Challenges of treating CMV in OPAT

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Guy's and St Thomas' NHS Foundation Trust

Oct 2022

Result in virology queue

– CMV viral load 8943 IU/ml (log 3.95)

Why was the test sent?

62M

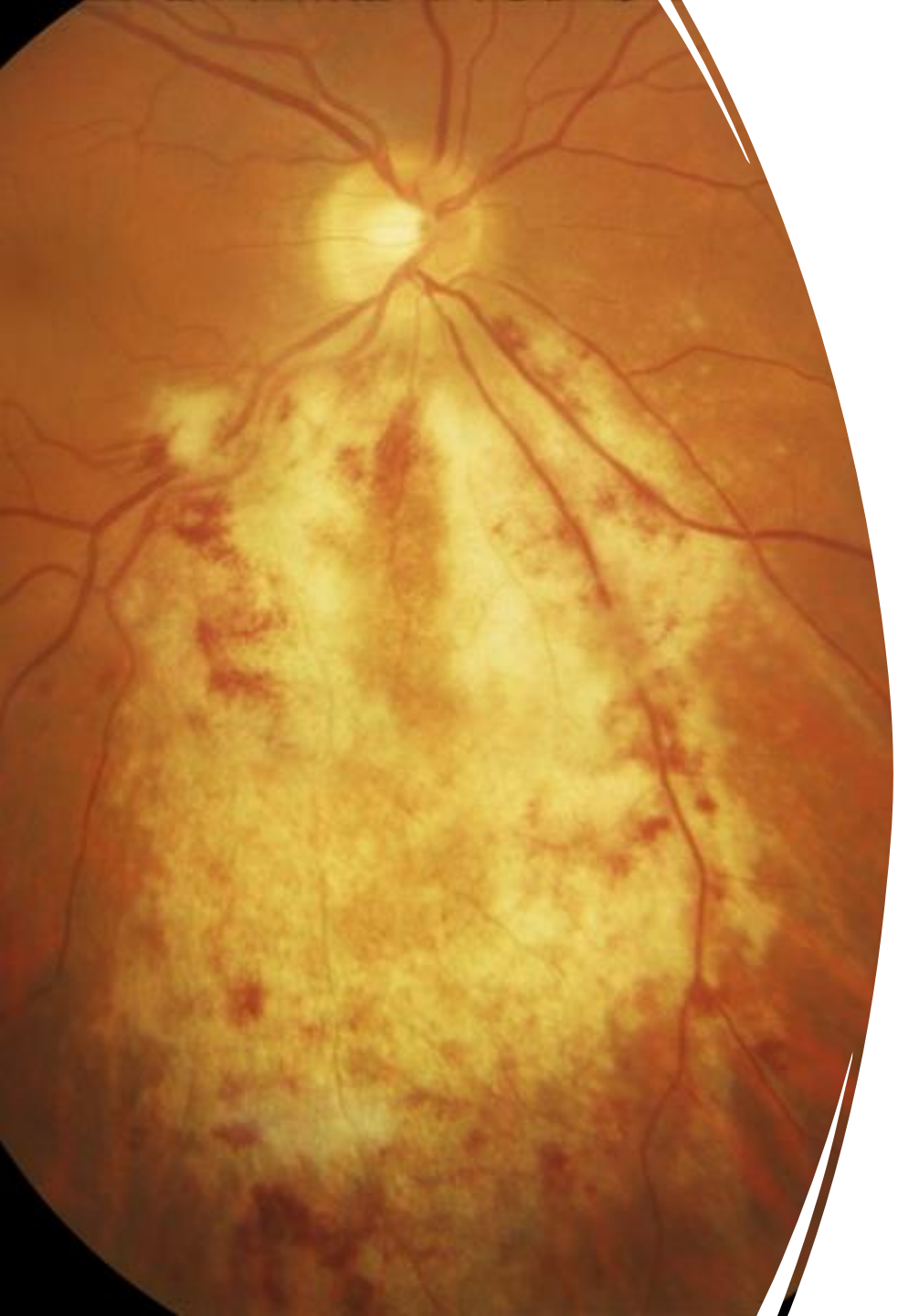
- Under regular review in haematology clinic for monitoring of a MALT lymphoma
- Significant weight loss from ~76kg to 61kg – now appears ‘gaunt’
- Loose stools in addition; initially intermittent
- Otherwise keeps active, still working, playing golf

PMHx

- Thymoma (resected 2005)
- Previous granulocytosis and Pure Red Cell Aplasia following resection
- MALT lymphoma resected through left partial pneumonectomy (2009)
  - No anti-lymphoma treatment since that time
- Oral lichen planus – previously on MMF and prednisolone
- Bronchiectasis
- Prostate cancer (2020) - robotic prostatectomy complicated by need for laparotomy due to bowel torsion (private sector; Jan 2021)

And…

- CMV retinitis



APRIL 2015

- Presents to eye casualty with 6/18 vision in the right eye, unchanged from his last visit. The left vision was 6/6, but he describes as shadow going across his vision
- On examination:
  - Old keratitic precipitates.
  - He had +1 of cells with debris in the right vitreous with a very occasional cell in the left vitreous.
  - In the right retina he had some small pale lesions adjacent to the fovea and a cotton wool spot along the supero-nasal arcade.
  - An OCT shows some thinning and oedema.
  - In the left eye, the lesion previously seen adjacent to his macula has increased in size.
- Presumed fungal endophthalmitis (whilst on fluconazole prophylaxis)

Results from ophthalmology department

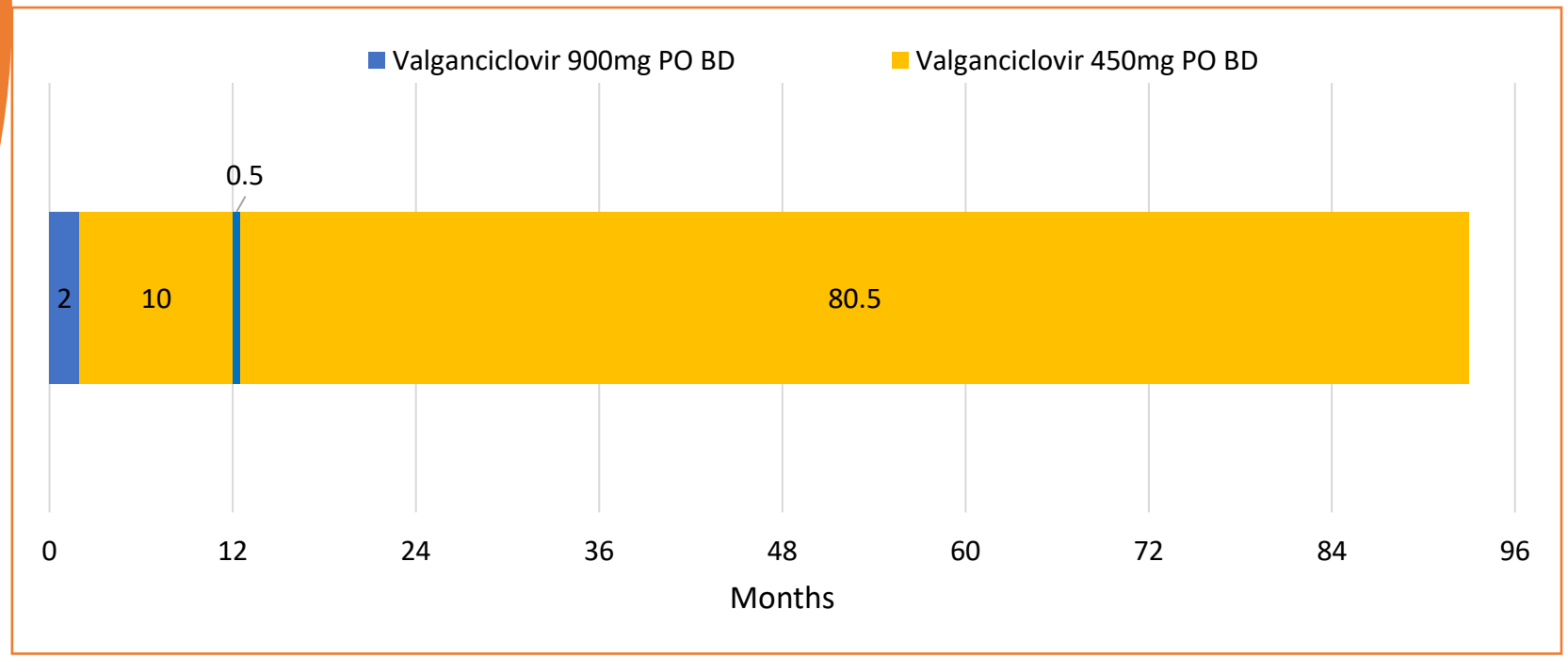
- CrAg negative
- Toxo serology negative
- Syphilis Ab negative
- Undergoes vitreous biopsy
  - MCS: No pus/organisms on gram. NG at 5 days and on Sab.
  - PCR: HSV, VZV, Toxo, JC negative. Pan-fungal PCR negative
  - CMV PCR positive

Initial Management

- **April 2015:** Started on valganciclovir 900mg PO BD reduced to 450mg PO BD after 6 weeks + steroid eye drops.
- **July – Sept 2015:** slowly improving. Decision to keep on valganciclovir 450mg PO BD for 6 months along with intermittent intravitreal triamcinolone.
- **December 2015:** over the Christmas week - his visual acuity dropped most noticeably in his left eye. Further intraviteal steroid injection given. Reactivation suspected and valganciclovir dose increased to 900mg PO BD.
- **February 2016:** Intravitreal foscarnet
- **March 2016:** Evidence of retinitis near the fovea now cleared but he continues to have loss of the retina around the macula, which has left him with a central scotoma. Valganciclovir continued 450mg PO BD
- **October 2016:** MMF stopped and prednisolone weaned

Mid 2016-Oct 2022

- **March 2016- March 2020:** Remained overall stable on valganciclovir 450mg PO BD
- **March 2020:** more blurring and increased floaters in his left eye Watch and wait. Remained on valganciclovir 450mg PO BD
- **August 2022:** plan to reduce dose to 450mg OD
- **Throughout this period; no CMV viral loads sent**



Back to 2022

To recap

- 62M with background of previous CMV retinitis
- Not currently on immunosuppressant medication
- On valganciclovir 450mg PO BD
- Now presenting with 10-15kg weight loss
- CMV viraemia – 8943 IU/ml (log 3.95)

Further investigations – imaging

CT Chest/Abdo/Pelvis:

- No suspicious abnormality demonstrated.
- Longstanding mild splenomegaly

OGD

- Small area of mild fading of pit pattern - bxs taken for reassurance. No obvious features of malignancy. Otherwise NAD
- Histopathology: Acute and chronic inflammation and CMV infection, collagenous duodenitis

Colonoscopy

- Normal study
- Histopathology: mild melanosis coli only

Virology advice Oct 2022

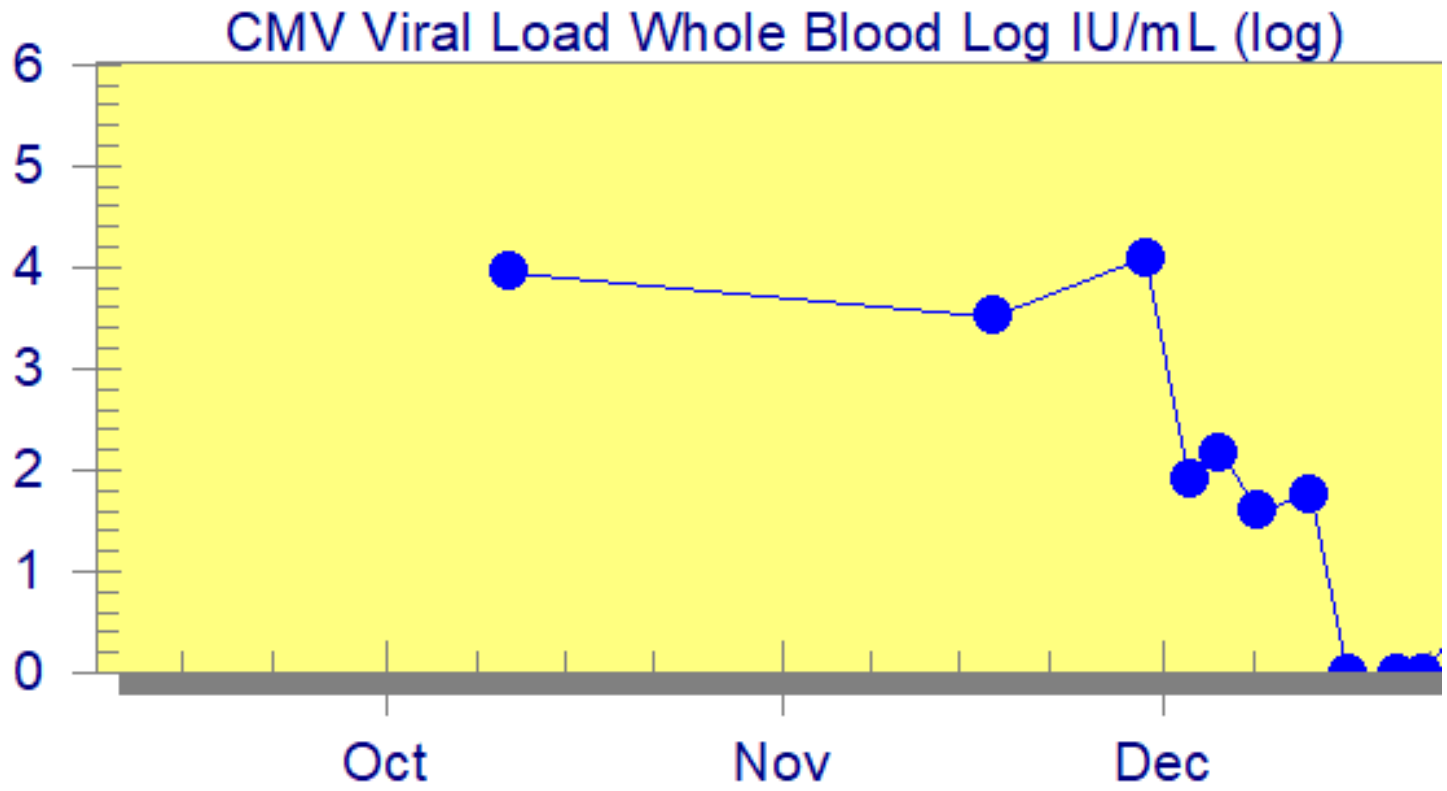
- Increase valganciclovir to treatment dose – 900mg PO BD
- Repeat HIV, lymphocyte subsets, repeat CMV viral load, immunoglobulins
- Check adherence
- **Resistance testing**

Resistance testing

- CMV resistance Gene UL97 : Resistant
- CMV resistance Gene UL54 : Resistant
- The A594V mutation conferring resistance to ganciclovir was detected in the UL97 gene.
- The P522A mutation conferring low level resistance to ganciclovir and cidofovir was detected in the UL54 gene.
- This CMV strain is RESISTANT to ganciclovir, has low level resistance to cidofovir and is SENSITIVE to foscarnet

November 2022 - Admitted for foscarnet

- Received treatment dose foscarnet IV for 3 weeks
- Ophthalmology review as inpatient – no signs active
- Stool work up performed
  - Bacterial PCR, Adeno, Entero, C diff, OCP x 3 negative
  - **Norovirus positive**
- BBV and HTLV negative
- Discharge: valganciclovir 900mg PO BD and repeat viral load



Recovery of Wild-Type Genotype after Documented Ganciclovir-Resistance in Transplant Recipients with Recurrent CMV Viremia

J. Fose, M. Jorgenson, Z. Degrave, R. Redfield, J. Smith, D. Mandelbrot.

University of Wisconsin Hospital, Madison
University of Wisconsin School of Medicine and Public Health, Madison.

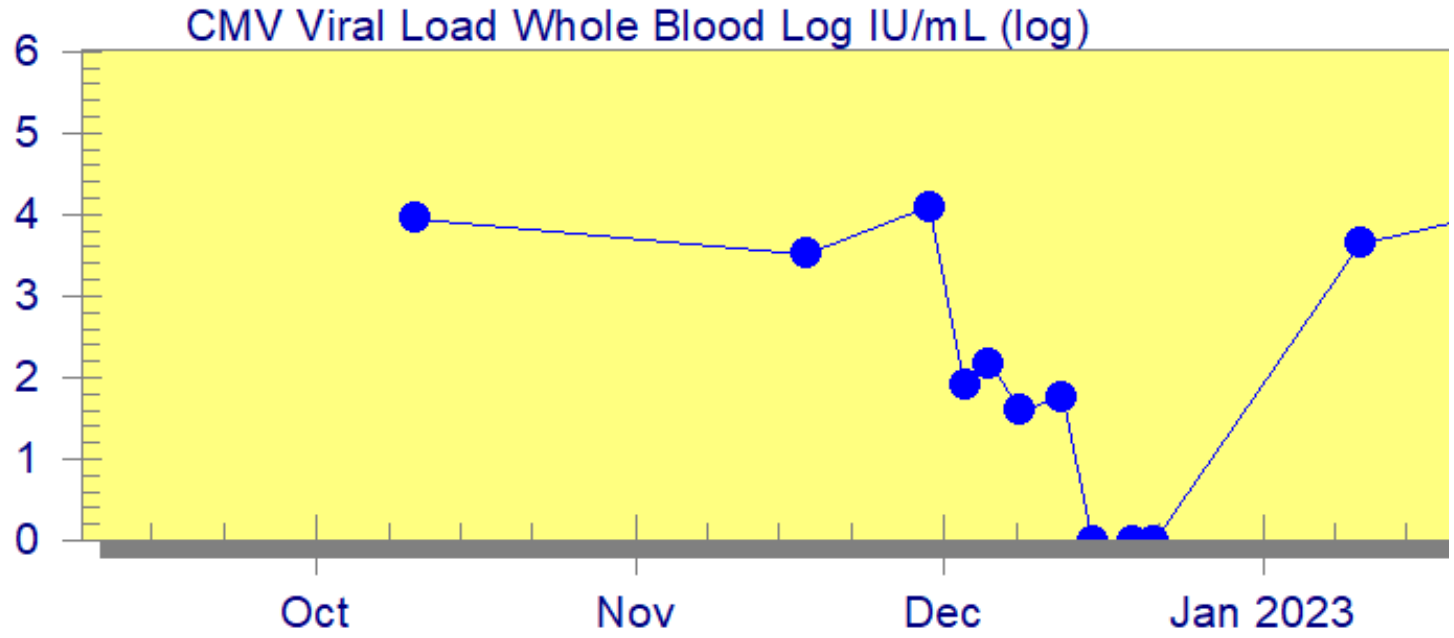
Meeting: 2018 American Transplant Congress

Abstract number: A171

Keywords: Cytomeglovirus, Ganciclovir, Infection, Recurrence

Am J Transplant. 2017;17 (suppl 3).

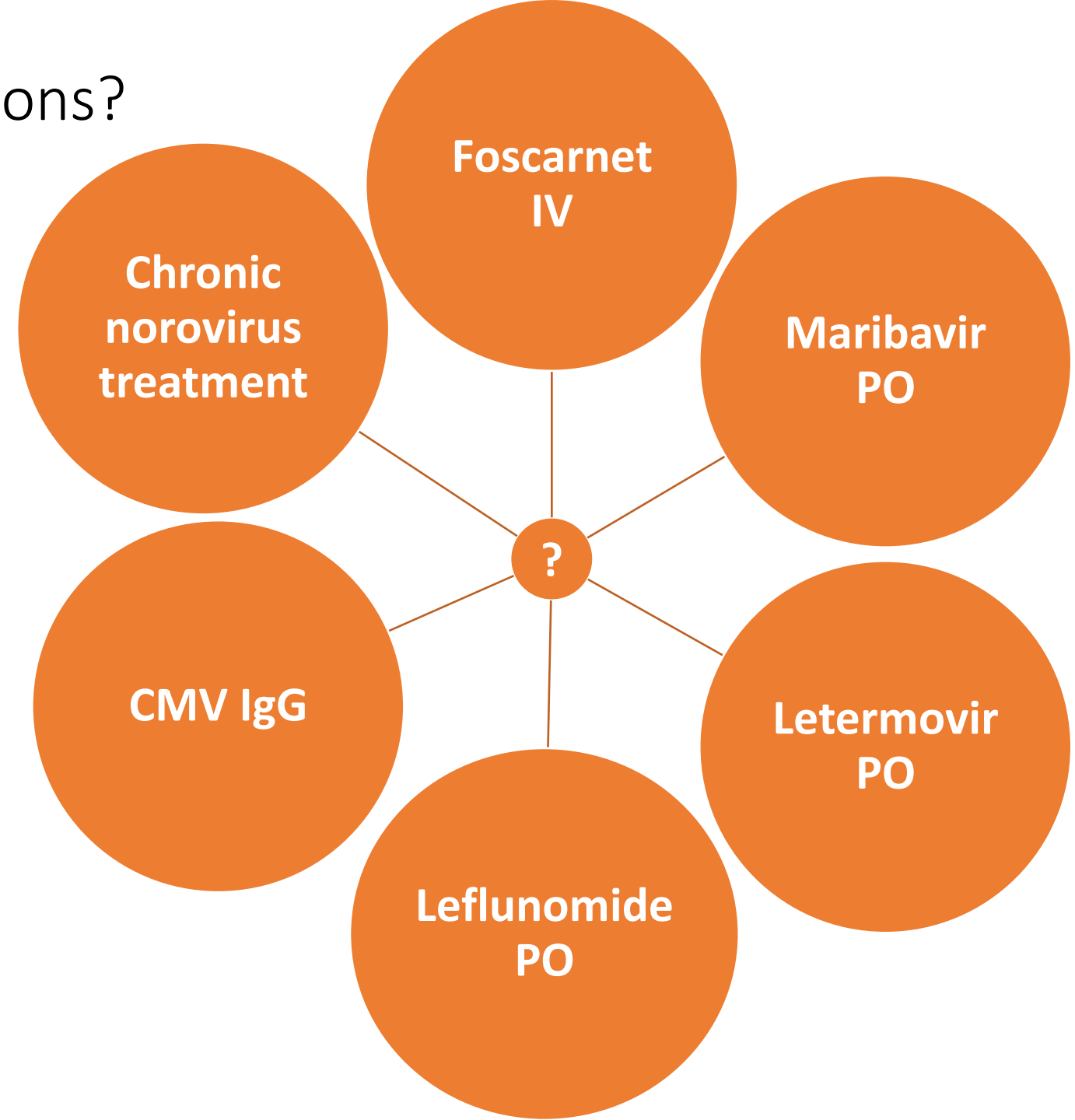
January 2023



Norovirus RNA.	DETECTED

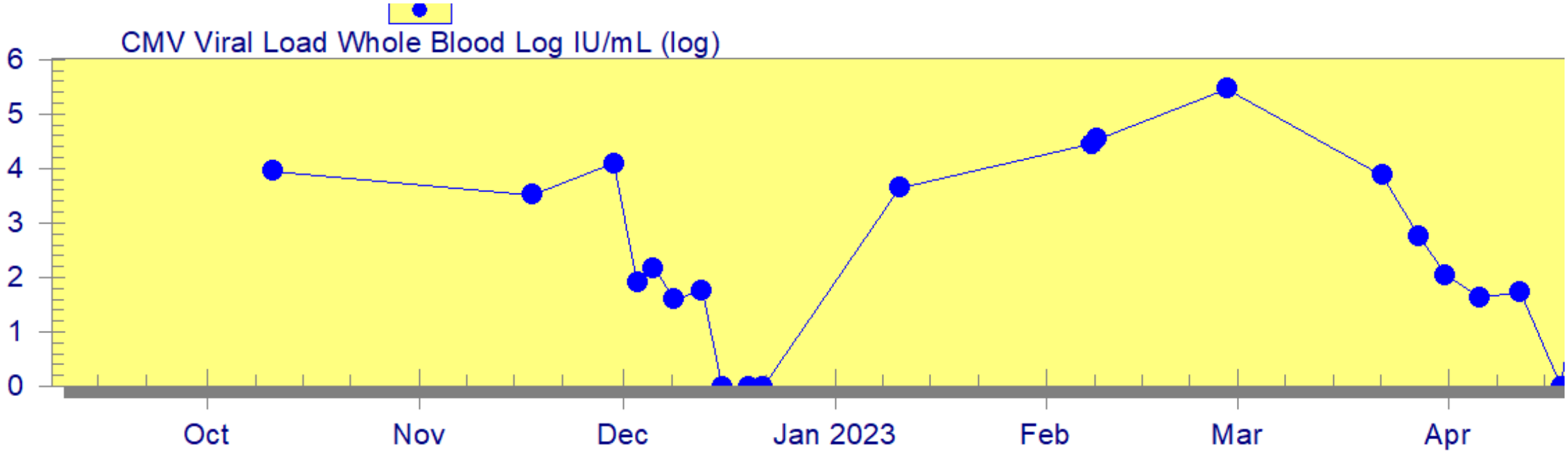
(Click to expand)

Treatment options?



Readmission March-April 2023

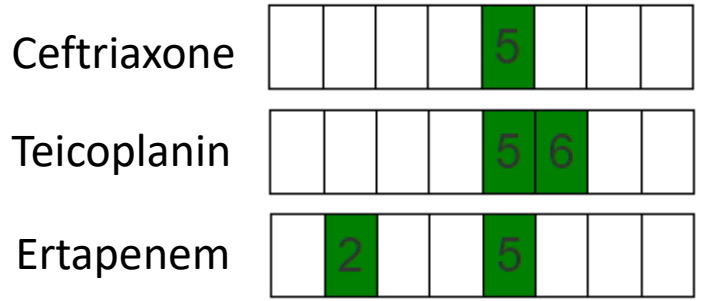
- Foscarnet 3200mg (55mg/kg) IV TDS
  - Adjusted for renal function



Immunology

- Unspecified immunological disorder
- Initially Good syndrome following thymoma - Good syndrome is a rare cause of combined B- and T-cell immunodeficiency that occurs in association with a thymoma. Patients affected with Good syndrome have increased susceptibility to bacterial, fungal, viral, and opportunistic infections.
- Most recent update from Immunology - CMV specific immunoglobulin (B-cell line) defect but reasonable T cell response. uncharacterised immunological condition.

Is foscarnet OPAT-able?



- Is it safe?

TOTAL RISK FACTORS: 6

  - Risk assessment
    - Therapeutic risk (hydration, risk of rapid infusion, electrolyte disturbance)
    - Part vial and complex calculation
      - 6g in 250mL glass bottles
    - Complex method, dilution usually required
    - Use of infusion pump
  - PPE: ideally manipulation in aseptic unit. PPE required if not.
- Suitable regimen?
  - TDS, possibly BD
  - Max infusion rate 1mg/kg/minute, each infusion >1 hour (infusion pump)
- Who?
  - District Nurses
  - Self/carer administration

Foscarnet via OPAT

- Options
  - Patient/nurse manipulation not considered safe
  - No commercially available product in closed system which would reduce risk
  - **Could our aseptic unit support with preparing foscarnet in a closed system under section 10?**
- Development of new product with pharmacy aseptics
  - Finding the right device for volume and rate→ Baxter LV100 device used
  - Prepare master worksheet for filling chosen device
  - Under filling infusor devices- in-house infusion rate testing with saline QA risk assessment
  - Microbiology testing: need 2 week broth test
  - Long and costly process
- Plan to discharge after 2 weeks of treatment dose foscarnet
  - 1 more week treatment dose (90mg/kg BD) via elastomeric pump
  - 3 weeks maintenance dose (60-120mg/kg OD) via elastomeric pump

Governance and financial approval

- Governance approval
  - Use of infusor devices and off-label dose of 90mg/kg BD
  - Quality Assurance approval of worksheets, risk assessment and change control

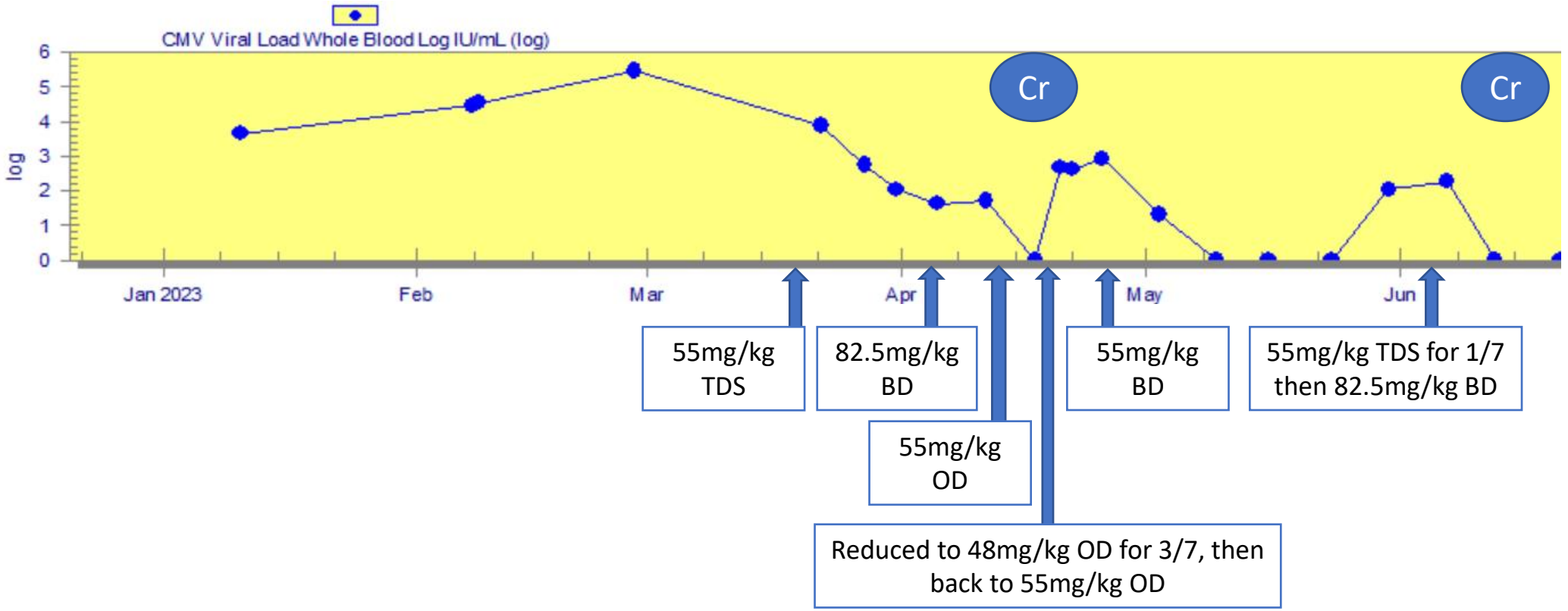
- Financial approval
  - Cost of infusor devices for 4 weeks approved (++++)
  - Inpatient bed day vs OPAT bed day

Monitoring

- Weekly bloods, usually taken by OPAT nurse
  - FBC
  - U+Es
  - Renal
  - Liver
  - CRP
  - Bone Profile
  - Magnesium
  - CMV viral load
- Weekly ECG

Monitoring and dose adjustments

- QTc ~460 → azithromycin (ind: bronchiectasis) held
- Required oral phosphate replacement throughout foscarnet course
- Dose amended multiple times due to renal function and CMV viral load



Challenges

- Manufacture
  - Aseptic team capacity
    - Half a day to prepare 12 infusors
    - Needed to manage this workload with other manufacturing demands
  - Pre-order day before manufacture then confirming once blood results available
  - Unable to action dose changes quickly due to manufacture time
  - 7 day expiry as made under section 10. Maximum order = 6 days, so needed more frequent hospital visits or courier at additional cost
- Cost
  - Batches of 12 devices preferred due to infusor pack size and cost of this
  - Increase in maintenance dose to BD incurred double costs, needed financial approval
- Patient
  - Chlorhexidine allergies/PICC line care

What went well?

- Engaged patient
  - Multiple hospital visits for bloods/OPAT clinic/collect infusors
  - Local, public transport
- Tolerated infusions with oral hydration
  - 500ml water before each infusion
- Safe self-administration
- Patient could continue going to work
- Aseptic filling of devices
  - Reduced wastage (1x 6g/250ml bottle to fill multiple infusors)

Next steps

- Letermovir and maribavir compassionate use rejected
- Maribavir
  - NHSE IFR rejected
  - Trust agreed funding for 3 months to bridge until outcome of immunology testing

? Leflunomide

? CMV IVIG

? T-cell therapy or bone marrow transplant- awaiting results of further immunology testing

Thank you to:

- St Thomas' Hospital Aseptic Pharmacy Team
- GSTT Virology, OPAT and ID Pharmacy teams