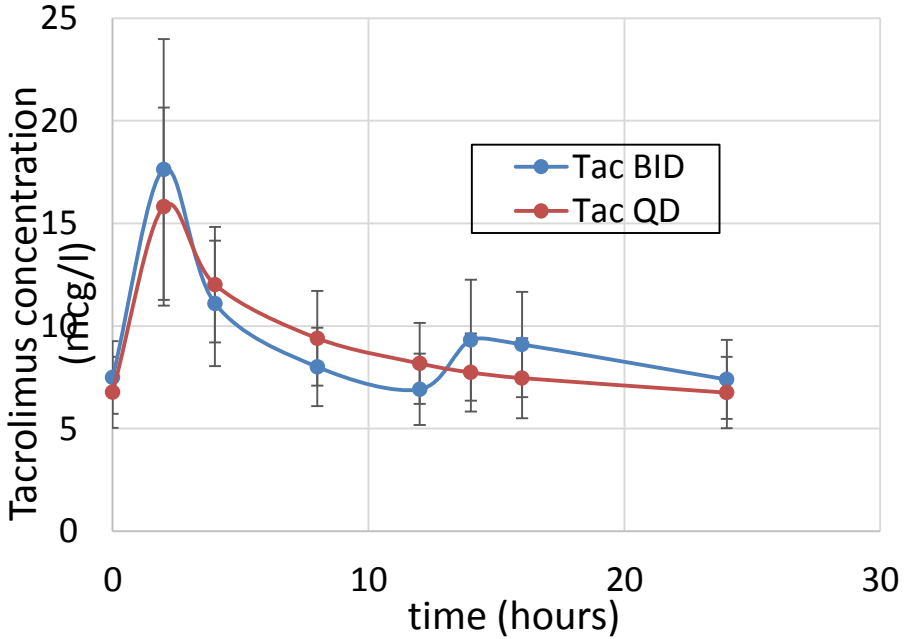
Keywords: Tacrolimus, Pharmacokinetics, Therapeutic drug monitoring, Intra-patient coefficient of variability, Drug exposure, Formulation.

(*Transplantation* 2014;97: 775–780)

Prograf™ and Advagraf™

Bioanalytics at St Georges
Forensic Toxicology at St Georges

40 kidney Tx patients
Stable renal function 6m
Converted 1:1 dose
10 PK profiles/pt



Mean pharmacokinetic profiles for Tac twice-daily (BID) and Tac once-daily (QD)

Stifft F et al. Transplantation 2014;97:775-80.

Figure adapted from Stifft et al, 2014.

Prograf™ and Advagraf™

Bioanalytics at St Georges
Forensic Toxicology at St Georges

- t_{max} - no significant difference
- Mean AUC_{0-24}
  - Immediate-release formulation = 219.2µg/L*h
  - Prolonged-release formulation = 213.3µg/L*h
- Mean C_{min}
  - Immediate-release formulation = 7.4µg/L
  - Prolonged-release formulation = 6.6µg/L
- Good correlation AUC_{0-24} vs C_{min} for both formulations.

Stifft F et al. Transplantation 2014;97:775-80.

Prograf™ and Advagraf™

Bioanalytics at St Georges
Forensic Toxicology at St Georges

- **Intra-patient variability (CV%) immediate-release formulation vs prolonged-release formulation**
  - **AUC_{0-24} 14.1 vs 10.9 (p=0.012)**
  - **C_{min} 15.3 vs 13.7 (n.s.)**
- **More pronounced effect on intra-patient variability in patients with CYP3A5*1/*3**
  - **AUC_{0-24} 18.2 vs 12.8 (p=0.062)**

Stifft F et al. Transplantation 2014;97:775-80.

Prograf™ and Advagraf™

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Forensic Toxicology at St Georges

129 stable kidney Tx pts intra-patient variability for C_{min} reduced from 14% to 8.5% ($p<0.05$)

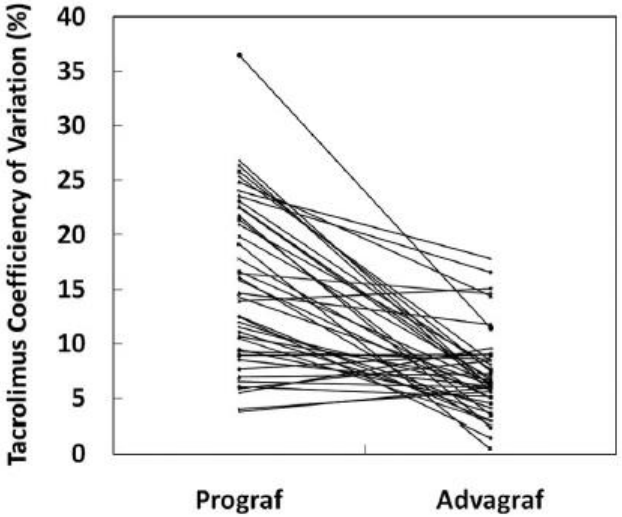

FIGURE 3. The individual change of percent coefficient of variation before and after conversion from Prograf to Advagraf.

Wu M-J et al. Transplantation 2011;92:648–52.

Dose Adherence

ASI
Bioanalytics at St Georges
Forensic Toxicology at St Georges

Improved Adherence to Tacrolimus Once-Daily Formulation in Renal Recipients: A Randomized Controlled Trial Using Electronic Monitoring

Dirk R.J. Kuypers,[1,9] Patrick C. Peeters,[2] Jacques J. Sennesael,[3] Mireille N. Kianda,[4] Bernard Vrijens,[5,6] Paulus Kristanto,[5] Fabienne Dobbels,[7] Yves Vanrenterghem,[1] Nada Kanaan,[8] on behalf of the ADMIRAD Study Team

Background. With effective agents available to prevent posttransplantation acute organ rejection, medication adherence becomes a key factor for successful treatment outcomes after renal transplantation. A once-daily, modified-release oral formulation of tacrolimus has been developed to simplify dosing and improve medication adherence.
Methods. Adherence Measurement in Stable Renal Transplant Patients Following Conversion From Prograft to Advagraf is a randomized multicenter controlled trial to evaluate adherence between a tacrolimus once-daily regimen and a tacrolimus twice-daily regimen using an electronic monitor to document drug intake. After enrolment, all patients continued the twice-daily regimen for 3 months and then were randomized 2:1 between the two formulations and followed for 6 months. Adherence was decomposed into patients' persistence and implementation of each regimen.
Results. Two hundred nineteen patients (45% male; 3±2 years after transplantation) were analyzed (145 once daily and 74 twice daily). At 6 months after randomization, 81.5% of the once-daily group and 71.9% of the twice-daily group remained persistent with the treatment (P=0.0824). Among patients who remained engaged with the regimen, 88.2% of the once-daily group and 78.8% of the twice-daily group (P=0.0009) took the prescribed number of daily doses. When the patients took the twice-daily regimen, the average percentage of missed doses was 11.7% in the morning and 14.2% in the evening (P=0.0035).
Conclusions. Regimen implementation of tacrolimus once daily is significantly superior to the twice-daily regimen. There was a residual prevalence of suboptimal adherence that will have to be countered by means other than reformulation and regimen simplification. Electronically compiled dosing histories provide detailed data on patient adherence that can be used for efficient medication management.

Keywords: Medical adherence, Tacrolimus, Regimen simplification, Electronic monitoring, Renal transplantation.

(*Transplantation* 2013;95: 333–340)

Dose Adherence

Bioanalytics at St Georges
Forensic Toxicology at St Georges

219 kidney stable kidney Tx patients
Randomised 2:1 prolonged-release formulation/immediate-release formulation.
Electronic data capture
Assessed after 6 months

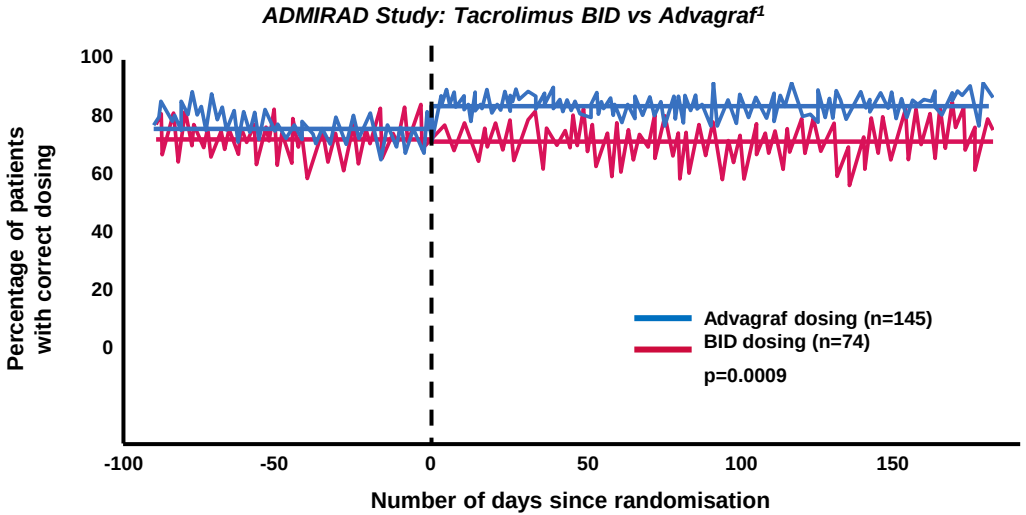

Figure adapted from Kuypers et al, 2013.

Kuypers DR et al. Transplantation. 2013;95:333-40.

Conclusions

Bioanalytics at St Georges
Forensic Toxicology at St Georges

- **Compared to tacrolimus immediate-release formulation, once daily dosing with prolonged-release formulation:**
  - **Comparable AUC[1]**
  - **Reduced intra-patient variability[1]**
  - **C_{min} correlates with AUC_{0-24}[1]**
  - **Same monitoring strategy[2,3]**
  - **Effect on dose adherence[4]**

1. Stifft F et al. Transplantation 2014;97: 775-80.
2. Wu M-J et al. Transplantation 2011;92:648–52.
3. Advagraf SmPC. Astellas Pharma Ltd. 2015.
4. Kuypers DR et al. Transplantation. 2013;95:333-40.

Intra-patient Variability (IPV) in kidney transplantation - does it matter?

Mr. Marc Clancy

Intra-patient variability in kidney transplantation
Does it matter?

Marc J. Clancy

Brighton

15th March 2018

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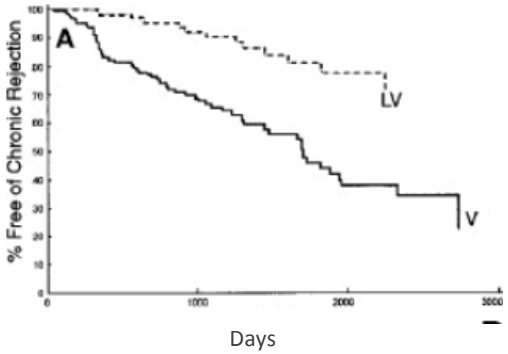
Mr Marc Clancy
Declarations of interest

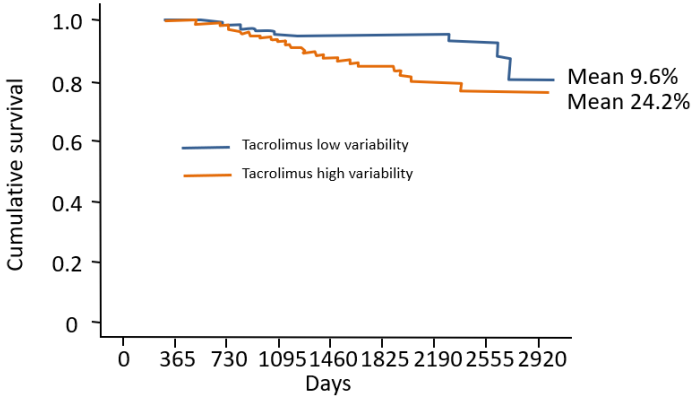
Research grants, speaker fees, travel support, advisory boards and hospitality.

Astellas, Novartis, Sandoz, Cytori, Sanofi, Chiesi

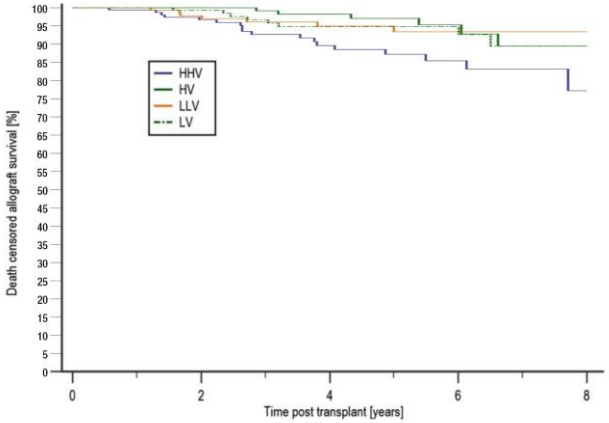
Multiple retrospective, associative studies of IPV in kidney transplantation



Adapted from Kahan et al. J Am Soc Nephrol 11: 1122–1131, 2000.



Adapted from Borra et al. Nephrol Dial Transplant 2010;25: 2757–2763.



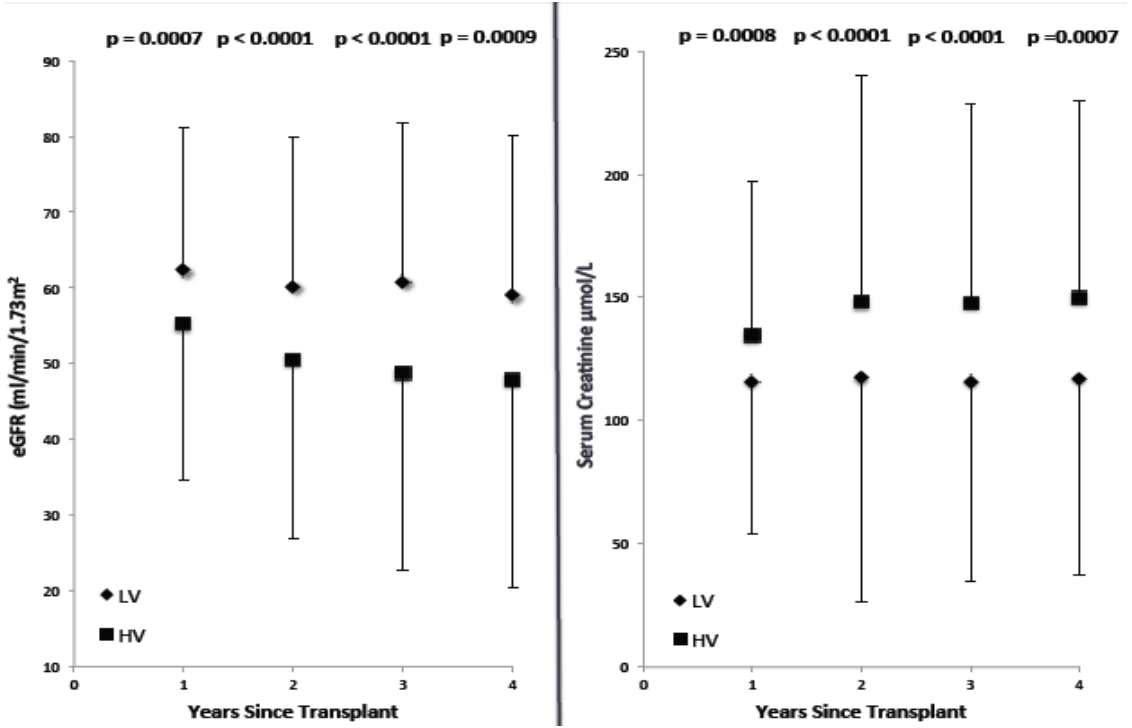
Adapted from Goodall et al. Transplant Direct. 2017 Aug; 3(8): e192.

HHV: highest variability; HV: high variability; IPV: intrapatient variability; LLV: lowest variability; LV: low variability; V: variable.

Immunosuppression variability
How much is harmful long-term?

How wide is the path?

Trends in renal function in 1 year rejection free Kidney Tx. Patients*



Failed Tx attributed eGFR of 0

eGFR: estimated glomerular filtration rate; HV: high variability; LV: low variability.
Whalen et al. Transplantation. 2017 Feb;101(2):430-436. (*author's own data).

Transplant International

INVITED COMMENTARY

Intrapatient variability in tacrolimus exposure – a useful tool for clinical practice?

Simon R. Knight[1,2]

1 Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK
2 Centre for Evidence in Transplantation, Royal College of Surgeons of England, London, UK

Transplant International 2016; 29: 1155–1157

Received: 31 May 2016; Accepted: 3 June 2016

remain to be answered: (i) How should the tacrolimus IPV be used to define patients at risk? and (ii) What interventions allow for the reduction of IPV and/or subsequent risk of events?

Outstanding questions about IPV in kidney transplantation

Open Access Protocol

BMJ Open

Impact of intrapatient variability (IPV) in tacrolimus trough levels on long-term renal transplant function: multicentre collaborative retrospective cohort study protocol

Petra M Goldsmith,[1,2] Matthew J Bottomley,[3] Okidi Okechukwu,[4] Victoria C Ross,[5] Ryan Ghita,[5] David Wandless,[6] Stuart J Falconer,[7] Stavros Papachristos,[4] Philip Nash,[8] Vitaliy Androshchuk,[3] Marc Clancy,[7,9] Transplant Audit Collaborative

Objectives

- To establish important baseline data about national and regional trends in IPV
- To investigate demographic associations and other characteristics for patients in high and low variability groups
- To establish whether there exists a 'danger' threshold for IPV, above which a patient is deemed at risk of graft loss or dysfunction, so they can then be targeted for intervention prior to organ damage or failure

Goldsmith et al. BMJ Open. 2017 Jul 28;7(7):e016144.

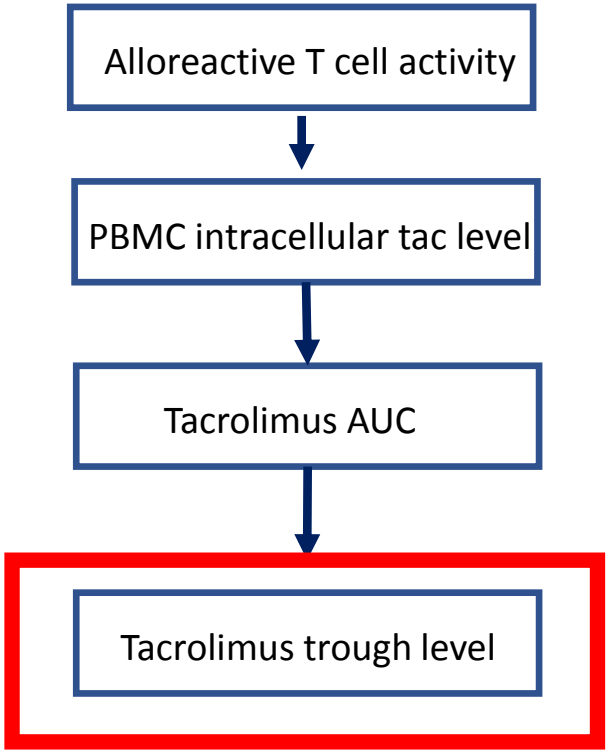
Widely conserved findings across 5 UK centres

TABLE 1: EGFR COMPARISON BETWEEN PATIENTS WITH HIGH AND LOW TACROLIMUS VARIABILITY IN UK TRANSPLANT CENTERS

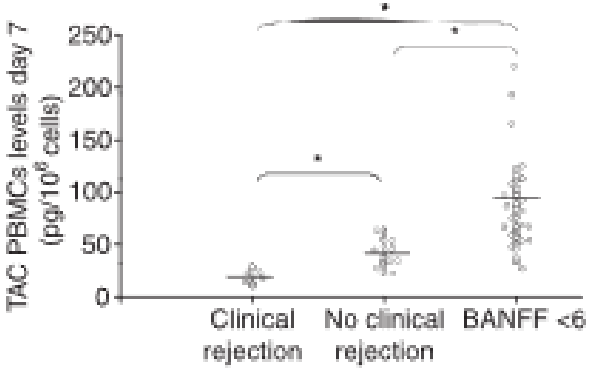
	Glasgow (n=168)	Oxford (n=284)	Liverpool (n=171)	Manchester (n=313)	King's London (n=134)
T1 MEDIAN (IQR) eGFR of low IPV patients	62 (49-77)	54 (45-64)	51.5 (38-57.3)	49 (38.5-61)	56 (48.3-73.3)
T1 MEDIAN (IQR) eGFR of high IPV patients	46 (34.3-58.6)	50 (35.5-58)	44 (36-52)	48.5 (39.3-59.3)	55 (43-67)
P – value	0.001	0.02	0.19	0.59	0.52
T2 MEDIAN (IQR) eGFR of low IPV patients	55 (47-73)	52 (39-65)	50 (36-56)	48 (38-56.5)	58.5 (48-73.8)
T2 MEDIAN (IQR) eGFR of high IPV patients	53.5 (28-64.8)	47 (37.5-64)	46 (33.5-58)	44 (30-60.6)	51 (28.8-63.8)
P – value	0.13	0.26	0.47	0.69	0.03

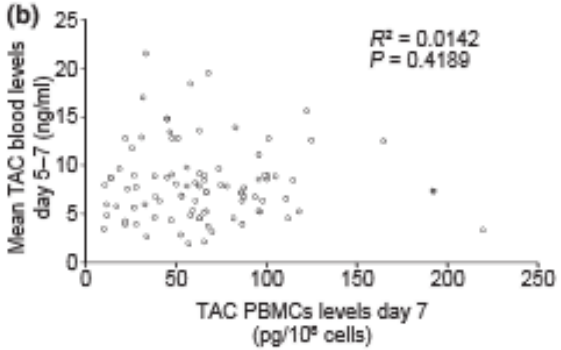
Ghita et al. J Am Soc Nephrol 28: 2017 SA-PO643.

Limitations in measurement of functional immunosuppression in clinical practice



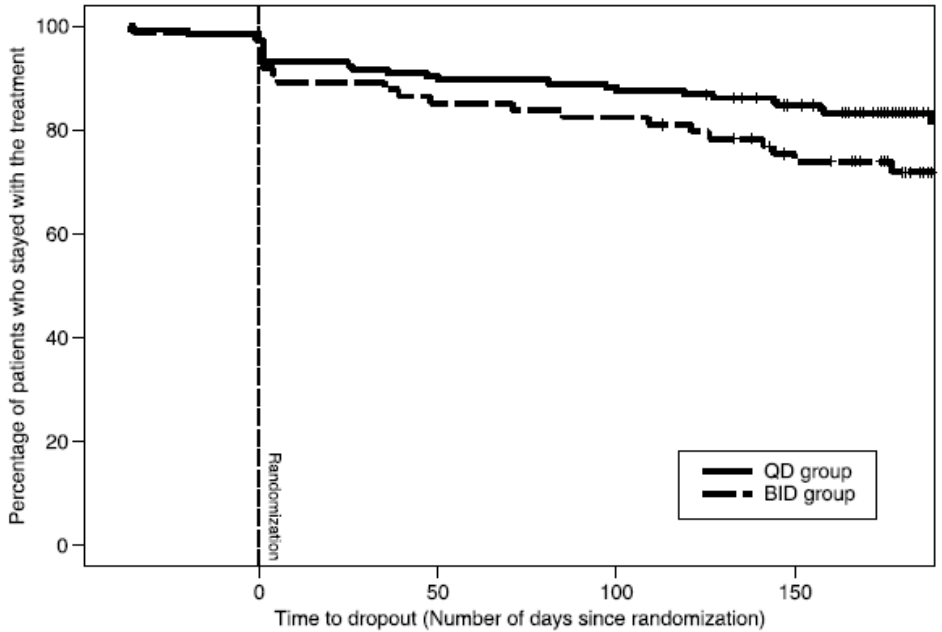
PBMC: peripheral blood mononuclear cells.





Capron et al. Transpl Int. 2012 Jan;25(1):41-7.

One approach proven to improve adherence
The ADMIRAD study: QD Tacrolimus v BD



Kuypers et.al. Transplantation 2013;95: 333-340.

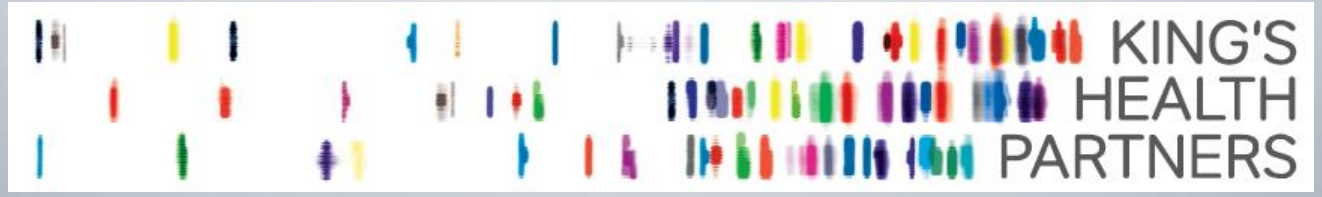
Conclusions

- High IPV consistently associates with worse outcomes in renal transplantation[1-3]
- Negative effect demonstrable in stable patients[1]
- Negligent not to address high IPV even if purely a surrogate for poor adherence[1]
- Prospective interventions require thorough evaluation
- Application of interventions effective in improving adherence are logical for IPV

1. Kahan et al. J Am Soc nephrol 11: 1122–1131, 2000.
2. Borra et al. Nephrol Dial Transplant 2010;25: 2757–2763.
3. Goodall et al. Transplant Direct. 2017 Aug; 3(8): e192.

Advagraf in liver transplantation - it matters?

Dr. Varuna Aluvihare



ADVAGRAF™ (tacrolimus prolonged release) in Liver Transplantation: it matters?

Astellas Symposium BTS, March 2018

VARUNA ALUVIHARE PhD MRCP
Transplant Hepatologist
Institute of Liver Studies
Kings College Hospital
London

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King's College Hospital NHS
NHS Foundation Trust

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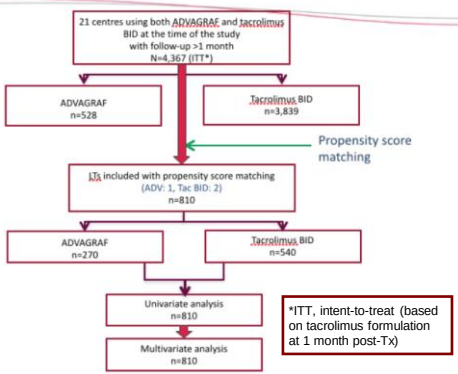
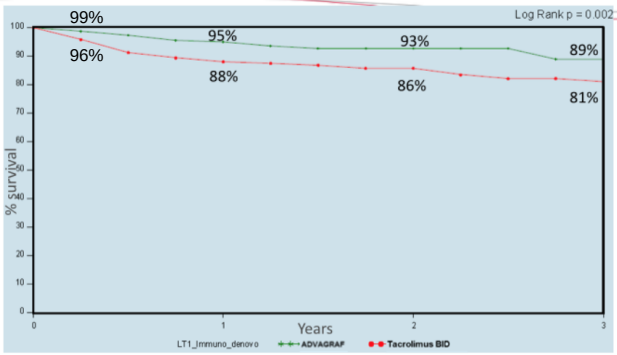
Improved Survival in Liver Transplant Recipients Receiving Prolonged-Release Tacrolimus in the European Liver Transplant Registry

Study design[1]



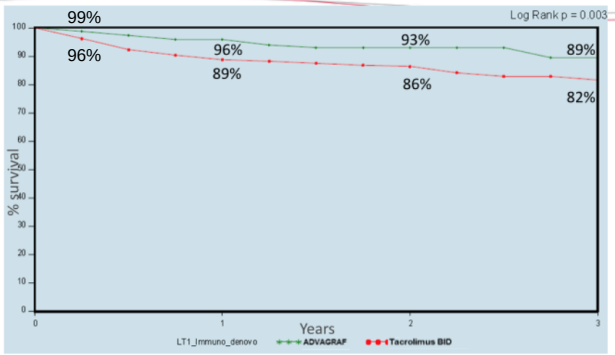
Graft survival after LT; ADVAGRAF vs tacrolimus BID[1]

FU <1 month excluded & PSM (ADV:1, Tac BID: 2)



Patient survival after LT; ADVAGRAF vs tacrolimus BID[1]

FU <1 month excluded & PSM (ADV:1, Tac BID: 2)



PSM: propensity score matching.

Adam et al. *Am.J.Transpl* 2015;15:1267–1282.

- ***Patients treated with*** *ADVAGRAF™ showed significant graft survival benefit over twice-daily tacrolimus (BD) of 8% at 3 years (p=0.01)*

- *Patients matched for baseline characteristics showed a long-term patient survival benefit of 7% at 3 years (p=0.003) when treated with ADVAGRAF™ over tacrolimus BD*

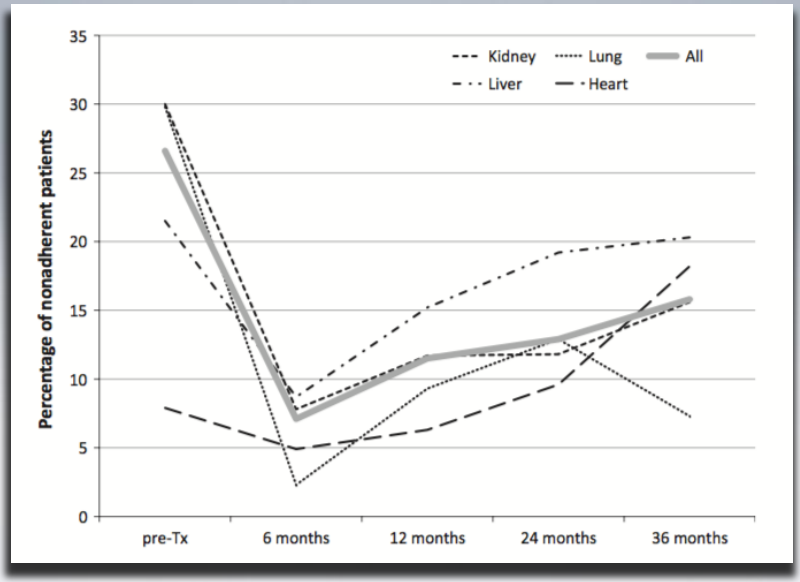
> *"We hypothesize that differences between the treatment regimens, including probable improved adherence to treatment and reduced variability of tacrolimus exposure observed with prolonged-release tacrolimus, have long-term beneficial effects."*

Adam et al. *Am.J.Transpl* 2015;15:1267–1282.

Graft longevity

Non-adherence

Immunosuppression exposure



De Geest et al. *Transplant International. 2014; 27: 657–666*

Abstract Preview - Step 3/4

- print version -

Topic: 6 Immunosuppression

Title: Comparison of Extended-Release, Once Daily Tacrolimus and Standard Twice Daily Tacrolimus in De Novo Liver Transplant Recipients

Author(s): Lim T.Y., Shah N., Shah A., Mahgoub S., Considine A., Joshi D., Sanchez-Fueyo A., Suddle A., Heaton N., O'Grady J., Heneghan M.A., Agarwal K., Aluvihare V.

Institute(s): Institute of Liver Studies, King's College Hospital, London, United Kingdom

Results

132 patients were transplanted; 59 in Prograf group (PG) and 73 in Advagraf group (AG). Exclusion criteria were multi-organ (n=3) and re-transplantations (n=14), deaths within 3months (n=4), patients in AG initiated on Prograf (n=2), switched from Advagraf-to-Prograf (n=7), switched from Prograf-to-Advagraf (n=6) and switched to cyclosporine (n=1). One patient from PG was re-transplanted for graft-failure due to rejection 8months post-LT.

After exclusions, there were 45 patients (male=26, median age at LT=55years) in PG and 50 (male=34, median age=52years) in AG. Indications for LT include alcoholic liver disease (PG=27%, AG=41%), viral hepatitis (PG=24%, AG=12%), non-alcoholic fatty liver disease (PG=11%, AG=14%) and autoimmune hepatitis/PBC/PSC (PG=9%, AG=14%). 16 (36%) patients received interleukin-2-receptor antibody induction in PG and 16 (32%) in AG. Median lengths of stay were comparable in hospital (15days) and ICU (3days).

PBC: primary biliary cirrhosis; PSC: primary sclerosing cholangitis.

Abstract presented at ILTS 2017

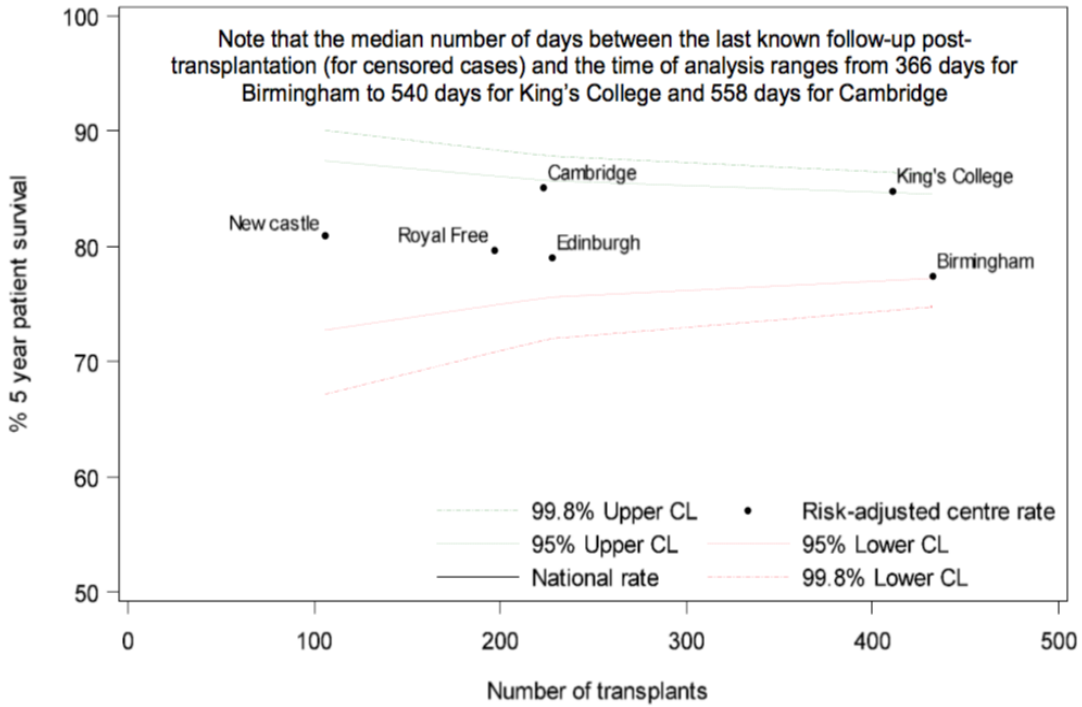
	Prograf	Advagraf
Median MELD (UKELD)	14 (50)	16 (53)
Biopsy proven acute rejection/BPAR – (within 1 month)	11, 24% (n=8, 18%)	9, 18% (n=9, 18%)
Creatinine (µmol/L) – Non-inducted		
• Pre-LT	72 (n=29)	68 (n=34)
• 3 months post-LT	79 (n=22)	74 (n=13)
CKD Stage ≥ 2 (Non-inducted)		
• Pre-LT	6/29 (21%)	3/34 (9%)
• 3 months post-LT	4/22 (18%)	3/13 (23%)
CKD Stage ≥ 2 (Inducted)		
• Pre-LT	5/16 (31%)	6/16 (38%)
• 3 months post-LT	4/10 (40%)	2/2 (100%)
Median total daily dose at discharge (mg)	8	8

[Clinical outcomes of denovo Prograf and Advagraf in LT.]

BPAR rate was higher in PG; 2 patients received ATG. There was no statistically significant difference in renal outcomes or rejection rates.

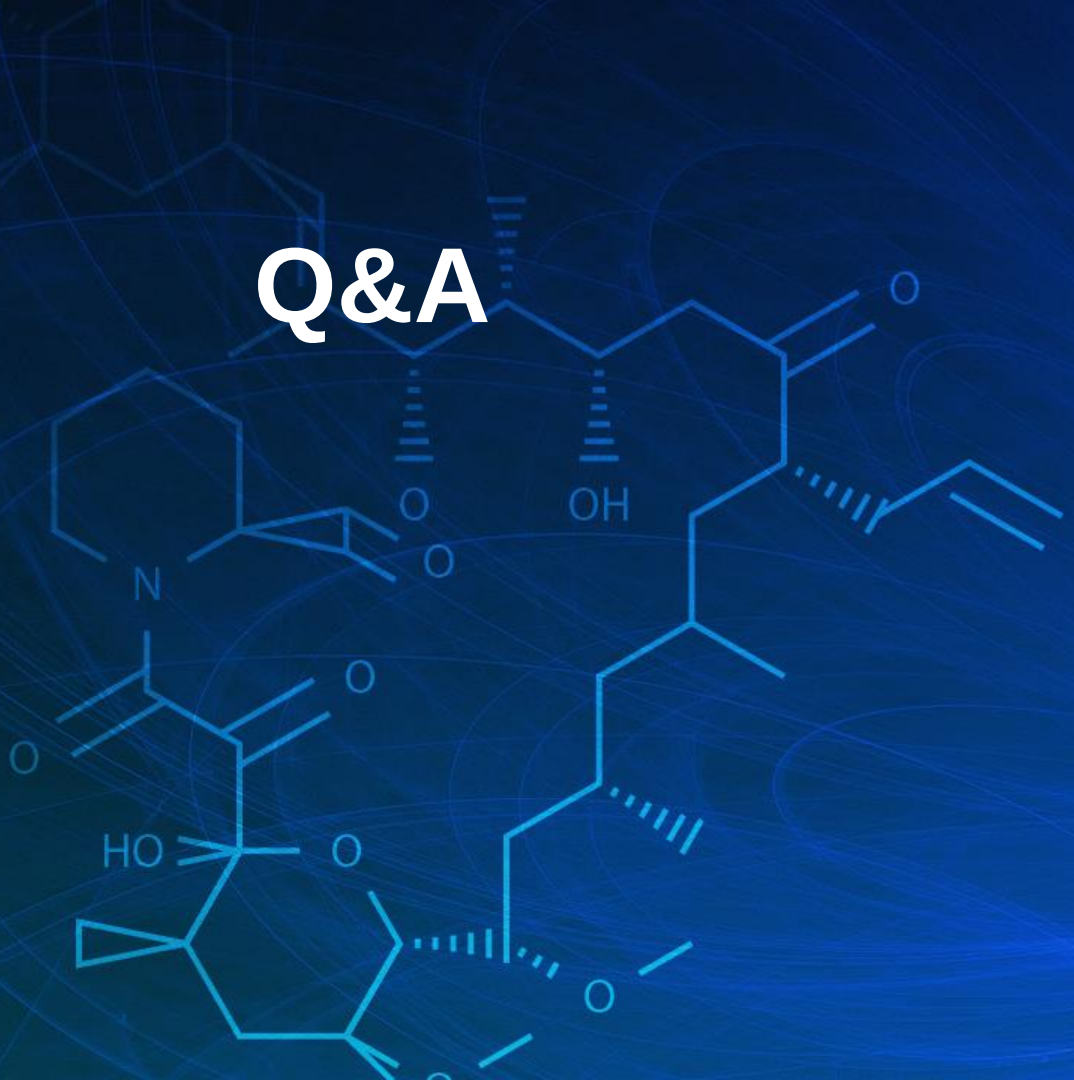
Abstract presented at ILTS 2017

Figure 3.13 **Risk-adjusted 5 year patient survival rates for adult elective deceased donor first liver transplants, 1 April 2008 - 31 March 2012**

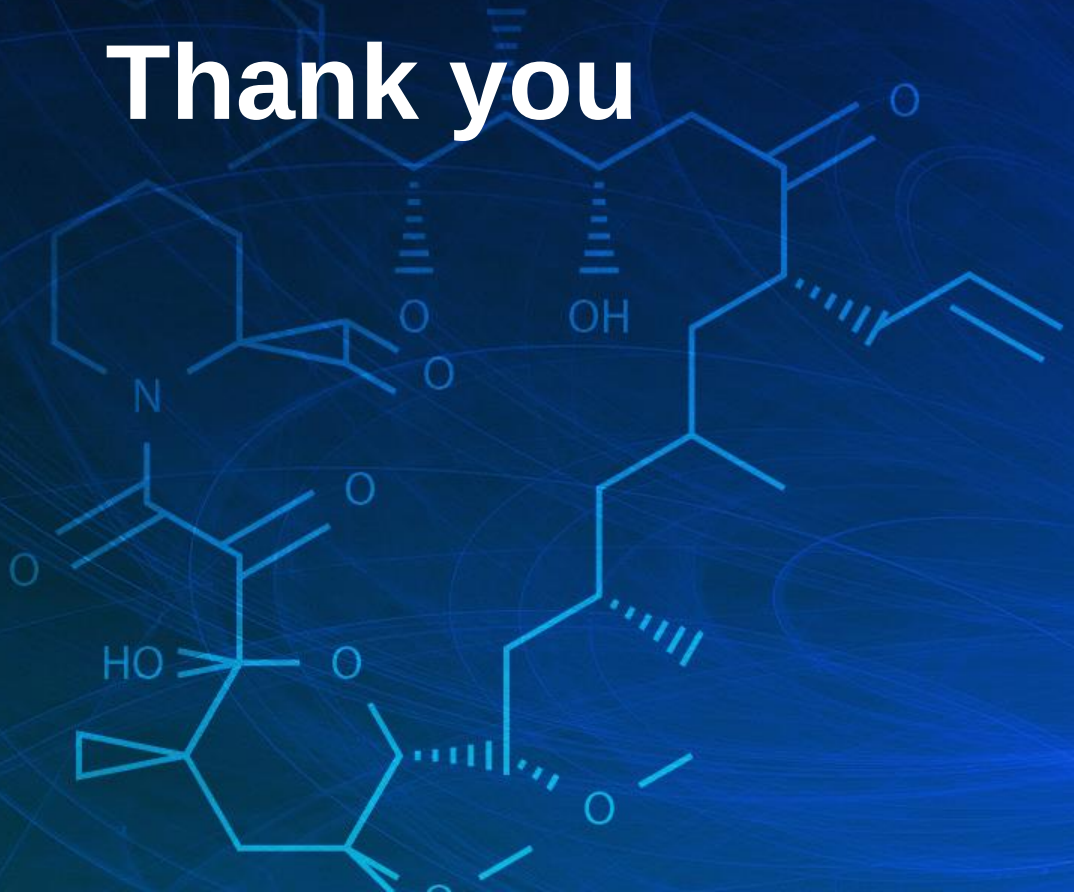


* Leeds have been excluded due to a lack of follow up beyond 12 months.

Q&A



Thank you



Prescribing Information: ADVAGRAF™ prolonged release hard capsules (tacrolimus) Prescribing Information: Prograf™ immediate release hard capsules (tacrolimus)

For full prescribing information, please refer to the Summary of Product Characteristics (SPC). **Presentations:** ADVAGRAF prolonged-release hard capsules containing 0.5 mg, 1 mg, 3 mg and 5 mg tacrolimus as monohydrate. Prograf immediate release hard capsules containing 0.5 mg, 1 mg and 5 mg tacrolimus as monohydrate. **Indications:** ADVAGRAF: Prophylaxis of transplant rejection in adult kidney or liver allograft recipients. Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients. Prograf: Prophylaxis of transplant rejection in liver, kidney or heart allograft recipients. Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products. **Posology and Administration:** ADVAGRAF is a once daily oral formulation of tacrolimus. Prograf is a twice daily oral formulation of tacrolimus. ADVAGRAF and Prograf therapy require careful monitoring by adequately qualified and equipped personnel. Immunosuppressive therapy should only be prescribed and any changes should only be initiated by physicians experienced in immunosuppressive therapy and the management of transplant patients. Dosage recommendations given below should be used as a guideline. ADVAGRAF or Prograf are routinely administered in conjunction with other immunosuppressive agents in the initial post-operative period. The dose may vary depending on the immunosuppressive regimen chosen. Dosing should be based on clinical assessments of rejection and tolerability aided by blood level monitoring. If clinical signs of graft rejection are apparent, alteration of the immunosuppressive regimen should be considered. To suppress graft rejection, immunosuppression must be maintained, so no limit to the duration of oral therapy can be given. ADVAGRAF capsules should be taken orally once daily in the morning with water on an empty stomach or at least 1 hour before or 2-3 hours after a meal and immediately following removal of blister. A forgotten morning dose should be taken as soon as possible on the same day. Prograf capsules should be taken as for ADVAGRAF but in two divided doses (e.g. morning and evening). If necessary Prograf capsules can be administered by administering the capsule contents suspended in water, via nasogastric tubing.

In patients unable to take oral medication during the immediate posttransplant period, tacrolimus therapy can be initiated intravenously (see Prograf IV SPC) at a dose of approx 1/5th of the recommended oral dose for the corresponding indication. ADVAGRAF: In stable patients converted from Prograf to ADVAGRAF on a 1:1 (mg:mg) total daily dose basis, the systemic exposure (AUC_{0-24}) to tacrolimus for ADVAGRAF was approximately 10% lower than for Prograf. The relationship between tacrolimus trough levels (C_{24}) and systemic exposure for ADVAGRAF is similar to that of Prograf. When converting from Prograf capsules to ADVAGRAF, trough levels should be measured before and within two weeks after conversion. In de novo kidney and liver transplant patients AUC_{0-24} of tacrolimus for ADVAGRAF on Day 1 was 30% and 50% lower respectively, when compared with that for Prograf at equivalent doses. By Day 4, systemic exposure as measured by trough levels is similar for both kidney and liver transplant patients with both formulations. Prophylaxis of transplant rejection: Liver transplant patients should be initiated on 0.10-0.20 mg/kg/day 12 hours after completion of surgery for Prograf and 12-18 hours after surgery for ADVAGRAF. Kidney transplant patients should be initiated on 0.20-0.30 mg/kg/day 24 hours after completion of surgery. Heart transplant patients should commence Prograf therapy at a dose of 0.075 mg/kg/day within 5 days after the completion of the surgery following antibody induction or 12 hours after completion of surgery without antibody induction. For patients who cannot receive oral therapy posttransplant, please see the Prograf IV SPC. For paediatric doses please see full SPC. Dose adjustment post-transplant: ADVAGRAF and Prograf doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy leading to ADVAGRAF monotherapy or Prograf dual therapy or monotherapy. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments. Dose recommendations – Conversion to tacrolimus. Following conversion, tacrolimus trough levels should be monitored and if necessary dose adjustments made. Care should be taken when converting patients from ciclosporin-based to tacrolimus-based therapy. Initiate ADVAGRAF or Prograf after considering ciclosporin blood concentrations and clinical condition of patient. Delay dosing in presence of elevated ciclosporin blood levels. In practice, tacrolimus-based therapy has been initiated 12 - 24

hours after discontinuation of ciclosporin. Monitor ciclosporin blood levels following conversion. Dose recommendations – Rejection therapy. For conversion of kidney and liver recipients from other immunosuppressants to once daily ADVAGRAF, begin with the respective initial dose recommended for rejection prophylaxis. In adult heart transplant recipients converted to ADVAGRAF, an initial oral dose of 0.15 mg/kg/day should be administered once daily in the morning. For other allografts: see SPC. Increased Prograf doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. For conversion to Prograf in treatment of liver and kidney rejection therapy, treatment should begin with the initial oral dose recommended for primary immunosuppression. In adult heart transplant patients converted to Prograf, an initial oral dose of 0.15 mg/kg/day should be administered in two divided doses (e.g. morning and evening). For paediatric patients treated with Prograf, see SPC. Dose adjustments in specific populations: see SPC. Dose reduction may be necessary in patients with severe liver impairment. No dose adjustment is required in patients with renal impairment, however owing to the nephrotoxic potential of tacrolimus careful monitoring of renal function is recommended. Black patients may require higher tacrolimus doses to achieve similar trough levels to Caucasians. ADVAGRAF is not recommended for use in children below 18 years due to limited data on safety and efficacy. Target whole blood trough concentration recommendations: ADVAGRAF: Blood trough levels for ADVAGRAF should be drawn approximately 24 hours post-dosing, just prior to the next dose. Frequent trough level monitoring in the first two weeks post-transplant is recommended, with periodic monitoring during maintenance therapy. Monitoring is also recommended following conversion from Prograf to ADVAGRAF, dose adjustment, changes in the immunosuppressive regimen, or co-administration of substances which may alter tacrolimus whole blood concentrations. PROGRAF: Blood trough levels for Prograf should be drawn approximately 12 hours post-dosing, just prior to the next dose. Blood trough levels should be monitored approximately twice weekly during the early post-transplant period and then periodically during maintenance therapy. Adjustments to the ADVAGRAF and Prograf dose regimen may take several days before steady state is achieved. Most patients can be managed successfully if tacrolimus blood concentrations are maintained below 20 ng/

mL. In clinical practice, whole blood trough levels have been 5-20 ng/mL in liver transplant recipients and 10-20 ng/mL in kidney and heart transplant recipients in the early post-transplant period, and 5-15 ng/mL for liver, kidney and heart during maintenance therapy. It is necessary to consider the clinical condition of the patient when interpreting whole blood levels.

Contraindications: Hypersensitivity to tacrolimus or other macrolides or any of the excipients. (see SPC).

Warnings and Precautions: Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate or prolonged-release tacrolimus formulations, have been observed. This has led to serious adverse reactions, including graft rejection, or other adverse reactions which could be a consequence of either under- or over exposure to tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimen; alterations in formulation or regimen should only take place under the close supervision of a transplant specialist (see SPC.). ADVAGRAF is not recommended for use in children below 18 years due to limited data on safety and/or efficacy. For treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients clinical data are not yet available for the prolonged-release formulation ADVAGRAF. For prophylaxis of transplant rejection in adult heart allograft recipients clinical data are not yet available for ADVAGRAF. ADVAGRAF and Prograf: During the initial post-transplant period, monitoring of the following parameters should be undertaken on a routine basis: blood pressure, ECG, neurological and visual status, fasting blood glucose levels, electrolytes (particularly potassium), liver and renal function tests, haematology parameters, coagulation values, and plasma protein determinations. If clinically relevant changes are seen, adjustments of the immunosuppressive regimen should be considered. Substances with potential for interaction: When substances with a potential for interaction (see SPC) – particularly strong inhibitors of CYP3A4 (such as telaprevir, boceprevir, ritonavir, ketoconazole, voriconazole, itraconazole, telithromycin or clarithromycin) or inducers of CYP3A4 (such as rifampicin, rifabutin) – are being combined with tacrolimus, tacrolimus blood levels should be monitored to adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure. Herbal preparations containing St. John's Wort *(Hypericum perforatum)* or other herbal preparations should be avoided when taking ADVAGRAF or Prograf due to the risk of interactions

that lead to either a decrease in blood concentrations of tacrolimus and reduced clinical effect of tacrolimus, or an increase in blood concentrations of tacrolimus and risk of tacrolimus toxicity (see SPC). The combined administration of ciclosporin and tacrolimus should be avoided and care should be taken when administering tacrolimus to patients who have previously received ciclosporin. High potassium intake or potassium-sparing diuretics should be avoided. Certain combinations of tacrolimus with drugs known to have nephrotoxic or neurotoxic effects may increase the risk of these effects (see SPC). Vaccinations: Immunosuppressants may affect the response to vaccination and vaccination during treatment with tacrolimus may be less effective. The use of live attenuated vaccines should be avoided. Gastrointestinal disorders: Gastrointestinal perforation has been reported in patients treated with tacrolimus. As gastrointestinal perforation is a medically important event that may lead to a life-threatening or serious condition, adequate treatments should be considered immediately after suspected symptoms or signs occur. Since levels of tacrolimus in blood may significantly change during diarrhoea episodes, extra monitoring of tacrolimus concentrations is recommended during episodes of diarrhoea. Cardiac disorders: Ventricular hypertrophy or hypertrophy of the septum, reported as cardiomyopathies, have been observed in Prograf treated patients on rare occasions and may also occur with ADVAGRAF. Most cases have been reversible, occurring with tacrolimus blood trough concentrations much higher than the recommended maximum levels. Other factors observed to increase the risk of these clinical conditions included preexisting heart disease, corticosteroid usage, hypertension, renal or hepatic dysfunction, infections, fluid overload, and oedema. Accordingly, high-risk patients receiving substantial immunosuppression should be monitored, using such procedures as echocardiography or ECG pre- and post-transplant (e.g. initially at 3 months and then at 9 -12 months). If abnormalities develop, dose reduction of ADVAGRAF or Prograf, or change of treatment to another immunosuppressive agent should be considered. Tacrolimus may prolong the QT interval and may cause Torsades de Pointes. Caution should be exercised in patients with risk factors for QT prolongation, including patients with a personal or family history of QT prolongation, congestive heart failure, bradyarrhythmias and electrolyte abnormalities. Caution should also be exercised in patients diagnosed or suspected to have Congenital Long QT

Syndrome or acquired QT prolongation or patients on concomitant medications known to prolong the QT interval, induce electrolyte abnormalities or known to increase tacrolimus exposure (see SPC). Lymphoproliferative disorders and malignancies: Patients treated with tacrolimus have been reported to develop Epstein-Barr-Virus (EBV)-associated lymphoproliferative disorders. Patients switched to Prograf therapy should not receive anti-lymphocyte treatment concomitantly (see SPC). A combination of immunosuppressives such as antilymphocytic antibodies (e.g. basiliximab, daclizumab) given concomitantly increases the risk of EBV-associated lymphoproliferative disorders. EBV-Viral Capsid Antigen (VCA)-negative patients, including very young children (<2 years), have been reported to have an increased risk of developing lymphoproliferative disorders. Therefore, in this patient group, EBV-VCA serology should be ascertained before starting treatment with ADVAGRAF or Prograf. During treatment, careful monitoring with EBV-PCR is recommended. Positive EBV-PCR may persist for months and is per se not indicative of lymphoproliferative disease or lymphoma. As with other potent immunosuppressive compounds, the risk of secondary cancer is unknown (see SPC). As with other immunosuppressive agents, owing to the potential risk of malignant skin changes, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor. Opportunistic infections: Patients treated with immunosuppressants, including ADVAGRAF and Prograf are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal). Among these conditions are BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML). These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms. Posterior reversible encephalopathy syndrome (PRES): Patients treated with tacrolimus have been reported to develop posterior reversible encephalopathy syndrome (PRES). If patients taking tacrolimus present with symptoms indicating PRES such as headache, altered mental status, seizures, and visual disturbances, a radiological procedure (e.g. MRI) should be performed. If PRES is diagnosed, adequate blood pressure and seizure control and immediate discontinuation of systemic tacrolimus is advised. Most patients completely

recover after appropriate measures are taken. Pure Red Cell Aplasia: Cases of pure red cell aplasia (PRCA) have been reported in patients treated with tacrolimus. All patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease or concomitant medications associated with PRCA. Special populations: There is limited experience with ADVAGRAF in non-Caucasian patients and patients at elevated immunological risk (e.g. retransplantation, evidence of panel reactive antibodies, PRA). ADVAGRAF: Dose reduction may be necessary in patients with severe liver impairment. Excipients: ADVAGRAF and Prograf capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. The printing ink used to mark ADVAGRAF (all strengths) and Prograf (0.5 mg and 1 mg) capsules contains soya lecithin. In patients who are hypersensitive to peanut or soya, the risk and severity of hypersensitivity should be weighed against the benefit of using ADVAGRAF or Prograf.

Interactions: See SPC. Tacrolimus is metabolised by CYP3A4. Concomitant use of CYP3A4 inhibitors or inducers may increase or decrease tacrolimus blood levels, therefore monitoring of tacrolimus blood levels, QT prolongation, renal function and other side effects is strongly recommended with concomitant use. Tacrolimus is a known CYP3A4 inhibitor; thus concomitant use with medicinal products metabolised by CYP3A4 may affect the metabolism of such medicinal products. Tacrolimus is extensively bound to plasma proteins. Possible interactions with other active substances known to have high affinity for plasma proteins should be considered (e.g., NSAIDs, oral anticoagulants, or oral antidiabetics). Other potential interactions that may increase systemic exposure of tacrolimus include prokinetic agents (such as metoclopramide and cisapride), cimetidine and magnesium-aluminium-hydroxide.

Pregnancy and lactation: Tacrolimus can be considered in pregnant women when there is no safer alternative and when the perceived benefit justifies the risk to the foetus. Cases of spontaneous abortion have been reported. Following in *utero* exposure, monitoring of the newborn for potential adverse effects is recommended (in particular those of the kidneys). There is a risk for premature delivery (<37 weeks) and hyperkalaemia in the newborn which, however normalises spontaneously. Tacrolimus is excreted in breast milk, as detrimental effects on the newborn cannot be excluded, women should not

breast-feed whilst receiving ADVAGRAF or Prograf. See SPC.

Undesirable effects: The adverse reaction profile associated with immunosuppressive agents is often difficult to establish owing to the underlying disease and the concurrent use of multiple medicinal products. Many of the adverse drug reactions stated below are reversible and/or respond to dose reduction. Oral administration appears to be associated with a lower incidence of adverse drug reactions compared with intravenous use (Prograf). The most commonly reported adverse reactions (occurring in > 10% of patients) are tremor, renal impairment, hyperglycaemic conditions, diabetes mellitus, hyperkalaemia, infections, hypertension and insomnia. The frequency of adverse reactions is defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Infections and infestations As is well known for other potent immunosuppressive agents, patients receiving tacrolimus are frequently at increased risk for infections (viral, bacterial, fungal, protozoal). The course of pre-existing infections may be aggravated. Both generalised and localised infections can occur. Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including ADVAGRAF and Prograf. Neoplasms benign, malignant and unspecified (incl. cysts and polyps) Patients receiving immunosuppressive therapy are at increased risk of developing malignancies. Benign as well as malignant neoplasms including EBV-associated lymphoproliferative disorders and skin malignancies have been reported in association with tacrolimus treatment. Blood and lymphatic system disorders *common:* anaemia, thrombocytopenia, leukopenia, red blood cell analyses abnormal, leukocytosis *uncommon:* coagulopathies, pancytopenia, neutropenia, coagulation and bleeding analyses, abnormal *rare:* thrombotic thrombocytopenic purpura, hypoprothrombinaemia *not known:* pure red cell aplasia, agranulocytosis, haemolytic anaemia. Immune system disorders Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus (see SPC). Endocrine disorders *rare:* hirsutism. Metabolism and nutrition disorders *very common:*

diabetes mellitus, hyperglycaemic conditions, hyperkalaemia *common:* metabolic acidoses, other electrolyte abnormalities, hyponatraemia, fluid overload, hyperuricaemia, hypomagnesaemia, hypokalaemia, hypocalcaemia, appetite decreased, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia, hypophosphataemia *uncommon:* dehydration, hypoglycaemia, hypoproteinaemia, hyperphosphataemia. Psychiatric disorders *very common:* insomnia common: confusion and disorientation, depression, anxiety symptoms, hallucination, mental disorders, depressed mood, mood disorders and disturbances, nightmare *uncommon:* psychotic disorder. Nervous system disorders *very common:* headache, tremor *common:* nervous system disorders, seizures, disturbances in consciousness, peripheral neuropathies, dizziness, paraesthesias and dysaesthesias, writing impaired *uncommon:* encephalopathy, central nervous system haemorrhages and cerebrovascular accidents, coma, speech and language abnormalities, paralysis and paresis, amnesia rare: hypertonia *very rare:* myasthenia. Eye disorders *common:* eye disorders, vision blurred, photophobia *uncommon:* cataract *rare:* blindness Ear and labyrinth disorders *common:* tinnitus *uncommon:* hypoacusis *rare:* deafness neurosensory *very rare:* hearing impaired. Cardiac disorders *common:* ischaemic coronary artery disorders, tachycardia *uncommon:* heart failures, ventricular arrhythmias and cardiac arrest, supraventricular arrhythmias, cardiomyopathies, ventricular hypertrophy, palpitations *rare:* pericardial effusion *very rare:* Torsades de Pointes. Vascular disorders *very common:* hypertension *common:* thromboembolic and ischaemic events, vascular hypotensive disorders, haemorrhage, peripheral vascular disorders *uncommon:* venous thrombosis deep limb, shock, infarction Respiratory, thoracic and mediastinal disorders *common:* parenchymal lung disorders, dyspnoea, pleural effusion, cough, pharyngitis, nasal congestion and inflammations *uncommon:* respiratory failures, respiratory tract disorders, asthma *rare:* acute respiratory distress syndrome. Gastrointestinal disorders *very common:* diarrhoea, nausea *common:* gastrointestinal signs and symptoms, vomiting, gastrointestinal and abdominal pains, gastrointestinal inflammatory conditions, gastrointestinal haemorrhages, gastrointestinal ulceration and perforation, ascites, stomatitis and ulceration, constipation, dyspeptic signs and symptoms, flatulence, bloating and distension, loose stools *uncommon:* acute and chronic pancreatitis,

ileus paralytic, gastrooesophageal reflux disease, impaired gastric emptying *rare:* pancreatic pseudocyst, subileus. Hepatobiliary disorders *common:* bile duct disorders (ADVAGRAF only), cholangitis (Prograf only), hepatocellular damage and hepatitis, cholestasis and jaundice *rare:* venoocclusive liver disease, hepatitic artery thrombosis *very rare:* hepatic failure, bile duct stenosis (Prograf only). Skin and subcutaneous tissue disorders *common:* rash, pruritus, alopecias, acne, sweating increased *uncommon:* dermatitis, photosensitivity *rare:* toxic epidermal necrolysis (Lyell's syndrome) *very rare:* Stevens Johnson syndrome. Musculoskeletal and connective tissue disorders *common:* arthralgia, back pain, muscle spasms, pain in limb *uncommon:* joint disorders rare: mobility decreased. Renal and urinary disorders *very common:* renal impairment *common:* renal failure, renal failure acute, nephropathy toxic, renal tubular necrosis, urinary abnormalities, oliguria, bladder and urethral symptoms *uncommon:* haemolytic uraemic syndrome, anuria *very rare:* nephropathy, cystitis haemorrhagic. Reproductive system and breast disorders *uncommon:* dysmenorrhoea and uterine bleeding General disorders and administration site conditions *common:* febrile disorders, pain and discomfort, asthenic conditions, oedema, body temperature perception disturbed *uncommon:* influenza like illness, feeling jittery, feeling abnormal, multi-organ failure, chest pressure sensation, temperature intolerance *rare:* fall, ulcer, chest tightness, thirst *very rare:* fat tissue increased. Investigations *very common:* liver function tests abnormal (ADVAGRAF only) *common:* blood alkaline phosphatase increased, weight increased, hepatic enzymes and function abnormalities (Prograf only) *uncommon:* amylase increased, ECG investigations abnormal, heart rate and pulse investigations abnormal, weight decreased, blood lactate dehydrogenase increased *very rare:* echocardiogram abnormal, electrocardiogram QT prolonged Injury, poisoning and procedural complications *common:* primary graft dysfunction. Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-release tacrolimus formulations, have been observed. A number of associated cases of transplant rejection have been reported (frequency cannot be estimated from available data).

Overdose: Experience with overdose is limited. Several cases of accidental overdose have been reported with tacrolimus; symptoms have included tremor, headache, nausea and vomiting, infections, urticaria, lethargy and increases in

blood urea nitrogen, serum creatinine and alanine aminotransferase levels. No specific antidote to tacrolimus therapy is available. It is anticipated that tacrolimus will not be dialysable. In isolated patients with very high plasma levels, haemofiltration or -diafiltration have been effective in reducing toxic concentrations. In cases of oral intoxication, gastric lavage and/or the use of adsorbents may be helpful, if used shortly after intake.

Package Quantities, Basic NHS cost: ADVAGRAF/ Prograf: 0.5 mg capsules x 50 = £35.79/£61.88, respectively. ADVAGRAF/Prograf: 1 mg capsules x 50 = £71.59/£80.28, respectively. ADVAGRAF/Prograf: 1 mg capsules x 100 = £143.17/£160.54, respectively. ADVAGRAF/Prograf: 5 mg capsules x 50 = £266.92 /£296.58, respectively. ADVAGRAF : 3 mg capsules x 50 = £214.76.

Legal Classification: POM.

Product licence numbers: ADVAGRAF: EU/1/07/387/001-026, Prograf: PL 00166/0203-0206

ADVAGRAF Marketing Authorisation Holder: Astellas Pharma Europe B.V., Sylviusweg 62, 2333 BE Leiden Netherlands

Prograf Marketing Authorisation Holder: Astellas Pharma Ltd, 2000 Hillswood Drive, Chertsey, Surrey, KT16 0RS, UK.

Date of Preparation of Prescribing Information: January 2018

Job bag number: PRE17016UK For full prescribing information, please see the ADVAGRAF and Prograf SPCs available at www.medicines.org.uk. Further information available from: Astellas Pharma Ltd. 2000 Hillswood Drive, Chertsey, KT16 0RS. Medical Information: 0800 783 5018.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/ yellowcard. Adverse events should also be reported to Astellas Pharma Ltd on 0800 783 5018