UKRPG
UK Renal Pharmacy Group

Welcome to the April Q&A!

Trusts represented today include: North Bristol, Cambridge, King's, Imperial, Ayrshire, Lister, Norfolk, Portsmouth, Exeter, Royal Free, Liverpool, Glasgow, Leicester, Brighton, Fife,

Updates

- **RPG conference 2024 11th/12th October** - save the date!! ☺
  - Birmingham Arden Hotel

- **UK Kidney week 10-12th June 2024**
  - Edinburgh Conference Centre – programme released
  - Liaise with Cathy Pogson to get involved (cathy.pogson@porthosp.nhs.uk)

- **CPC London 10th/11th May**
  - Volunteers to help promote RPG
  - Liaise with Cathy Pogson to get involved (cathy.pogson@porthosp.nhs.uk)

- Monthly teams chat for advanced/consultant portfolios
  - Email cathy.pogson@porthosp.nhs.uk if you would like to join

- Reminder to check your RPG membership is up to date
  - Large number of lapsed memberships, currently being checked against the Q&A whastapp group list

Updates

- NICE TA: Budesonide (Kinpeygo) expected mid April
  - IgA Nephropathy – ICB Funded
  - May need to purchase via HealthNet Wholesale (not necessarily needed to be on homecare)

- NICE applications:
  - Vadadustat (renal anaemia likely to be RRT)
  - Sparsentan (IgA Nephropathy)

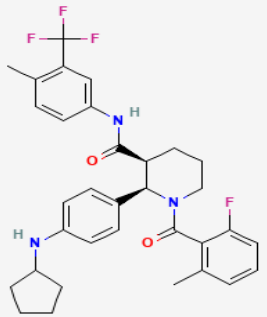
- RDD issues:
  - Sara resolved some issues at Bristol – email sara.perkins@nbt.nhs.uk for info on creating forms
  - New paper book due end of 2024

Supply Problems

- Basiliximab
  - ULM route possible, cost pressure (?can't recoup as block contract ?contract deviation possible)
  - Deliveries may be becoming more regular but still under regional monitoring
- Salbutamol Nebs
  - ?ULM options available
  - Prioritising stock currently not using ULM
- Sando K/slow Na/sando phos
  - Supply not yet robust for phosphate Sandoz & sando K but largely available
- Taurolock U/Alteplase
  - Taurolock U on allocation scheme –becoming tighter and likely to need review on priority
  - Alteplase 2mg still OOS – options include ULM alteplase (cost pressure) or urokinase
- Ganciclovir (pre made bags +/- raw ingredient) ?make on ward with appropriate PPE
  - Please share if you have information on safely making on ward
- Belimumab – out of stock (IV)
- Adoport 0.75 mg – delay until 17th May (0.5mg/1mg/5mg tablets not affected)

Q&A Themes - Guidelines

- IV iron in CKD and HD
- ESA monitoring for BP cut off
- Parathyroidectomy guideline



Avacopan

Indicated for the treatment of adult patients with severe, active granulomatosis with polyangitis (GPA) or microscopic polyangitis (MPA)

Medication details

A complement 5a receptor (C5aR1) antagonist that inhibits C5a-mediated neutrophil activation, thereby reducing the pro-inflammatory effects of the C5a protein on blood vessels.

Dose – 30mg twice a day
- Taken as 3 x 10mg capsules, to be used in combination with cyclophosphamide or rituximab regimens.

Administration - To be taken with food,
- Concurrent PJP prophylaxis is recommended
- Vaccinate preferably before starting treatment. Avoid live vaccines

Common side effects
- Abdominal pain upper; diarrhoea; headache; hepatic disorders; increased risk of infection; leucopoenia; nausea; neutropenia; vomiting

Cautions / Contra-indications
- Neutrophils < 1.5 x 10^9/litre
- Lymphocyte < 0.5 x 10^9/litre (do not initiate);
- WBC < 3.5 x 10^9/litre (do not initiate)
- Signs of liver disease - LFT >3x ULN
- Caution in patients with a history of hepatitis B or C, HIV infection or TB

Pregnancy and lactation
- Toxicity in pregnancy demonstrated in animal studies.

Monitoring
- Full blood count
- Liver function

Volume of Distribution
- apparent volume of distribution of 345 L

Protein binding
- 99.9% protein bound

Excretion
- Mainly eliminated in faeces

Metabolism
- Major circulating active M1 metabolite (mono-hydroxylated form of avacopan) - represents 12% of drug plasma levels, acts as a C5aR antagonist, similar efficacy to avacopan.

Drug Interactions- https://bnf.nice.org.uk/interactions/avacopan/
- **CYP3A4 enzyme - Potent inhibitors or moderate/potent inducers** – may require dose reductions or withholding / not starting therapy. e.g Carbamazepine, Clarithromycin, Grapefruit, Itraconazole, Phenytoin, Phenobarbital, Posaconazole, Rifampicin, St Johns wort, Voriconazole (this list is NOT

Renal Recovery for Patients With ANCA-Associated Vasculitis and Low eGFR in the ADVOCATE Trial of Avacopan

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Methods and cohort

ADVOCATE trial

Post hoc analysis

Patients with ANCA - associated vasculitis

eGFR ≤20mL/min/1.73m² N = 50

Intervention

Prednisone group

n = 23

52 weeks follow-up

Avacopan group

n = 27

Results

	Baseline eGFR mL/min/1.73m²	Change in eGFR mL/min/1.73m²	Increase in eGFR of ≥2-fold (%)
Prednisone group	17.5	7.7	13.0
Avacopan group	17.6	16.1	40.7
	P = 0.846	P = 0.003	P = 0.030

ANCA, antineutrophil cytoplasmic antibody

KI REPORTS Kidney International Reports

Cortazar F et al, 2023

Visual abstract by: Denisse Arellano, MD @deniise_am

Conclusion Among patients with baseline eGFR ≤20 mL/min/1.73m² in the ADVOCATE trial, eGFR improved more in the avacopan group vs. the prednisone group.

Checklist – hyperlinks to further resources

https://www.nice.org.uk/guidance/ta825

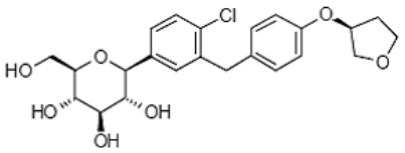
NHS discount via Commercial Access and Pricing (CAP) Portal

Register patient with Blueteq

Black triangle - Yellow Card ADR reporting

Birmingham Vasculitis Activity Score

Corticosteroid Toxicity Index Cumulative Worsening Score



Empaglifozin

$C_{23}H_{27}ClO_7$ - a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated to prevent the progression of CKD.

Medication details

A reversible, highly-potent, selective, competitive inhibitor of sodium-glucose co-transporter 2 (SGLT2) receptors, reducing glucose reabsorption within the proximal tubule. The underlying mechanisms for preventing the progression of CKD have yet to be elucidated. Most patients with chronic kidney disease die from cardiovascular causes before reaching ESRD.

EMPA-Kidney was stopped early due to the observed beneficial effects of empagliflozin.

For people living with CKD, empagliflozin significantly reduces cardiovascular death, hospitalization for heart failure, all-cause hospitalization, and all-cause mortality compared with placebo.

NNT: 26 CKD patients for 2 years to prevent 1 case of ESKD, dialysis initiation, kidney transplant or death from CVD

Dose

- 10mg orally daily (with or without food)

NICE TA 942 - an **add-on** to standard care **after** ACE inhibitors or ARBs have been optimised (unless contraindicated) and:

- eGFR is 20 - 45 ml/min/1.73 m^2

OR

- eGFR is 45 - 90 ml/min/1.73 m^2 to 90 ml/min/1.73 m^2 **AND** urine albumin-to-creatinine ratio of 22.6 mg/mmol or more, **OR** type 2 diabetes.

Co-morbidities – consider NICE TA 929 - as an option for treating symptomatic chronic heart failure with preserved or mildly reduced ejection fraction in adults.

Renal effects - Acute decrease in eGFR (2-3ml/min) in first 2-months after initiation of empagliflozin. After 3-years, total decline empagliflozin 2.16(+/-0.8)ml/min, placebo 2.92ml/min. Decline in eGFR sig. lower in empagliflozin treated group after 2-months.

Side effects - Incidences of serious urinary tract infection, hyperkalaemia, AKI, serious or symptomatic dehydration, liver injury, and bone fracture were broadly similar in the two groups. There was no apparent evidence that empagliflozin treatment increased the incidence of serious adverse events overall or increased serious adverse events.
Hypoglycaemia (type-II-diabetes treated with insulin or sulphonylurea), care with volume depletion if >75yrs, increased urination, increased serum lipids.

Special precautions

- Ketoacidosis has been reported in diabetic patients with only moderately increased glucose levels.
- Risk of AKI due to volume depletion - stop empagliflozin in patients hospitalised for acute surgical procedures or acute serious medical illness. **Counsel patients on sick day rules. Restart empagliflozin once risk of AKI reduced or recovered.**
- Do not initiate in type 1 diabetics.
- **Diabetes mellitus is a risk factor for the development of Fournier's gangrene. 6 Yellow Card reports (4 in men and 2 in women) have been received in UK by Jan-19 after 548,565 patient-years of SGLT2-treatment.** Drug-safety-update

Renal impairment - not recommended for initiation in patients with eGFR<20mL/min/1.73m2
Hepatic impairment – not recommended in severe impairment.
Estimated volume of distribution – 73.8 L
Protein binding – 86.2%
Metabolism - mainly glucuronidation
Excretion - mainly faeces
Drug Interactions – No known drug interactions

Is Empagliflozin Beneficial in Patients With Variable Chronic Kidney Disease and Diabetes Status?

EMPA-KIDNEY Collaborative Group

#NephJC

6609 patients randomized

2-year follow up

eGFR ≥ 20-45 ml/min/1.73 m^2 **or**

eGFR ≥ 45-90 ml/min/1.73 m^2 **and** Urine Albumin to creatinine ratio of > 200 mg/g

	Progressive CKD* or CV death	Hospitalization for CHF or CV death	Hospitalization any cause (per 100 patient yrs)
Placebo n=3305	16.9%	4.6%	29.2
	HR 0.72 (0.64-0.82) p< 0.001	HR 0.84 (0.67-1.07) p=0.15	HR 0.86 (0.78-0.95) p= 0.003
Empagliflozin 10mg n=3304	13.1%	4.0%	24.8

*sustained 40% eGFR decline / eGFR <10 ml/min / ESKD

or

Results were consistent in patients with and without diabetes

Empagliflozin in Patients with Chronic Kidney Disease: The EMPA-KIDNEY Collaborative Group. Herrington WG, Staplin N, Wanner C, et al. N Engl J Med. 2022 Nov 4. doi: 10.1056/NEJMoa2204233

Conclusion: Among a wide range of patients with CKD who were at risk for progression, empagliflozin therapy led to a lower risk of progression of CKD or death from cardiovascular causes than placebo.

@brian_rifkin

Further reading

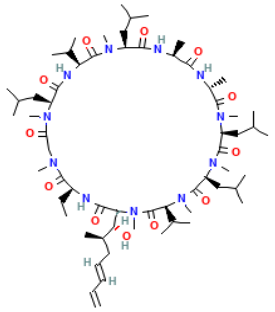
Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes | NEJM

Empagliflozin in chronic kidney disease: nephroprotection is independent of albuminuria, primary kidney disease, and baseline eGFR - The Lancet Diabetes & Endocrinology

Impact of primary kidney disease on the effects of empagliflozin in patients with chronic kidney disease: secondary analyses of the EMPA-KIDNEY trial - PubMed (nih.gov)

Effects of empagliflozin on progression of chronic kidney disease: a prespecified secondary analysis from the empa-kidney trial - ScienceDirect

E&T RPG sub-group Mar 2024



Voclosporin

a novel calcineurin inhibitor for the treatment of adults with lupus nephritis

Medication details

A novel calcineurin inhibitor for the treatment of adults with lupus nephritis, used in combination with MMF and low dose steroids.

Dose

- 23.7mg twice daily, taken as 3x7.9mg caps (can be taken with or without food)

Eligibility

- Active class 3,4 or 5 lupus nephritis – needs blueteq
- eGFR >30 (voclosporin has not been studied in eGFR <30 and should only be used where benefit > risk)
- Age <75
- Used in combination with MMF for 9-12 months

Monitoring

- Baseline eGFR, reassess every two weeks for the first month, and every four weeks thereafter. Adjust dose if eGFR falls by >20% or is <60ml/min as follows:

EGFR reduction from baseline	Recommendation
≥ 30% reduction	Stop voclosporin. Restart once eGFR recovered at 7.9mg BD. Increase as tolerated
> 20 % and < 30 % reduction	Reduce voclosporin by 7.9mg BD. Recheck in two weeks; if eGFR not recovered, reduce by further 7.9mg BD
≤ 20 % reduction	Maintain dose & monitor

Common side effects

- **Haemodynamic reduction in eGFR** is common (26.2% incidence) within the first four weeks; subsequently stabilises even if voclosporin continued (see dose adjustment above)
- **Hypertension** (19.1% incidence) – monitor BP fortnightly for first month, withhold voclosporin if BP >165/105
- **Infections** – viral and bacterial
- **Hyperkalaemia**

Hepatic impairment – not studied in severe impairment; avoid. Mild and moderate reduce starting dose to 15.8mg BD

Pregnancy and lactation – no data; avoid

Protein binding

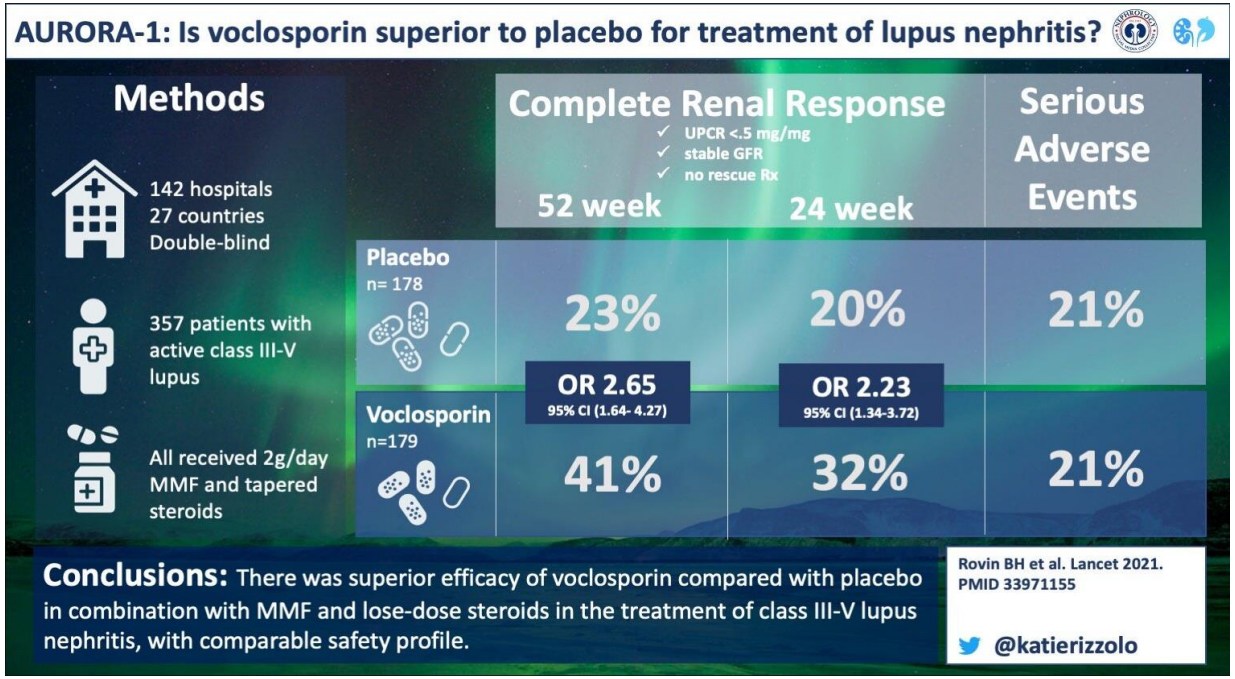
- 97%

Excretion

- Healthy population – 2.1% of the dose is excreted in urine - 92.7% via faecal excretion.

Drug Interactions

- Reduce voclosporin dose with moderate CYP450 inhibitors to 15.8mg mane, 7.9mg nocte
- Risk of QTc prolongation NB Hydroxychloroquine also prolongs QTc



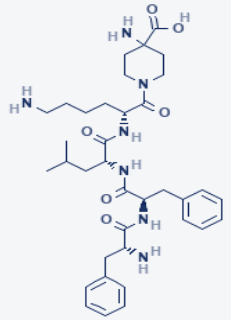
Further resources

- ✓ NICE TA 882 - Voclosporin with mycophenolate mofetil for treating lupus nephritis
- ✓ NHS discount via Commercial A
- ✓ Register patient with Blueteq
- ✓ SPC product information
- ✓ EMA product information
- ✓ Black triangle – Yellow Card AD reporting

Further Reading

Saxena A, Ginzler EM, Gibson K, et al. Safety and efficacy of long-term voclosporin treatment for lupus nephritis in the Phase 3 AURORA 2 clinical trial. *Arthritis Rheumatol*. 2023;10.1002/art.42657.

E&T RPG sub-group Jan 2024



Difelikefalin

"Dye fel" i "kef" a "lin"

$C_{36}H_{53}N_7O_6$ – an opioid peptide for itch in people with chronic kidney disease receiving haemodialysis

Medication details

- A novel, selective κ-opioid receptor agonist that works mainly by activating κ-opioid receptors on peripheral sensory neurons and immune cells

Dose

- 0.5**micrograms**/kg dry body weight (i.e., the target post-dialysis weight).

Administration

- 3 times per week by intravenous bolus injection into the venous line of the dialysis circuit at the end of the haemodialysis treatment during rinse-back or after rinse-back**. – once blood has stopped.**

Common side effects (usually mild/moderate)

- affect up to 1 in 10 people - sleepiness and paraesthesia.
- affect up to 1 in 100 people - dizziness, headache, nausea, vomiting, diarrhoea and mental status changes (including confusion).

Cautions / Contra-indications

- **Hyperkalaemia** – slightly high rates in difelikefalin treated group in RCT
- **Cardiac failure and arrhythmias** – higher rates of CCF and AF in difelikefalin treated group. NYHA class IV excluded from trials.
- **Impaired blood brain barrier** – opioid might enter CNS e.g. primary brain malignancies, CNS metastases or CNS inflammatory conditions, active multiple sclerosis, advanced Alzheimer's disease.
- Taking **sedating antihistamines**, **opioid analgesics** or other **CNS depressants e.g clonidine, ondansetron, gabapentin, pregabalin, zolpidem, alprazolam, sertraline, trazodone** – risk of dizziness and somnolence increased.
- Severe hepatic impairment – not studied, metabolism maybe impaired.
- Pregnant and lactating women – no data

Driving or Operating Machinery

- Must advise cautioned about driving or operating hazardous machinery until the effect of difelikefalin on the patient's ability to drive or operate machinery is known. Somnolence tends to occur within 1st 3 weeks of treatment and to subside. Dizziness occurs within 1st 9 weeks of treatment and is generally transient.

Volume of Distribution

- 145 to 189 mL/kg in healthy subjects and from 214 to 301 mL/kg in haemodialysis patients with moderate-to-severe pruritus.

Protein binding

- 24 – 32% - low to moderate

Excretion

- Healthy population - 81% of the dose is excreted in urine - 11% via faecal excretion.
- HD population - 59% eliminated via faeces; about 19% were recovered in dialysate and about 11% were found in urine.
- Haemodialysis for 4 hours using a high-flux dialyzer effectively cleared approximately 70-80% of difelikefalin from plasma.

Metabolism

- minimal

Safety and efficacy of difelikefalin for the treatment of CKD-associated pruritus in patients on hemodialysis

Kidney Medicine

Phase 3 RCTs
KALM-1 & KALM-2
12 weeks (N = 851)

Open label supportive studies
CLIN 3101 & CLIN 3105
54 weeks (N = 1,306)

Adults on hemodialysis with **moderate-to-severe CKD-associated pruritus** (CKD-aP)

Clinically meaningful improvements in:

	Itch intensity ≥ 3-point ↓ of WI-NRS* at 12 weeks	Itch-related QOL ≥ 15-point ↓ of Skindex-10 at 12 weeks	Itch-related QOL ≥ 5-point ↓ of 5-D Itch at 12 weeks**
Difelikefalin 0.5 mcg/kg IV x3/week	51%	55%	52%
1:1	P < 0.001	P < 0.001	P = 0.01
Placebo	35%	40%	42%

*WI-NRS - Worst Itching Intensity Numerical Rating Scale; **Effect maintained > 64 weeks

Adverse events

Placebo-controlled cohort, AEs mostly mild-to-moderate

	Placebo	Difelikefalin
Diarrhea	5.7%	9.0%
Dizziness	3.8%	6.8%
Nausea	4.5%	6.6%
Gait disturbance	5.4%	6.6%
Hyperkalemia	3.5%	4.7%
Headache	2.6%	4.5%

Conclusion: Results from the pooled KALM studies show rapid and sustained efficacy of difelikefalin for the treatment of CKD-aP in patients treated by hemodialysis. Difelikefalin demonstrated an acceptable safety profile and was well tolerated with long-term use.

References: (1) Topf J, Wooldridge T, McCafferty K, et al. Efficacy of difelikefalin for the treatment of moderate-to-severe pruritus in hemodialysis patients: pooled analysis of KALM-1 and KALM-2 phase 3 studies. **(2)** Fishbane S, Wen W, Munera C, et al. Safety and tolerability of difelikefalin for the treatment of moderate-to-severe pruritus in hemodialysis patients: pooled analysis from the phase 3 clinical trial program. *Kidney Medicine*, 2022.

VA by @CTeodosiu

Checklist – hyperlinks to further resources

- ✓ NICE TA 890 - Pruritus in adults with chronic kidney disease having haemodialysis
- ✓ Register patient with Blueteq
- ✓ WI-NRS itch scores used by Blueteq
- ✓ Itch Scores used in Kalm-1 & Kalm-2
- ✓ SPC product information
- ✓ EMA product information
- ✓ Black triangle - Yellow Card ADR reporting

Further Reading

Rajiv Agarwal, James Burton, Maurizio Gallieni, Kamyar Kalantar-Zadeh, Gert Mayer, Carol Pollock, Jacek C Szepietowski, Alleviating symptoms in patients undergoing long-term hemodialysis: a focus on chronic kidney disease-associated pruritus, Clinical Kidney Journal, Volume 16, Issue 1, January 2023, Pages 30–40,

UKKA

E&T RPG sub-group Nov

Q&A Themes - Renal

- Hydroxychloroquine levels for lupus – levels for adherence at Imperial
- Patient survey around polypharmacy
- Opening avacopan capsules – difficult to administer via NGT, opening caps and dispersing ~ 10mins will result in dispersion but not supported by SPC. Info on RDD monograph is updated to reflect this. Any further experience please share
- Finerenone formulary status – work to try and get to green status but variable across ICBs. Olivia happy to help if needed
- Hep B vaccination if history of Hep C and detected HCV – hepatology advise is definitely to vaccinate
- Tolvaptan bloods and supply for long trip aboard
- PCP prophylaxis in septrin allergy
- Bisphosphonates in CKD
- PCP prophylaxis with rituximab for membranous nephropathy

Q&A Themes - Dialysis

- Vitamin k dosing in calciphylaxis
- Roxadustat for HD patient – funding
- IVIG administration on dialysis
- Levetiracetam dosing on HD – post HD on dialysis days
- Gentamicin eye drops around PD sites – there is an unlicensed gentamicin cream which works well at NBT
- Daptomycin IP for VRE peritonitis in PD – Royal Free have experience, based on info from ISPD guidelines
- Laxatives for PD patients
- BP monitoring in patients receiving EPO
- Daptomycin for line locks
- Daptomycin larger doses over 72 hour interval – yes, extra 2 mg/kg then send levels. PG to link in with Aileen to add to RDD monograph
- EPO dose adjustments in multiple amputations
- Sodium thiosulfate in 4 x weekly dialysis
- Diafer in home HD patients

Q&A Themes - Transplant

- Vaccinating patients on transplant waiting list for VZV (chicken pox) on dialysis
- Advice switching from ciclosporin to advagraf
- Crushing advice for sirolimus down NG
- Cytotect (Biotest) CMV 1 g as part of imlifidase protocol
- Ciclosporin sublingual – no, use liquid

Q&A – New Qu

- Rachna - European Society of transplantation (ESOT) conference in London in 2025.
  - Open to pharmacist members but EU experience is v different to the UK
  - Drive for pharmacy abstracts to reflect the UK experience
  - All submissions would be valuable – consider our everyday practise/case studies as well as bigger projects
  - All submissions from RPG/SOTPA can be resubmitted

Q&A – New Qu

- Question on switching from Advagraf to Dailiport as regional switch
  - Plan for enhanced monitoring and pt info

Q&A – New Qu

- New medication slides available on E&T section of RPG site, ? Plans to circulate more widely ?

Q&A – New Qu

- Vasculitis patients receiving methotrexate – do you use co-trimox as PCP prophylaxis
  - May depend on dose of MTX ? Ok with low dose but poor quality evidence
  - Other options available so likely not seen much.

Q&A – New Qu

- Vanc or gent in HD – request for guidelines to be sent to Nicola at Norwich Nicola.korn@nnuh.nhs.uk

March Q&A - Close

Thank you for attending!

Next Q&A: Tuesday 21st May

Keep in touch throughout the month on **WhatsApp Q&A Group**

- >100 participants throughout UK and Ireland
- Useful real time forum for clinical Q's
- Please consider joining!


UKRPG