Facing down COVID

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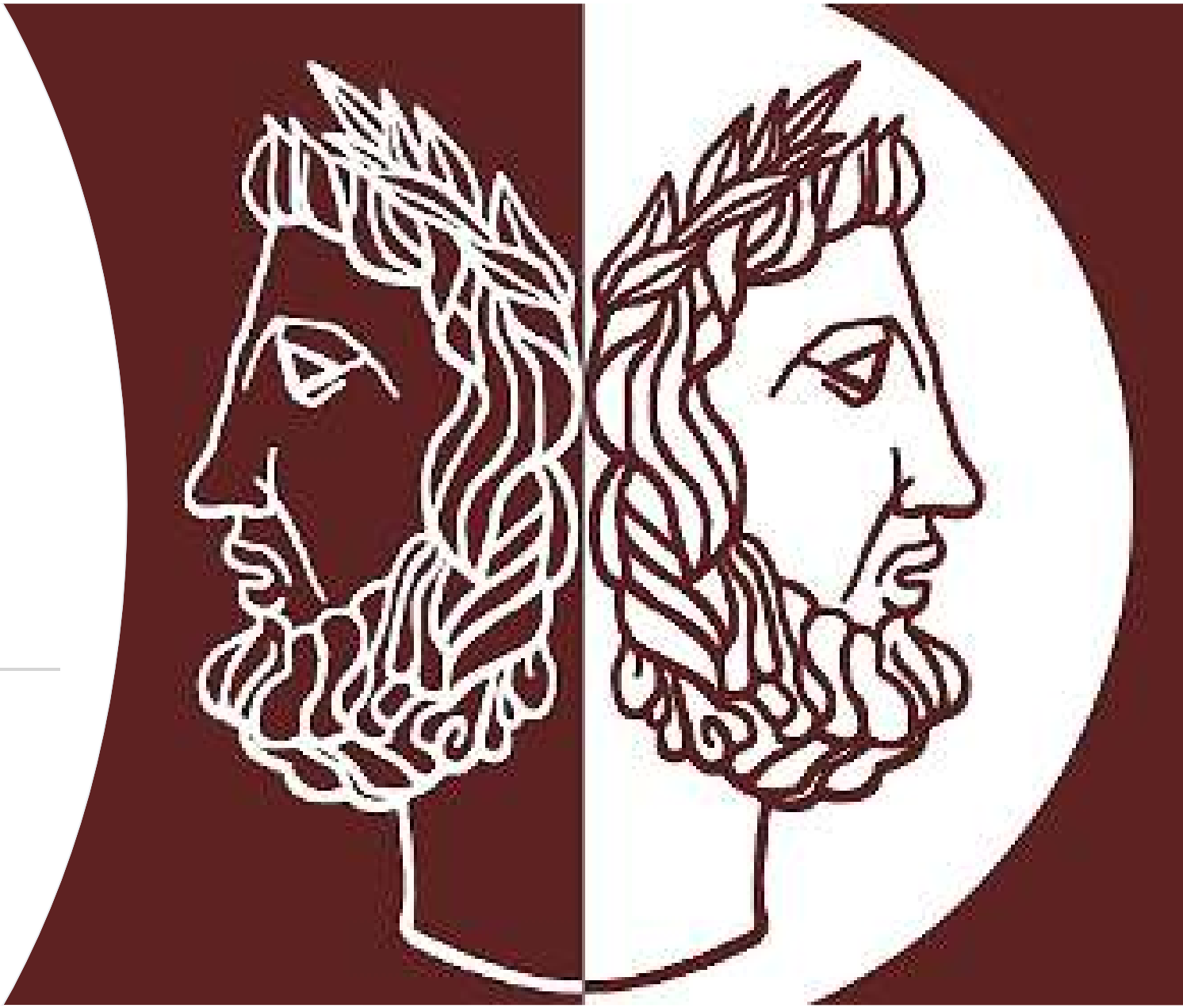
Frances Hall

Rheumatology



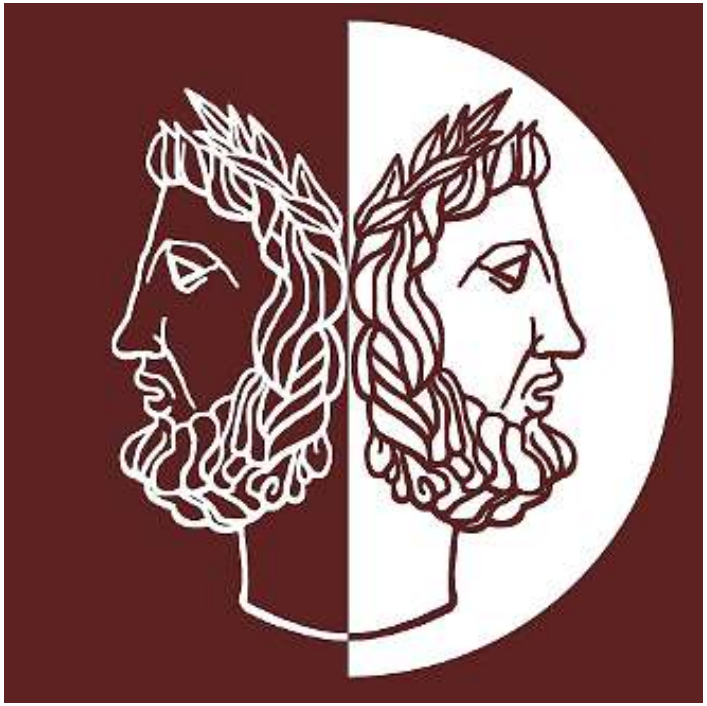
NF, male, 58 years, airline pilot for Ryanair

PMHx:

- Sleep apnoea (on CPAP)
- Obesity (BMI 33.2)
- Hypercholesterolemia

Medication: simvastatin 20 mg OD

Normally fit and well
Occasional alcohol; non-smoker



Day 0: at home

- intermittent fevers; generally unwell; fatigue
- wife and son also symptomatic

- COVID swab +ve in the community at Day 2 after symptoms' onset
- self-isolating at home

Day 10: ED → hospital admission

- Shortness of breath
- Cough
- Confusion
- Pyrexia
- Fatigue

SYMPTOMS

- BP: 115/67
- HR 120
- Temp: 39.8 °C
- RR: 23
- Chest - decreased AE both bases with fine crepitations
- SpO2: 92% on 10L/min oxygen

EXAMINATION
VITALS

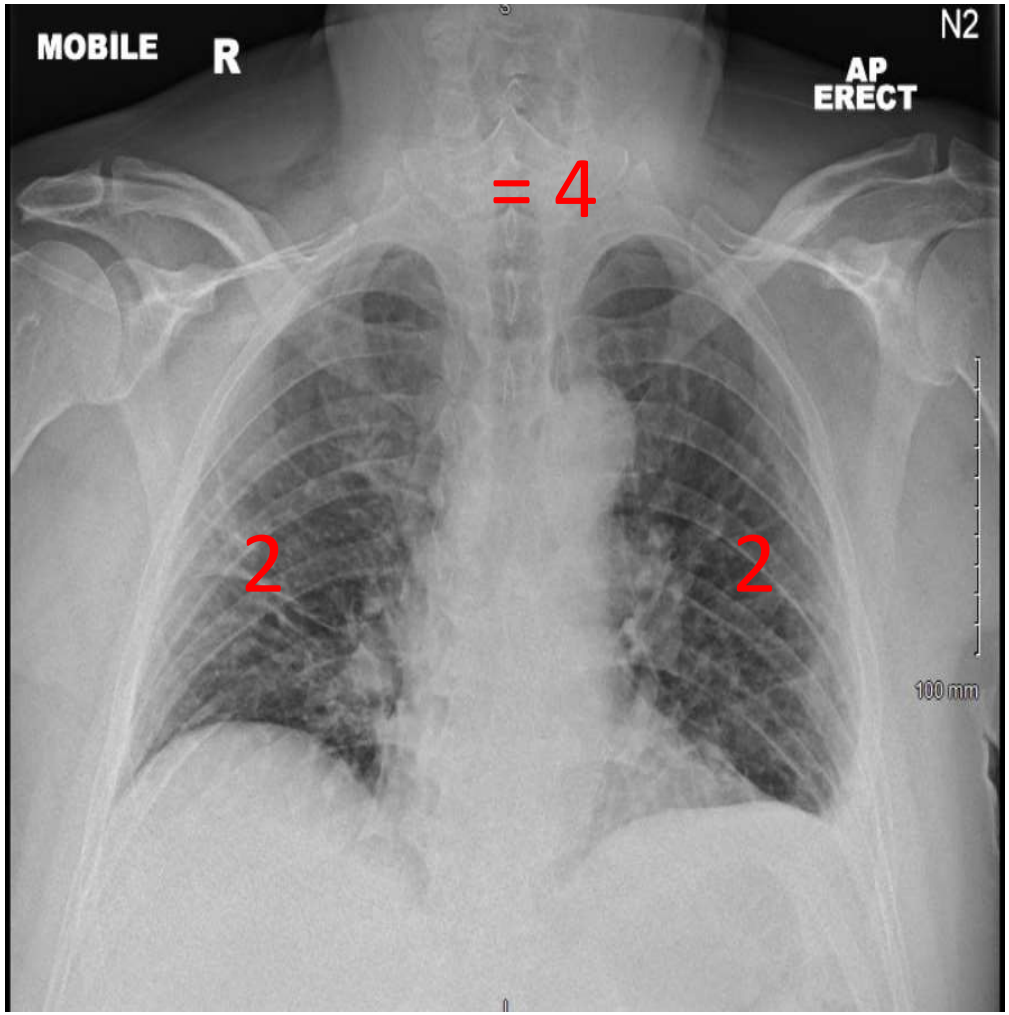
Day 10: ED → hospital admission

Blood test	Value
Hb (g/L)	156
WBC *10^9/L	8.7
Neutrophils*10^9/L	7.63
Lymphocytes *10^9/L	0.58
PLT *10^9/L	143
CRP (mg/L)	89
ALT (U/L)	55
Creatinine (umol/L)	89

Blood gas
- pH=7.47
- pCO2= 4; pO2=8.3

Blood test	Range	Value
TNF Alpha (pg/ml)	0.00 - 5.00	8.84
Interleukin-1 Beta (pg/ml)	0.00 - 3.10	0.92
Interleukin-10 (pg/ml)	0.00 - 1.00	2.58
Interferon Gamma (pg/ml)	<=10.00	<0.94
Interleukin-6 (pg/ml)	0.00 - 2.00	1.09
D-Dimer (ng/mL)	0 - 230	112
LD (U/L)	120 - 246	355
FGN (g/L)	1.46 - 3.33	5.20

Day 10: ED → hospital admission



COVID-19 pneumonitis Radiological severity score		
0	No involvement	extent of involvement by • consolidation or • ground glass opacities
1	< 25%	
2	25 - 49 %	
3	50 -75 %	
4	> 75 %	
Score 0 - 4 for each lung Score 0 – 8 final severity score (for both lungs)		

CTPA: No pulmonary embolus. Predominantly peripheral moderate ground glass opacities and atelectasis

Wong et al, Radiology 2020

Day 12: hospital admission

DAY 12

- No fever
- SpO2: 94 %
- On Venturi 15L (FiO2 60%)
- CRP 47 mg/L

✓ **Dexamethasone**

- Oral, tablets 6 mg OD, 10 days

✓ **Remdesivir**

- IV 200 mg in sodium chloride 0.9% 250 mL infusion – one dose
- IV 100 mg in sodium chloride 0.9% 250 mL infusion – every 24h, 4 doses

✓ **Thromboprophylaxis**

- SC, Dalteparin 7500 UI, daily

✓ **Antibiotic (co-amoxiclav)**

- IV 1.2 g every 8 h

TACTIC -R

Multi-Arm Therapeutic Study in Pre-ICU Patients Admitted with COVID-19 – Repurposed Drugs

3-arm open label, phase IV randomized controlled trial

baricitinib	ravulizumab	standard of care
• Oral, 4 mg OD, for 14 days • JAK inhibitor, used in RA	• IV, single dose, weight adjusted • inhibitor of C5 activation, used in PNH	• Dexamethasone and remdesivir permitted

Risk count – 1 point each for item
Radiographic severity score >3
Male gender
Non-white ethnicity
Diabetes
Hypertension
Neutrophils >8.0 10^9
Age >40 years
CRP >40 mg/L

Risk score >3
or ≥3 if Radiographic score included

Included: Patients at increased risk of developing severe COVID19 → high likelihood of benefit from immunomodulation (based on risk score)

https://www.camcovidtrials.net/
Galloway et al. J Infect 2020

TACTIC - R

Multi-Arm Therapeutic Study in Pre-ICU Patients Admitted with COVID-19 – Repurposed Drugs

Primary outcome measure:

Time to incidence (up to and including Day 14) of any of the following events, whichever comes first:

Death
Invasive mechanical ventilation
ECMO
Cardiovascular organ support (balloon pump or inotropes)
Renal failure (estimated creatinine clearance by Cockcroft-Gault formula)

Safety

- Serious adverse events (including SARs, SUSARs)
- Adverse events of special interest (AESIs):

➢ New infections requiring antimicrobials

➢ Venous thromboembolism

https://www.camcovidtrials.net/

TACTIC^{R}

*R*epurposing drugs to save lives

Day 12→ 13: hospital admission

DAY 12

SpO2: 94 %
On Venturi 15 L (FiO2 60%)

BARICITINIB
tablets, 4 mg OD,
14 days

DAY 13

Steroid induced diabetes

SpO2: 95 %
On Venturi 15L (FiO2 60%)

TACTIC R
Repurposing drugs to save lives

Day 14: ICU → Day 16: Ward

DAY 14

Transferred to ICU

for CPAP

Continues BARICITINIB

CPAP

FiO2: 60% → 30%

SpO2 95-96%

DAY 16

- SpO2: 95 %
- 3L oxygen on NC

(CPAP at night)

- CRP <4 mg/L
- ALT 109 U/L

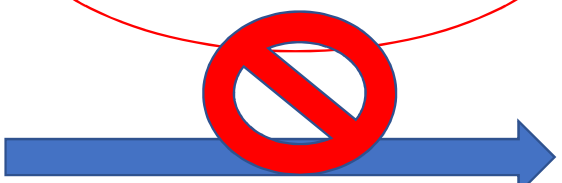
Day 22 → discharge

DAY 22

- Off oxygen
- Fit for discharge

- ALT 192 U/L

BARICITINIB
STOPPED
(10 days)



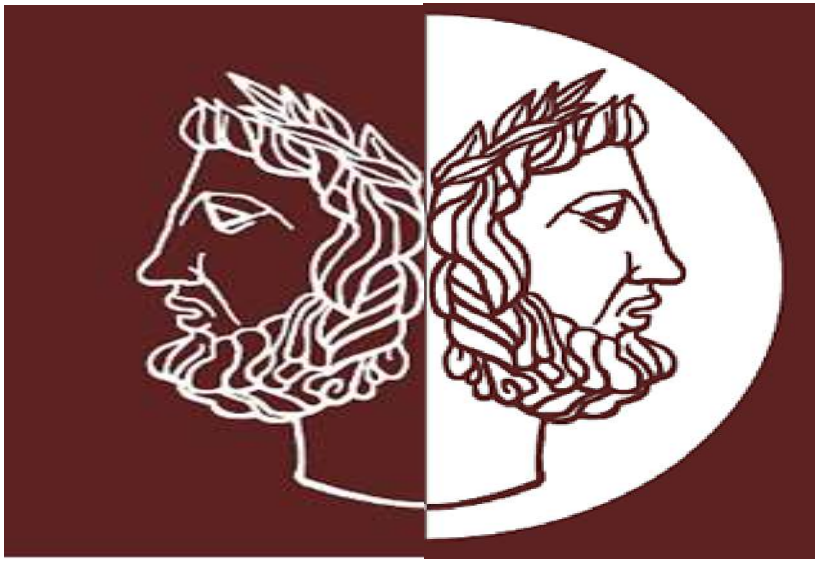
TACTIC R
Repurposing drugs to save lives

DAY 23
DISCHARGE

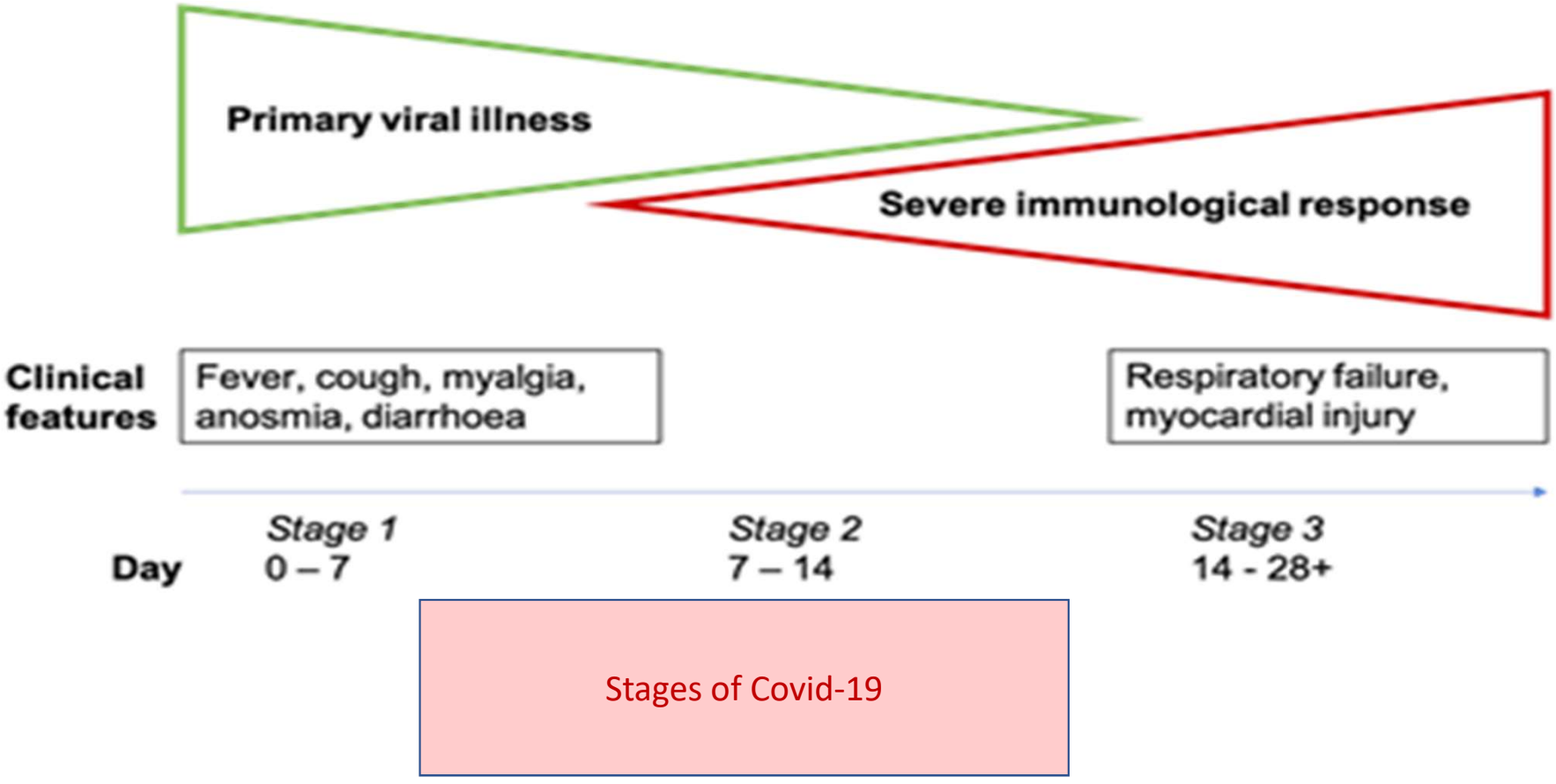
Rivaroxaban 10 mg, OD, 14 days
LFTs monitoring (GP)
DM community follow up

Baricitinib in Covid-19: rationale

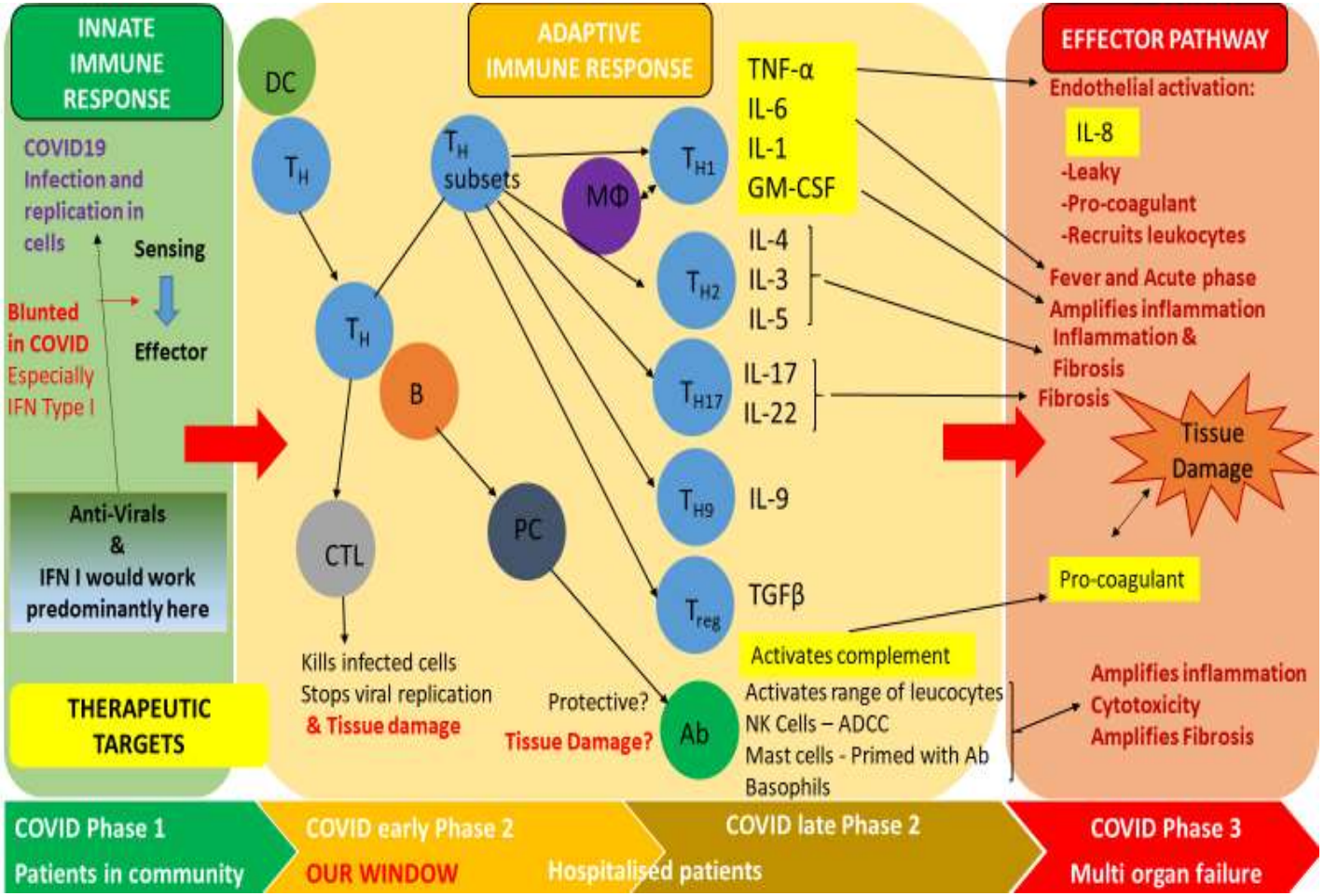
WHY ?



Stages of COVID-19



COVID-19 immunopathology



- 1. innate immune response
- 2. adaptative immune response
- 3. complement activation
- 4. endothelial dysfunction & prothrombotic status

From TACTIC-R protocol
https://www.camcovidtrials.net/

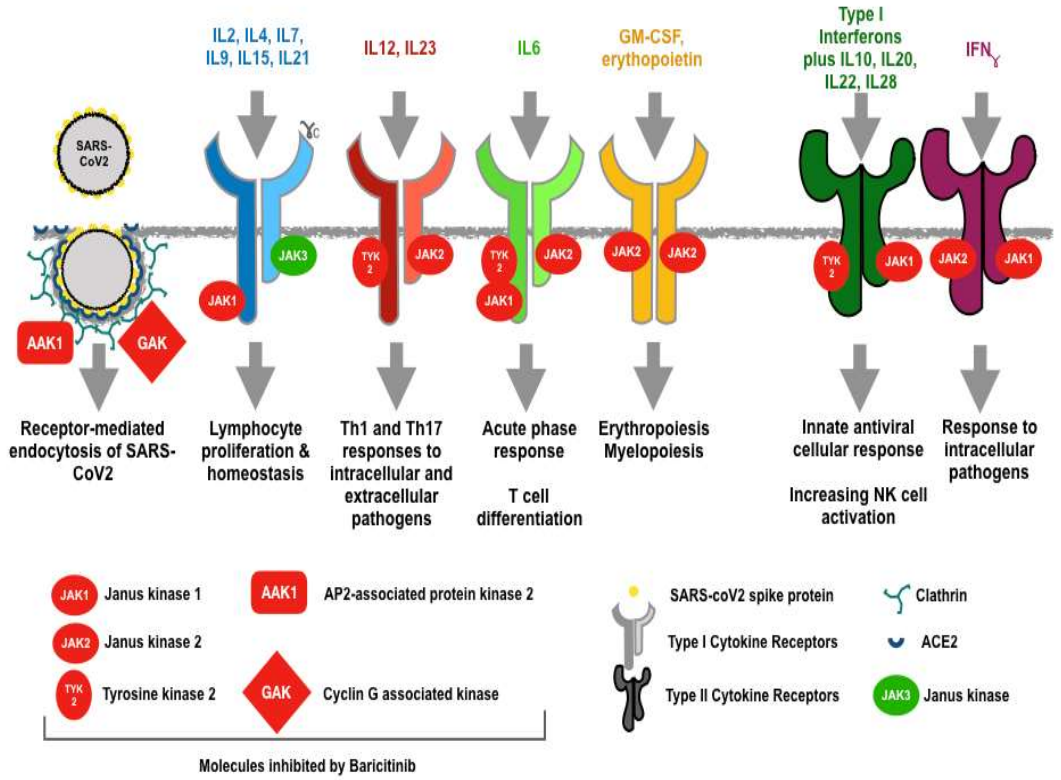
Baricitinib in Covid-19: rationale

Mechanism of action:

1) Janus Kinase inhibitor (JAKi)

- JAKi interfere with the JAK/STAT pathways as communication highways in the immune system, transducing signals through >50 cytokine and growth factor receptors
- inhibits multiple cytokine signalling pathways (IL6; Tyk2/Jak1 kinases; type I and II interferons)

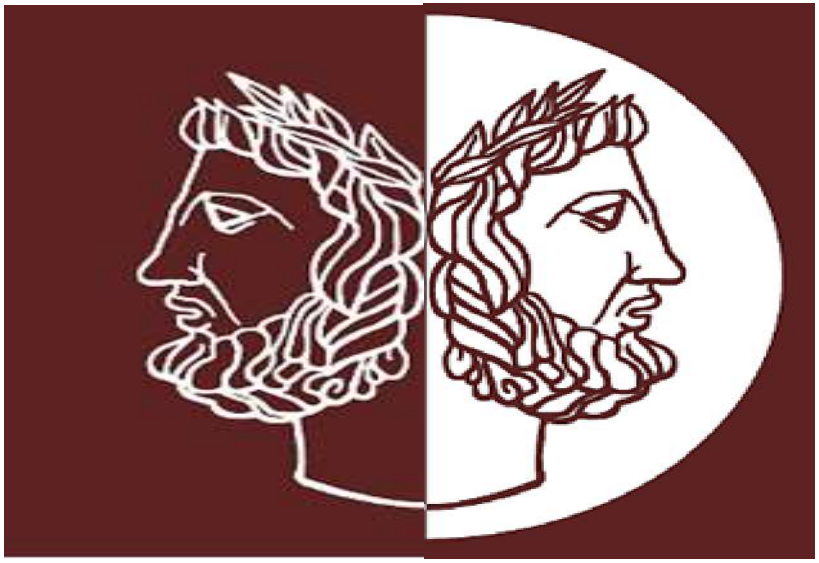
- 2) Baricitinib: direct antiviral effect: by inhibiting AAK1 and GAK -> inhibition of endocytosis -> prevents viral entry into cells



Gudu et al. Rheumatology 2020 (under peer review)

Baricitinib in Covid-19: concerns

WHY NOT ?



Baricitinib in Covid-19: concerns

INFECTIONS:

broad range of cytokine signals transduced via JAK1/2

could accelerate viral replication or increase risk of bacterial infection

BUT:

- a meta-analysis on 66,159 patients with immune mediated inflammatory diseases and long-term exposure to JAKi: serious infection events were not increased
- in Covid-19: duration of treatment with baricitinib is short (up to 14 days)

Olivera, Gastroenterology 2020

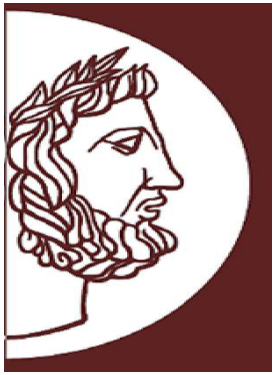
Baricitinib in Covid-19: concerns

VENOUS THROMBOEMBOLIC (VTE) RISK

- SARS-CoV2 infection specifically promotes prothrombotic pathways
  -incidence of pulmonary embolism in severe Covid-19 = 2X historical cohorts of patients requiring critical care for influenza
- reports of increased VTE events in rheumatoid arthritis patients treated with JAKi

BUT:

- in a meta-analysis of RCT on immune mediated inflammatory diseases; 6,542 JAKi patient-exposure years : incidence rate ratio for VTE was not increased
- all patients with Covid-19 receive thromboprophylaxis as standard of care
- by reducing inflammatory response, baricitinib might actually reduce prothrombotic risk



Yates et al. Arthritis Rheumatol. 2020

Baricitinib in Covid-19: data from observational studies

Cantini et al

113 baricitinib + SoC (lopinavir/ritonavir + HCQ)
vs
78 SoC (lopinavir/ritonavir + HCQ)

OUTCOMES:	
mortality	0% (0/113) vs 6.4% (5/78) p-value = 0.01
ICU admission	0.88% (1/113) vs 17.9% (14/78) p-value = 0.02

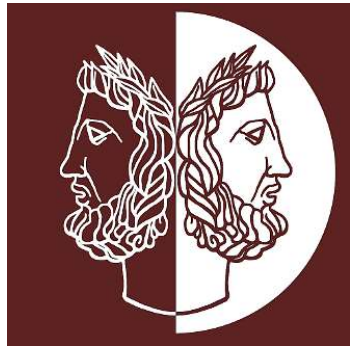
Rodriguez-Garcia et al

62 baricitinib + corticosteroids + SoC (lopinavir/ritonavir and HCQ)
vs
50 corticosteroids + SoC (lopinavir/ritonavir and HCQ)

OUTCOMES:	
Change in SpO2/ FiO2 ratio mmHg	Mean differences 49 p-value < 0.001
Oxygen requirements at discharge	62.0% vs 25.8% p -value < 0.001

Cantini et al, J Infect 2020
Rodriguez-Garcia et al, Rheumatology 2020

Baricitinib in Covid-19: data from trials



ACCT2

515 baricitinib + remdesivir

vs

518 placebo + remdesivir

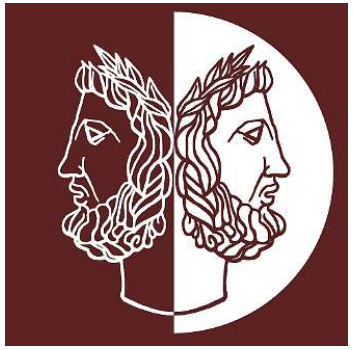
OUTCOMES:	
median time to recovery	Reduced from 8 to 7 days p–value =0.04
ordinal status (8-point scale) on Day 15	odds ratio 1.3 p-value =0.04
decreased mortality on Day 29	hazard ratio: 0.65 p-value =0.09

! **No new safety signals associated with baricitinib use**

Ordinal Scale used in ACTT2 study	
1	Not hospitalized, no limitations on activities
2	Not hospitalized, limitation on activities and/or requiring home oxygen
3	Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care
4	Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care
5	Hospitalized, requiring supplemental oxygen
6	Hospitalized, on non-invasive ventilation or high flow oxygen devices
7	Hospitalized, on mechanical ventilation or ECMO
8	Death

https://mod.isirv.org/repository/avg_2020/John_Beigel.pdf

Baricitinib in Covid-19: data from trials



benefits appeared to be greater in patients **requiring supplemental O2** and to a lesser extent for those requiring IMV at baseline

FDA issued an EUA (19 Nov 2020) for baricitinib in combination with remdesivir

for the treatment of suspected/ laboratory confirmed COVID-19

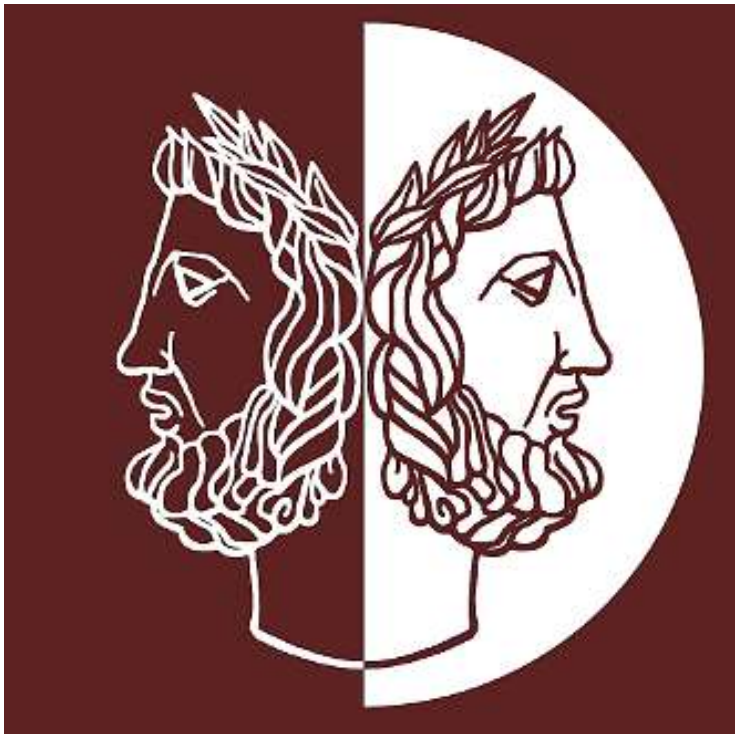
in hospitalized adults and paediatric patients≥ 2 y requiring:

- supplemental oxygen
- invasive mechanical ventilation
- extracorporeal membrane oxygenation (ECMO)

https://mod.isirv.org/repository/avg_2020/John_Beigel.pdf

Baricitinib facing down COVID

Should baricitinib be incorporated in Covid-19 standard of care?



TACTIC R

Repurposing drugs to save lives

26 active sites
132 patients randomized

How to refer patients to trial team:

- Telephone: 01223 274915 (consultant on-call)
- Bleep: 157864 (SpR on-call)

https://www.camcovidtrials.net/

Acknowledgements

TMG members

- Dr Frances Hall
- Prof David Jayne
- Dr Joseph Cheriyan
- Prof Andrew Cope
- Dr James Galloway
- Prof Ian Wilkinson

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- Dr Peta Masters

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- Stella Burns
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- Valentina Ruffolo
- Debbie Read
- Aileen Nacorda
- Jason Domingo
- Ciro Pasquale
- Vivien Mendoza
- Areti Bermperi
- Fevie Leal
- Danielle Johnson
- Sherly Jose
- Laura Canna
- Merry Jay
- Anne Meadows
- Jane Rowlands
- Sam Wright
- Donna Abercrombie
- Thelma Mushapaidzi
- Lissamma Titti

- **Ward medical teams**
- **Patients**