DR. DEEPA JAYAKODY ARACHCHILLAGE (Orcid ID : 0000-0001-5993-4850)

PROF. MIKE LAFFAN (Orcid ID : 0000-0002-8268-3268)

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Anticoagulation with Argatroban in patients with acute antithrombin deficiency in severe COVID -19

Deepa J Arachchillage[1,2,3], Christopher Remmington[1], Alex Rosenberg[1], Tina Xu[1], Maurizio Passariello[1], Donna Hall[1], A, Mike Laffan[3], Brijesh V Patel[1,4]

[1] Royal Brompton & Harefield NHS Foundation Trust and Imperial College London, UK, [1]

[2] Department of Haematology, Imperial College Healthcare NHS Trust, London, UK

[3] Centre for Haematology, Imperial College London, London, UK

[4] Division of Anaesthetics, Pain Medicine and Intensive Care

Address for correspondence:

Dr Deepa RJ Arachchillage,

Department of haematology,

Imperial College Healthcare NHS Trust and Imperial College London,

Hammersmith Hospital,

4th Floor, Commonwealth Building,

Du Cane Road,

London

W12 ONN

United Kingdom

Tel: +44 (0) 20 7351 8403, FAX: +44 (0) 2073518402

E-mail: d.arachchillage@imperial.ac.uk

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COVID-19 is a highly prothrombotic disease, frequently requiring anticoagulation for prevention or treatment of thrombosis and to enable organ support (Bikdeli, Madhavan et al. 2020). The reported incidence of thrombosis in patients with COVID-19 varies considerably depending on anticoagulant regimen, severity of disease and additional risk factors such as central lines. The most commonly used in-hospital anticoagulants, unfractionated heparin (UFH) and low molecular weight heparin (LMWH), require antithrombin (AT) to exert their anticoagulant effect (Bussey and Francis 2004). Therefore, AT deficiency can result in failure achieve adequate anticoagulation with UFH or LMWH at usual doses. AT levels of approximately 50IU/dL are required to achieve an anticoagulant effect using UFH (Hirsh, Bauer et al. 2008). A multicentre study of 150 COVID-19 patients, demonstrated a 43% prevalence of thrombosis, despite prophylactic or therapeutic anticoagulation (Helms, Tacquard et al. 2020). Pathophysiology of thrombosis in COVID-19 is most likely multifactorial and the high rate of thrombosis appears to be driven by endothelial inflammation and elevated coagulation factors such as fibrinogen and factor VIII (Helms, Tacquard et al. 2020). In severely ill patients there may also be reduction in AT due to increased consumption, reduced production or both. Some studies reported patients with COVID-19 have reduced AT levels associated with nephritis (Gross, Moerer et al. 2020).

We describe a cohort of 10 patients with COVID-19 (9/10 patients had confirmed thrombosis on admission to our unit despite being on prophylactic dose LMWH) who were resistant to heparinisation due to reduced AT levels but who were successfully anticoagulated with argatroban (table 1). Median

age was 44.5 years (range 22-61) and 9/10 were male. All were mechanically ventilated (including 8 on ECMO). All patients were started on UFH as per institutional protocol with a weight adjusted IV bolus followed by a starting infusion rate of 12units/kg/hour (reflecting concern for increased risk of bleeding in critically ill patients) adjusted to maintain a heparin level of 0.3-0.7 anti-Xa units/mL (Arachchillage, Kamani et al. 2017). Testing of AT level from all patients on admission to our intensive care unit was part of the COVID-19 laboratory panel and was found to be reduced in all of the patients reported here (table 1). Anticoagulation with argatroban; a direct thrombin inhibitor exerts its anticoagulant effect independent of AT was commenced after failing to achieve therapeutic heparin levels with UFH due to low AT (Table 1). Argatroban was started at 0.3μg/kg/min (supplementary document 1), and gradually increased to achieve an APTT of target of 47-78 seconds. There were no further thrombosis complications observed including thrombosis of renal replacement or ECMO circuits and no ECMO cannula related thrombosis. The AT level gradually improved as the patients recovered from COVID-19 or remained low at the time of death.

Some studies reported more frequent AT reduction in non-survivors (84% of normal in non-survivors vs 91% in survivor) in patients with COVID-19; however, they suggested that plasma concentrations rarely drop below 80% of normal (Tang, Li et al. 2020). It is possible that disease severity in patients included in these studies was different and included more patients who were not critically unwell. All ten patients in our cohort were critically unwell requiring ventilation. In addition to its anticoagulant effect, AT also plays a central role in mediating inflammation. Although d-dimer level was elevated as expected patients with COVID-19, there was no other evidence to suggest disseminated intravascular coagulation as prothrombin time, platelet count, and fibrinogen levels were within the normal ranges in all 10 patients or had elevated platelets count and fibrinogen levels in some patients. Acquired AT deficiency is common in patients on ECMO due to a combination of accelerated consumption and reduced synthesis by liver. However, AT levels in our cohort were tested before the initiation of ECMO therefore reduced AT levels were not affected by ECMO. Few studies have evaluated the effect of AT supplementation during ECMO without a consensus on the appropriate level to be maintained in patients without COVID-19 (Esper, Levy et al. 2014). AT supplementation may increase the anticoagulant effect on UFH or LMWH without increasing heparin dosage. However, elevation of AT levels to normal values in our patients would require large and repeated doses of AT, incurring significant cost.

Limitations of this study include its small sample size, limiting the ability to detect adverse effects. However, three patients had bleeding complications whilst on argatroban warranting further discussion (Table 1). Patient 4 had clinically relevant non-major bleeding from haemorrhoids which required

temporary suspension of argatroban for 6hrs. Patient 5 who developed haemorrhagic transformation of a middle cerebral artery (MCA) infarct had anticoagulation initiated on admission with clopidogrel 75 mg daily due to the subacute right MCA infarct, pulmonary embolism and right iliac vein thrombus. In patients with cerebral infarcts, it is our standard practice to withhold anticoagulation for at least 10 day and repeat the brain scan to assess the progression of infarction/haemorrhagic transformation prior to starting anticoagulant. However, due to the additional venous thromboses, the patient was started anticoagulation on admission which may have contributed to the haemorrhagic transformation of this patient. Patient 6 had bleeding from rectal artery requiring embolisation.

These cases with severe COVID-19 highlight that acute AT deficiency can be severe and may contribute both to development of thrombosis and failure to achieve therapeutic anticoagulation with heparin so that an alternative anticoagulant independent of AT may improve the outcome. We suggest the measurement of AT and institution of alternative anticoagulant strategies in patients resistant to heparin in COVID-19. Argatroban works independently of antithrombin and is seems to be a suitable alternative for acute anticoagulation in such circumstances. However, recommendation for use of Argatroban in this setting, with little data to support safety or efficacy is debatable and needs further evaluation in a larger study. Anticoagulant therapy is becoming an increasingly important aspect of COVID-19 management. These cases important for clinical practice and current randomised clinical trials (https://www.remapcap.org/) as they indicate the need for more personalised anticoagulation regimens in Covid-19. Careful monitoring for bleeding is required as with any anticoagulant regimen.

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Author contributions

DJA was involved in design of the study, data collection, interpretation of the data and writing the manuscript. CR was involved in data collection and approving the final draft of the

manuscript. All other authors were involved in data interpretation and writing the manuscript. All authors approved the final version of the manuscript.

Conflicts of interest

Authors declared no conflicts of interest.

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Table 1: Clinical and laboratory characterises of patients received argatroban due to acute antithrombin deficiency in patients with severe COVID-19

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Age (years)	36	38	48	54	22	61	54	43	45	44
Sex (male/Female)	Male	Male	Male	Male	Male	Male	Male	Male	Female	Male
Previous history of thrombosis	No	No	No	Yes	No	No	No	No	No	No
Thrombotic event at presentation to our unit	PE	PE	PE	No acute thrombosis Sickle cell trait	Subacute right MCA infarct, PE, right iliac vein thrombus	PE	PE	PE	Bilateral PE and ischaemic basilar stroke	Pulmonary microvascular disease and bowel ischaemia
On VV-ECMO	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes
On renal replacement therapy	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
AT level on admission (IU/dL)	28	26	43	20	19	49	44	32	43	39
Max dose of UFH	17	16	21	12.5	20	23	18	20	15	15

given prior to change to argatroban (units/Kg/hr)										
Bleeding complication whilst on argatroban including evidence of ICH in brain CT	None	None	None	Clinically relevant minor bleeding from haemorrhoids	haemorrhagic transformation of MCA infarct	Bleeding from rectal artery requiring embolisation	None	None	None	None
Progression or new thrombosis whilst on argatroban	No	No	No	No	No	No	No	No	No	No
Thrombosis in ECMO or RRT circuit whilst on **argatroban**	No	No	No	No	No	No	No	No	No	No
Clinical outcome (alive or dead)	Alive	Alive	Alive	Alive	Dead	Dead	Alive	Alive	Dead	Dead

Cause of death	NA	NA	NA	NA	MOF and haemorrhagic transformation of MCA infract	MOF and Bleeding from rectal artery	NA	NA	MOF	MOF and bowel preformation
AT level on discharge or death (IU/dL	106	76	107	75	47	56	81	86	64	105

VV-ECMO = veno=venous extracorporeal membrane oxygenation; AT= antithrombin; PE= pulmonary embolism; MCA = middle cerebral artery; MOF= multiorgan failure; RRT = renal replacement therapy