AcelRx KOL Event on Niyad™ and the Nafamostat Program

May 4, 2022
1:00 p.m. EDT

AcelRx Pharmaceuticals, Inc.

Forward-Looking Statements

Forward-Looking Statements

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Portfolio of Commercial and Late-Stage Development Products

Approval

	Phase 1	Phase 2	Phase 3	NDA submitted	Post-approval
 DSUVIA (sufentanil) sublingual tablet 30 mcg	30 mcg sublingual sufentanil tablet in a single-dose applicator; HCP administered			Approved in U.S. Approved in E.U.	• Investigator-initiated studies ongoing • Aguettant commercializing in EU
 Zalviso	15 mcg sublingual sufentanil tablet in a pre-programmed handheld PCA device			NDA-ready in the U.S. Approved in E.U.	• Various EU studies performed
Niyad™	Anticoagulation of the extracorporeal circuit – regulated as device				
LTX-608	Various indications regulated as drugs**				
 **PFS-01**	Ephedrine 10 ml ready to use pre-filled syringe of 3 mg/ml ephedrine hydrochloride				• Licensed from Aguettant
 **PFS-02**	Phenylephrine 10 ml ready to use pre-filled syringe of 50 mcg/ml phenylephrine hydrochloride				• Licensed from Aguettant

** AcelRx is not currently investing resources in these development stage products; these are investigational products and are not approved by the FDA or any other regulatory agency ; ** Post-toxicology, expect to be in phase 2 development*

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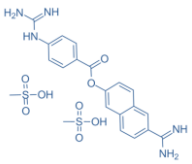
Overview of Nafamostat Portfolio Opportunity

A single molecule with multiple potential indications already proven outside the U.S., and with FDA Breakthrough Designation and CMS reimbursement code



	Indication	Stage	Available U.S. market (# of patients)	Available U.S. market ($ value)
1 Niyad™	Anticoagulation for renal replacement therapy (RRT); FDA regulated as a device	EUA/ Phase 3	500,000	$575 M
2 Niyad™	Anticoagulation for intermittent dialysis (IHD); outpatient dialysis clinics; FDA regulated as a device	Phase 3	350,000	$3.5 B
3 LTX-608a	Disseminated intravascular coagulation (DIC)	Phase 2	260,000	$1.5 B
4 LTX-608b	COVID-19	Phase 2	TBD	TBD
5 LTX-608c	Acute respiratory distress syndrome (ARDS)	Phase 2	TBD	TBD

The order of priority to develop indications 3-5 may be changed based on further evaluation of market; excludes several other therapeutic indications

Key Opinion Leader (KOL) Speaker Biographies

Lakhmir "Mink" Chawla, MD

Dr. Chawla is currently the Chief Medical Officer of Silver Creek Pharmaceuticals. Previously, Dr. Chawla was CMO at La Jolla Pharmaceutical Company. While he was at LJPC, he oversaw the development and conduct of the Phase 3 ATHOS-3 trial. Prior to joining LJPC, Dr. Chawla was a Professor of Medicine at the George Washington University, where he had dual appointments in the Department of Anesthesiology and Critical Care Medicine and in the Department of Medicine, Division of Renal Diseases and Hypertension. Dr. Chawla was previously the Chief of the Division of Intensive Care Medicine at the Washington D.C. Veterans Affairs Medical Center. Dr. Chawla is an internationally renowned expert in the field of acute kidney injury (AKI) and shock. He remains an active investigator in the fields of AKI biomarkers, AKI risk prediction, AKI therapeutics and chronic kidney disease caused by AKI.

Dr. Chawla is also the author of over 150 peer-reviewed publications and a recipient of the International Vicenza Award for Critical Care Nephrology; an award that recognizes individuals who have made seminal clinical research advancements that have significantly improved the care of critically ill patients with AKI and have been adopted worldwide.

Stuart Goldstein, MD, FASN

Stuart L Goldstein, MD, is Professor of Pediatrics and Director, Center for Acute Care Nephrology at Cincinnati Children's Hospital Medical Center. He received his medical degree from Columbia University and completed both clinical and research fellowships in pediatric nephrology at the Children's Hospital in Boston, Massachusetts. Dr Goldstein is Founder and Principal Investigator for the Prospective Pediatric Acute Kidney Injury Research Group and has evaluated novel urinary AKI biomarkers in the pediatric critical care setting. He was one of two pediatric work group members for the KDIGI International AKI Guideline Work Group and has served on the KDOQI Hemodialysis Adequacy, Vascular Access and Pediatric Nutrition Guideline Work Groups. He has written over 300 journal articles, served as editor of two textbooks, and contributed book chapters to numerous texts including, Critical Care Nephrology, Evidence-Based Nephrology, Handbook of Dialysis Therapy, Management of Acute Kidney Problems, Pediatric Critical Care, Pediatric Nephrology, and Pediatric Nephrology in the ICU.

Agenda

- Niyad™ : Nafamostat for Anticoagulation of the Extracorporeal Circuit — Dr. Palmer
- Standard of Care and Unmet Need for Dialysis Anticoagulation — Dr. Chawla
- Initial Q and A
- Recent Publication of Nafamostat vs. Citrate for RRT — Dr. Goldstein
- Clinical Development of Niyad in U.S. — Dr. Palmer
- LTX-608: Nafamostat for Intravenous Injection — Dr. Chawla
- Final Q and A

Niyad™ : Nafamostat for Anticoagulation of the Extracorporeal Circuit

Pamela Palmer, MD PhD
Chief Medical Officer, AcelRx

What is Nafamostat?

Broad-spectrum serine protease inhibitor

- Serine proteases are enzymes that contain the amino acid serine at the active site that cleaves peptide bonds
  - Many complicated cellular cascades in the body (clotting cascade, immune cascade, inflammatory cascade) are a series of activated proteins cleaved from precursor proteins
- When these cascades go awry, an inhibitor of the cascade at key steps can be therapeutic
  - For example, blocking thrombin from cleaving fibrinogen to fibrin
- Careful titration of this inhibition is critical as these systems are vital to survival
- Nafamostat is broad-spectrum meaning it inhibits a wide variety of serine proteases but it has a half-life of 8 minutes

What is an Extracorporeal Circuit?

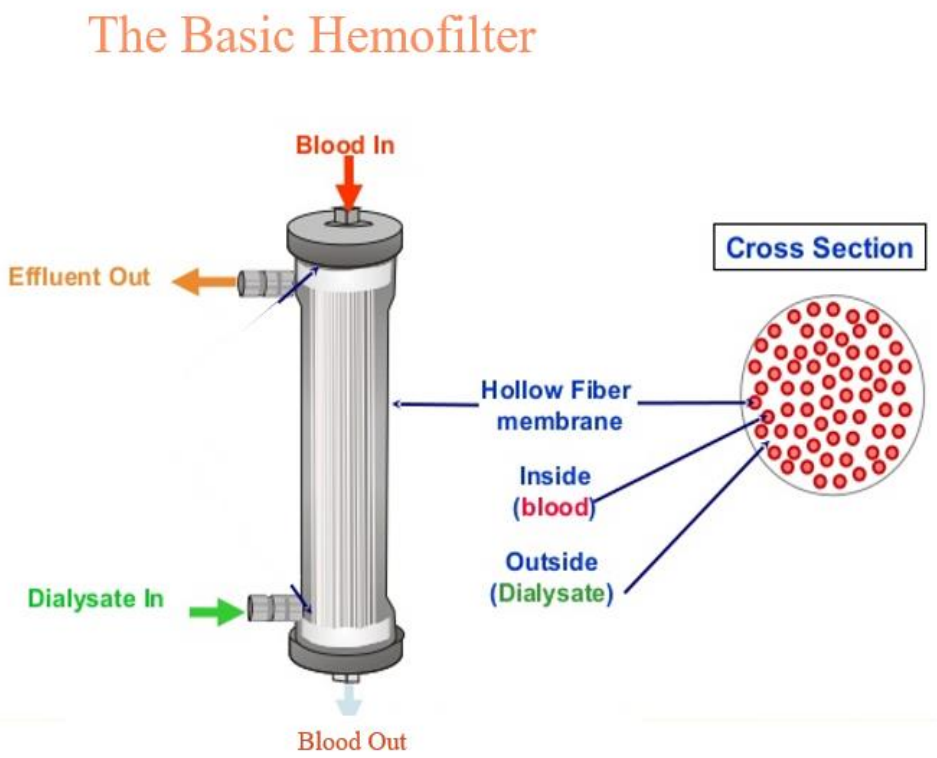
Extracorporeal means "outside the body"

- Extracorporeal circuits transit the blood outside of the body through a machine that temporarily assumes an organ's functions
  - Dialysis replaces function of the kidneys
  - Extracorporeal membrane oxygenation (ECMO) replaces function of the lungs
  - Cardiopulmonary bypass replaces function of both heart and lungs

- To avoid clotting of the blood passing through the circuit, an anticoagulant is often used
  - Systemic anticoagulant: both the patient and the circuit are anticoagulated (eg, heparin)
  - Regional anticoagulant: only the circuit is anticoagulated (eg, citrate, nafamostat)

Anticoagulation During Dialysis

- Renal Replacement Therapy (RRT) used in hospitalized patients with acute or chronic kidney disease
- Regional anticoagulation is desirable due to systemic anticoagulants risk of excessive bleeding
- In the US there is one *regional* anticoagulant available and only under an Emergency Use Authorization (EUA).
- Niyad™ to be regulated as a device due to mechanism of action



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Standard of Care and Unmet Need for Dialysis Anticoagulation

Lakhmir “Mink” Chawla, MD

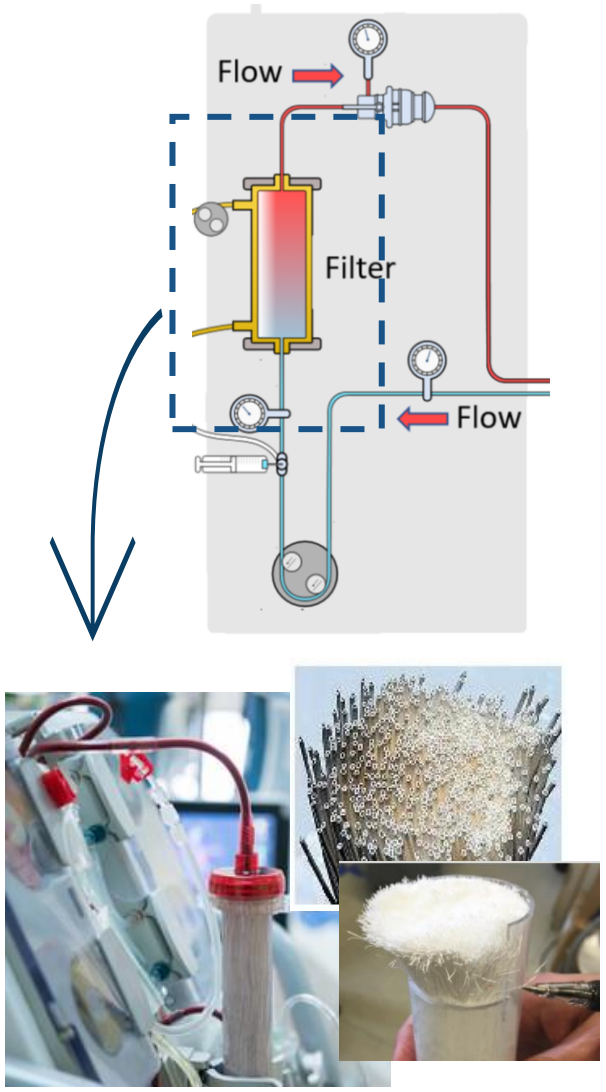
Exposure of Blood to the Dialysis Filter Causes Clotting

More frequent filter changes required to ensure efficacy

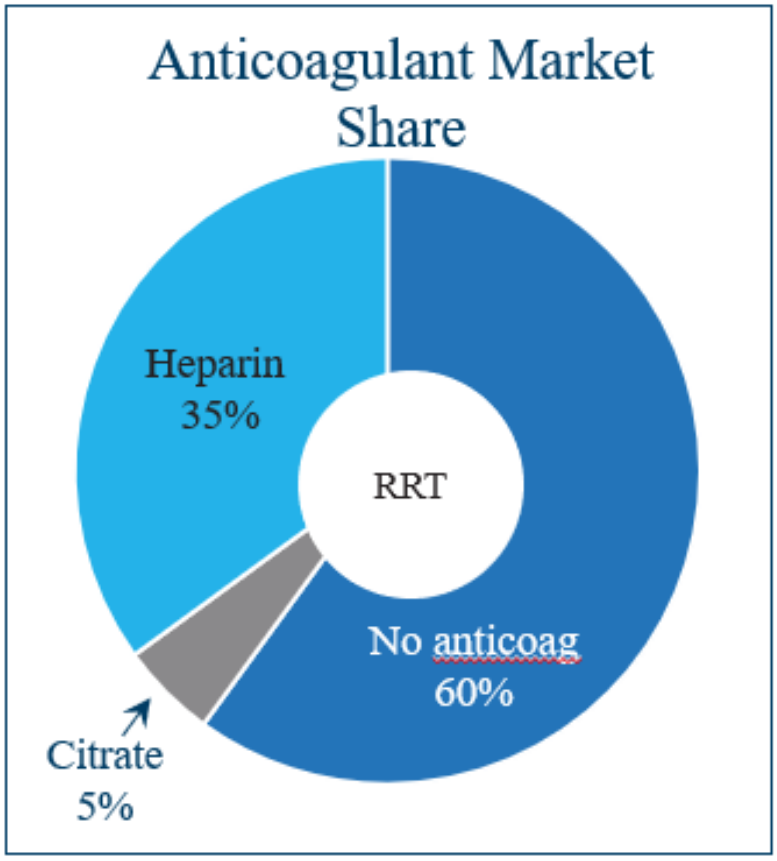
Increased blood loss; increased platelet transfusions

Delayed/prolonged treatment time

Burden on healthcare professional



The Standard of Care in RRT



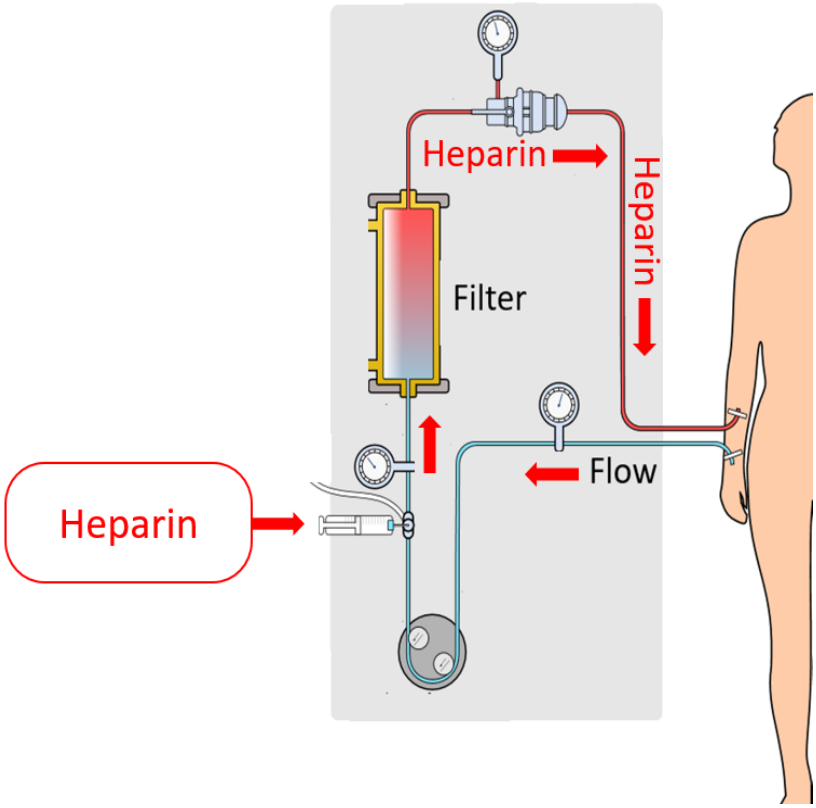
- Heparin (systemic anticoagulant)
- Citrate (regional anticoagulant used in U.S. only via an EUA*)
- No anticoagulant is unfortunately the default when physicians are concerned with safety of heparin or citrate

*EUA = Emergency Use Authorization

FDA-Approved Systemic Anticoagulant

Heparin

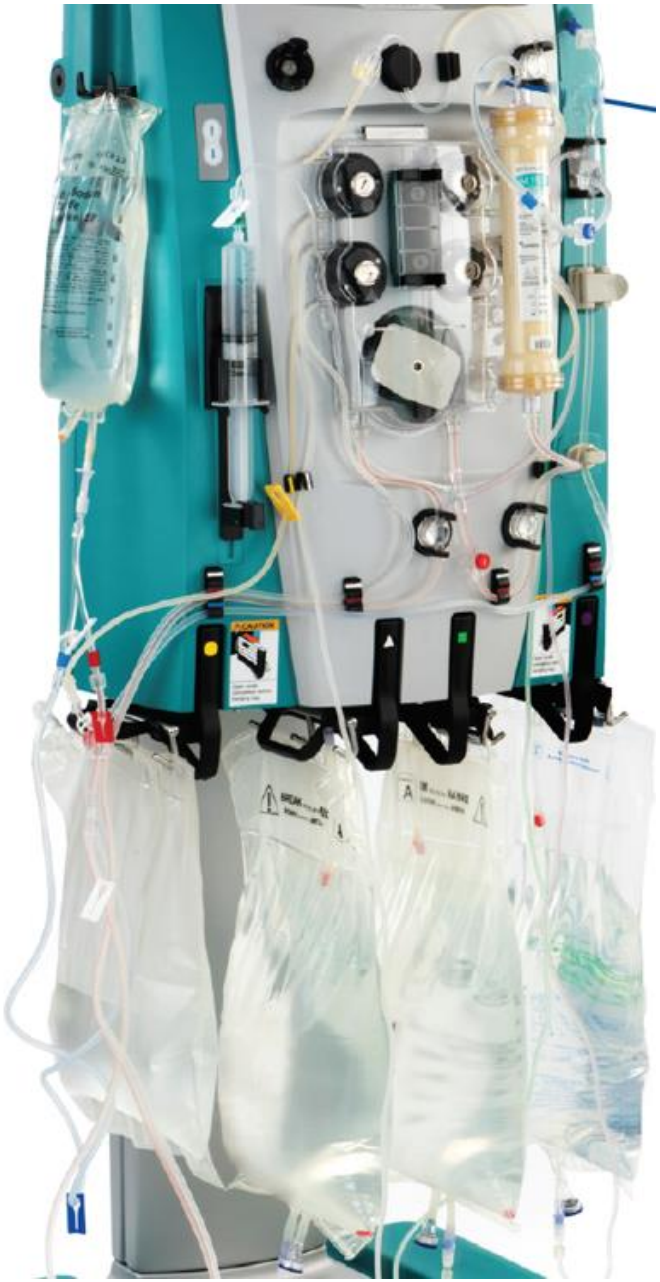
- Systemic anticoagulant
- Prolonged half-life up to 6 hours makes it difficult to titrate
- Clinicians fear over anticoagulating the patient
- Significant safety concern for patients at risk of bleeding
- Thrombocytopenia



1) Ohtake Y. Nafamostat as Anticoagulant in Continuous HD. Contrib Nephrol. 1991;93;215-217.

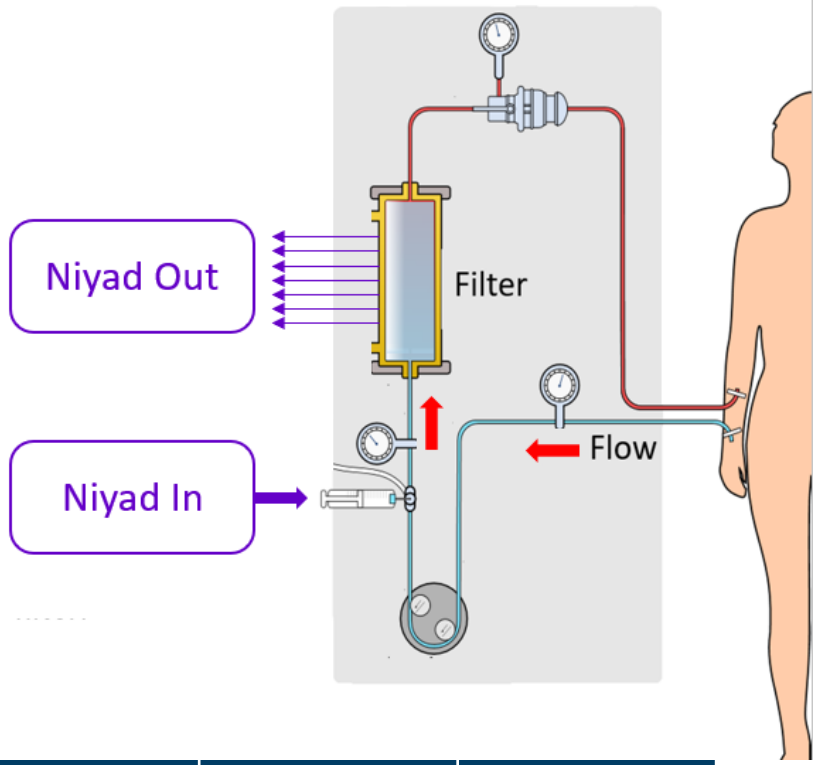
Risks Associated with Citrate (used under EUA)

- Citrate chelates calcium, which inhibits the generation of thrombin.
- Use of citrate requires infusion of calcium on the return side of the filter (back into patient).
- Extensive, complicated protocol
- Frequent blood draws to measure calcium are time-consuming and expensive
- Rapid changes in calcium levels which can cause hypotension, ventricular fibrillation, and possibly cardiac arrest.
- Even more complicated in patients with liver failure



Benefits of Niyad in RRT

- Standardized international guidelines recommend using an anticoagulant during RRT
- **Niyad provides short half-life, titratable, *regional* anticoagulation** without the shortcomings of heparin or citrate
- Advantages of Niyad
  - Niyad can be used in patients at risk of bleeding, whereas heparin is limited
  - Niyad can be used easily in patients with liver failure – whereas citrate is limited
- Compared to no anticoagulation: fewer filter changes, fewer transfusions, more importantly – lower cost of doctor and nursing time



	Heparin	Nafamostat
Incidence of Bleeding[1]	66.7 % (8/12)	4.3 % (1/23)

1) Ohtake Y. Nafamostat as Anticoagulant in Continuous HD. Contrib Nephrol. 1991;93;215-217.

Decades of Nafamostat Studies To Support U.S. Approval

Reference	Study Type	N (nafamostat/total)	Author's Conclusions
Murase, 1988	RCT	20/40	Nafamostat reduced transfusion requirements ($p<0.01$), blood loss ($p<0.05$), and heparin dose ($p<0.05$). Nafamostat inhibits fibrinolysis and preserves platelet counts and function during cardiopulmonary bypass during open heart surgery.
Koshikawa, 1988	RCT	77/157	Nafamostat is a more useful and safer anticoagulant for hemodialysis patients with hemorrhagic complications than methods using regional or low-dose heparin.
Baek, 2012	Retrospective	62/243	The use of nafamostat in patients with a high risk of bleeding who required CRRT lengthenedthe filter survival time from 10.2 to 19.8 hours ($p<0.001$) without an increase in RBC transfusions
Hwang, 2013	Retrospective	25/212	Nafamostat lengthened filter life with minor side effects comparable to heparin use or no anticoagulation. Median filter lifespan with nafamostat was significantly greater than heparin (24.3 vs. 17.5 hours, $p<0.001$).
Lee, 2014	RCT	36/73	The number of filters functioning over 12 hours was significantly higher in the nafamostat group than in the no-anticoagulation group ($p=0.037$). No significant differences in transfusion or survival were found between the nafamostat group and the group not receiving an anticoagulant.
Choi, 2015	RCT	31/55	The nafamostat group had a 42.2%longer filter lifespan ($p=0.022$). Conversion of CRRT to conventional intermittent hemodialysis was significantly higher in the NM group than in the no anticoagulation group (20.8% versus 1.8%: $P=0.002$).

Initial Q & A Session

Recent Publication of Nafamostat vs. Citrate for RRT

Stuart Goldstein, MD

Published March 28, 2022 in *Pediatric Nephrology*

- Pediatric and adult dialysis anticoagulation needs are similar, but margin for error is narrower in children
- Regional citrate anticoagulation is considered gold standard but is complex to perform
- Important to compare the two regional techniques (nafamostat and citrate) to assure nafamostat has equivalent efficacy, and to evaluate safety

Pediatric Nephrology
https://doi.org/10.1007/s00467-022-05502-8

ORIGINAL ARTICLE

Check for updates

Comparison of nafamostat mesilate to citrate anticoagulation in pediatric continuous kidney replacement therapy

Mai J. Miyaji[1,2,3] · Kentaro Ide[2] · Kohei Takashima[2] · Mikiko Maeno[2] · Kelli A. Krallman[1] · Danielle Lazear[1] · Stuart L. Goldstein[1,4]

Miyaji, M.J., Ide, K., Takashima, K. *et al.* Comparison of nafamostat mesilate to citrate anticoagulation in pediatric continuous kidney replacement therapy. *Pediatr Nephrol* (2022). https://doi.org/10.1007/s00467-022-05502-8

Methods

- Retrospective study of patient records at one children's hospital in Japan (nafamostat) and one in the US (citrate).
- Starting June 2019, the most recent 100 medical records of children receiving RRT with either citrate or nafamostat were reviewed
- Primary endpoint
  - the number of hours a single dialysis filter was in use (filter life)
  - Filter life also censored for non-CRRT ACG reasons (scheduled circuit change, patient transport to Radiology etc.)
- Safety
  - bleeding complications
  - anaphylaxis
  - citrate toxicity (systemic ionized hypocalcemia)
  - electrolyte imbalance

Efficacy Results: Similar Filter Life for Nafamostat and Citrate

- Eighty patients received nafamostat and 78 patients received citrate
- Patients receiving nafamostat were younger, smaller and had smaller catheters—all factors that are associated with reduced filter life
- Patients receiving nafamostat had a higher prevalence of liver disease, which creates a more complicated citrate protocol
- Median filter life was slightly longer for the nafamostat group (38 hrs) vs. citrate (36 hrs), $p = 0.02$)
- There was no difference in filter survival after controlling for filter surface area, catheter diameter, and pre-treatment platelet count
- When evaluating circuit clotting with nafamostat versus citrate over time, there was never any difference between citrate and nafamostat

Miyaji, M.J., Ide, K., Takashima, K. *et al.* Comparison of nafamostat mesilate to citrate anticoagulation in pediatric continuous kidney replacement therapy. *Pediatr Nephrol* (2022). https://doi.org/10.1007/s00467-022-05502-8

Adverse Events

- Nafamostat (NM) had similar bleeding events compared to citrate (RCA)
- However, 11 citrate-treated patients developed citrate toxicity and 3 patients had refractory metabolic alkalosis from citrate - 8 of these 14 patients had to have regional citrate anticoagulation stopped

	RCA ($N=78$)	NM ($N=80$)	p value
Major bleeding, n (%)	7 (9.0)	4 (5.0)	0.33
Minor bleeding, n (%)	9 (11.5)	11 (13.8)	0.68
Adverse effect specific to each ACG, n (%)	Citrate toxicity 11 (14.1)	Anaphylaxis 0 (0)	NA

Miyaji, M.J., Ide, K., Takashima, K. *et al.* Comparison of nafamostat mesilate to citrate anticoagulation in pediatric continuous kidney replacement therapy. *Pediatr Nephrol* (2022). https://doi.org/10.1007/s00467-022-05502-8

Citrate Anticoagulation is Expensive

- Published in the supplemental materials of this study is a detailed analysis calculating the cost of daily citrate anticoagulation
- Not included is the extensive nursing time required to run/troubleshoot multiple infusions, draw calcium levels, check labs, etc

Regional citrate anticoagulation specifics

1) 30 kg patient would have a CKRT blood pump flow rate of of 150 ml/min
2) Protocol leads to:
    a. ACD-A™ ($12.32 per 1 liter bag)[a] at 225 ml/hour = **$66.53/day**
    b. Calcium chloride (8 mg/ml) = $24.25/vial (10% 10 mL vial); leads to $CaCl_2$ at 90 ml/hour = **$419.04/day**
    c. Every 8-hour ionized Ca^{2+} $13.68 per check[b] = **$41.04 per day**
    d. Total cost + iCal = **$526.61/day**

Miyaji, M.J., Ide, K., Takashima, K. *et al.* Comparison of nafamostat mesilate to citrate anticoagulation in pediatric continuous kidney replacement therapy. *Pediatr Nephrol* (2022). https://doi.org/10.1007/s00467-022-05502-8

Conclusions

- Both citrate and nafamostat provide satisfactory anticoagulation for RRT with no difference in major bleeding rates
- Nafamostat is a much simpler technique with fewer risks for serious adverse events, including citrate toxicity
- Citrate anticoagulation is more complex, time-consuming and expensive

Clinical Development of Niyad in U.S.

Pamela Palmer, MD PhD

Niyad Awarded Breakthrough Device Designation Status *and* ICD-10 Procedural Code

- Breakthrough Device Designation
  - Interactive and timely communication with FDA
  - Pre/post-market balance of data collection
  - Efficient and flexible clinical study design
  - Review team support
  - Senior management engagement
  - Priority review
  - Manufacturing considerations for PMA submission

- Pre-approval procedural code
  - Extracorporeal Introduction of Nafamostat Anticoagulant, New Technology Group 7 (code XY0YX37)
  - CMS New Technology Add-On Payments (NTAP) cover 65% of the cost exceeding the DRG[1]

1. https://www.govinfo.gov/content/pkg/FR-2019-08-16/pdf/2019-16762.pdf and https://s3.amazonaws.com/public-inspection.federalregister.gov/2019-16762.pdf.

Opportunity for Emergency Use Authorization (EUA)

Correspondence with FDA suggests that EUA submission, after initial drug product lot is manufactured/tested, would be actively considered

- FDA opined on 8/24/21:
  - "We believe that your device has the potential to address an unmet need in patients who cannot tolerate heparin or….who are treated in facilities that are ill-equipped for use of a citrate anticoagulant."
  - "Additionally, we recognize that there may be an unmet need for patients…who also cannot tolerate citrate due to another condition such as liver disease."
  - "We believe that you have provided significant evidence demonstrating that the potential benefits of the Niyad device could be greater than the reasonably foreseen risks."

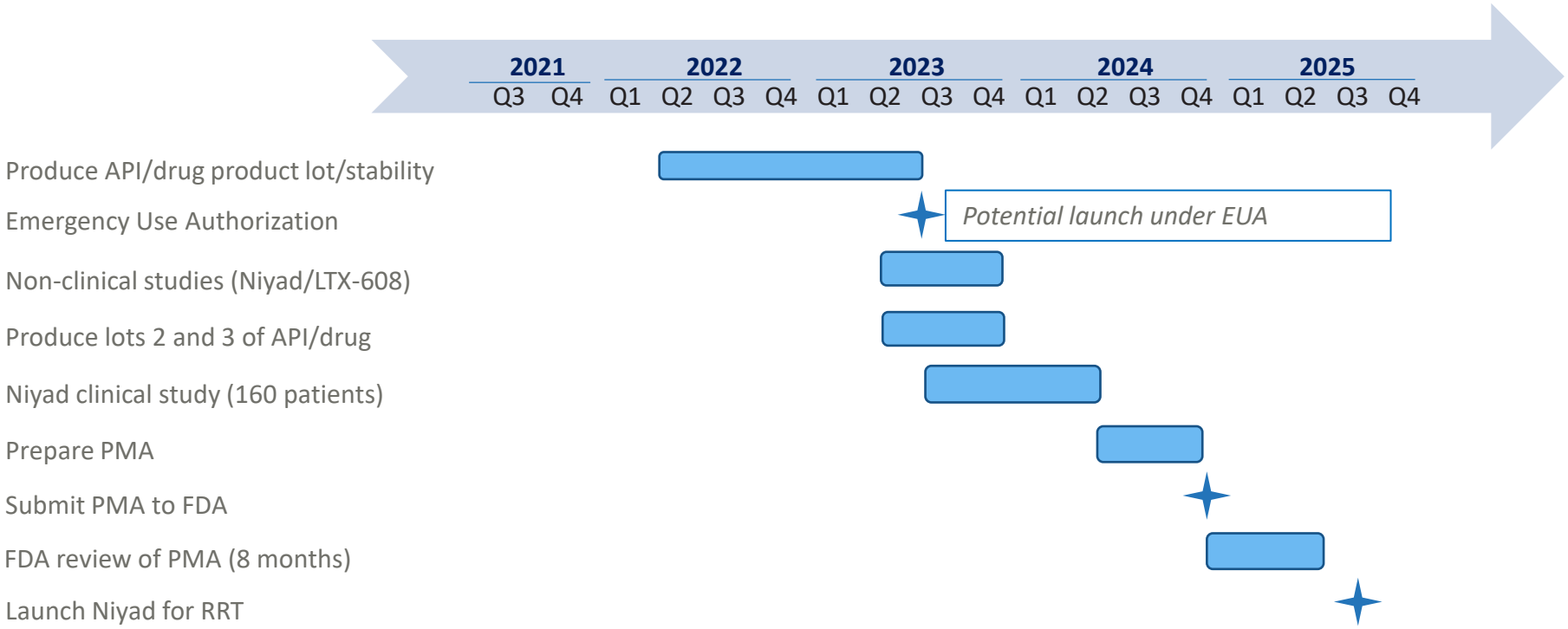
Phase 3 Protocol – Design/Endpoints Affirmed by FDA

FDA review of IDE is complete with agreement on a single registrational study

- Prospective, randomized, placebo-controlled
- 160 adult patients (80 active:80 placebo) undergoing RRT for up to 7 days who cannot tolerate heparin or are at risk for bleeding
- Up to 10 clinical sites
- Primary endpoint: mean post-filter activated clotting time (ACT) over first 24 hours
- Key secondary endpoints:
  - Filter lifespan
  - Number of filter changes over 72 hours
  - Number of transfusions over 72 hours
  - Dialysis efficacy (based on urea concentration) over first 24 hours
- Key safety endpoints
  - Bleeding, electrolyte disorders, 28-day all-cause mortality

Timeline to PMA approval for Niyad

Estimated development cost for Niyad through approval in Q2 2025 is $14M, much of which can be leveraged for other nafamostat indications



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Nafamostat Intellectual Property Status and Regulatory Exclusivity

6

Six years regulatory exclusivity upon PMA approval

PATENT

Niyad™ patent pending

Claims drawn to priming of the extracorporeal circuit and blood flow when using nafamostat.

PATENT

LTX-608 (nafamostat) multiple patents pending

Claims drawn to use of nafamostat in disseminated intravascular coagulation (DIC), as an antiviral agent (e.g., COVID treatment), in acute respiratory distress (ARDS) and other conditions.

LTX-608: Nafamostat for Intravenous Injection

Lakhmir “Mink” Chawla, MD

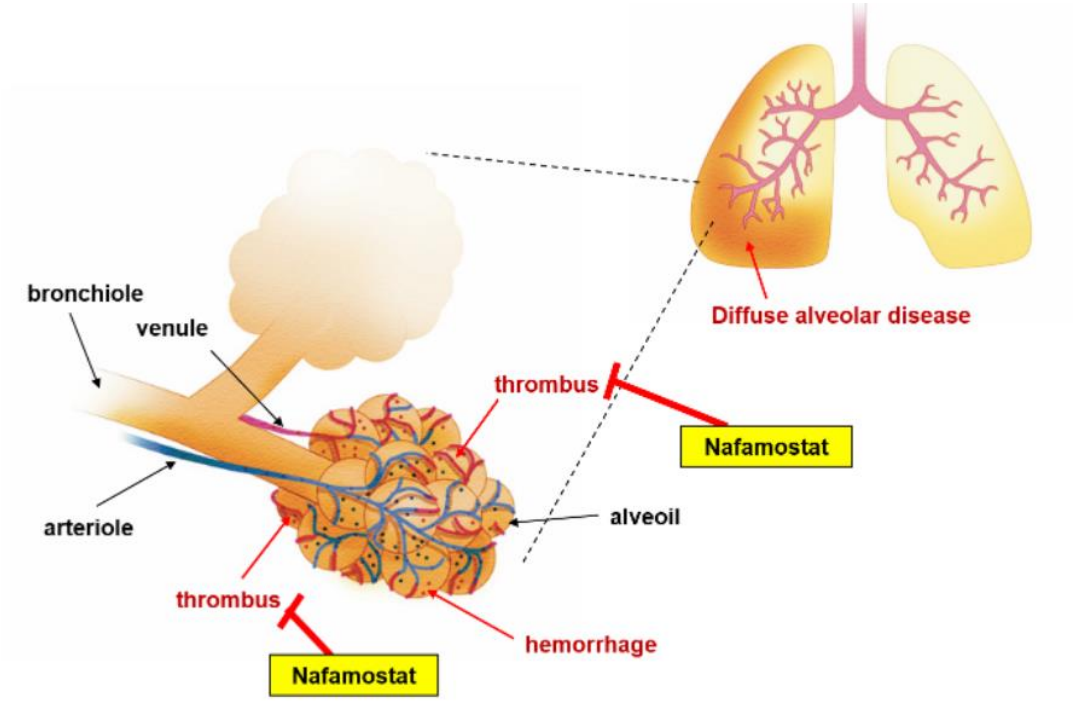
LTX-608

- Nafamostat follow-on indications will focus on:
  - *Disseminated Intravascular Coagulation (DIC)*- approved indication in Japan and South Korea
  - *COVID treatment* – various ex-US studies have demonstrated promising results; AcelRx has a published patent regarding nafamostat antiviral for COVID and other viruses
  - *Acute Respiratory Distress (ARDS)*

DIC: Nafamostat is already approved in Japan for DIC

High chances of approval, therefore, intellectual property protection will focus on method of use patents based on the complexity of DIC treatment

Mechanism of Action



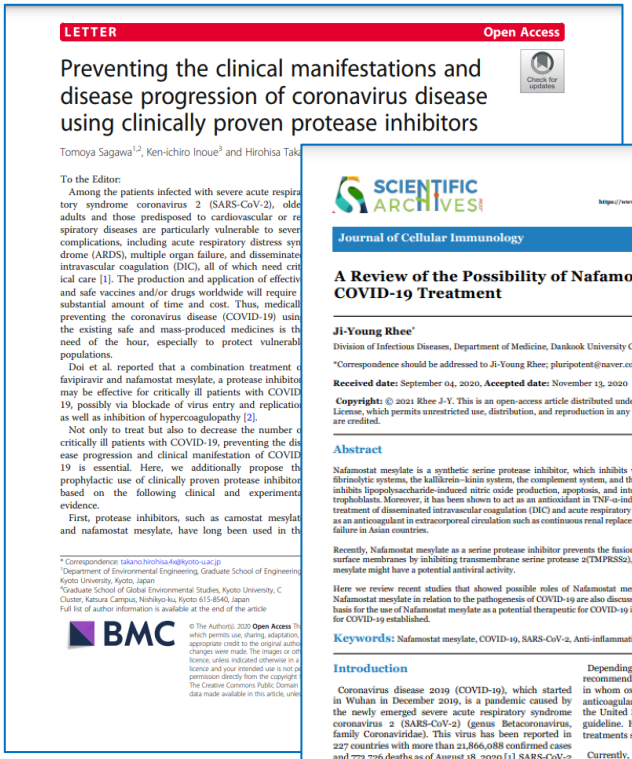
Clinical/ Regulatory strategy

- Further evaluate potential clinical study and related development cost; ability to leverage non-clinical work performed on other indications and potential safety database
- Complexity of treating DIC may allow methods of use patents to be filed

LTX-608 studies supporting potential COVID treatment

A potent broad-spectrum serine protease inhibitor that blocks host protease activation of the viral spike protein [1]

- No US clinical studies for IV nafamostat have been done



LETTER Open Access

Preventing the clinical manifestations and disease progression of coronavirus disease using clinically proven protease inhibitors

Tomoya Sagawa[1,2], Ken-ichiro Inoue[3] and Hirohisa Tak

To the Editor:

Among the patients infected with severe acute respira tory syndrome coronavirus 2 (SARS-CoV-2), olde adults and those predisposed to cardiovascular or re spiratory diseases are particularly vulnerable to sever complications, including acute respiratory distress syn drome (ARDS), multiple organ failure, and disseminate intravascular coagulation (DIC), all of which need crit ical care [1]. The production and application of effectiv and safe vaccines and/or drugs worldwide will require substantial amount of time and cost. Thus, medicall preventing the coronavirus disease (COVID-19) usin the existing safe and mass-produced medicines is th need of the hour, especially to protect vulnerabl populations.

Doi et al. reported that a combination treatment favipiravir and nafamostat mesylate, a protease inhibito may be effective for critically ill patients with COVID 19, possibly via blockade of virus entry and replicatio as well as inhibition of hypercoagulopathy [2].

Not only to treat but also to decrease the number critically ill patients with COVID-19, preventing the dis ease progression and clinical manifestation of COVID 19 is essential. Here, we additionally propose th prophylactic use of clinically proven protease inhibitor based on the following clinical and experimenta evidence.

First, protease inhibitors, such as camostat mesylat and nafamostat mesylate, have long been used in th

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BMC

SCIENTIFIC ARCHIVES

Journal of Cellular Immunology Review Article

A Review of the Possibility of Nafamostat Mesylate in COVID-19 Treatment

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*Correspondence should be addressed to Ji-Young Rhee; pluripotent@naver.com

Received date: September 04, 2020, Accepted date: November 13, 2020

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Abstract

Nafamostat mesylate is a synthetic serine protease inhibitor, which inhibits various fibrinolytic systems, the kallikrein–kinin system, the complement system, and the activ inhibits lipopolysaccharide-induced nitric oxide production, apoptosis, and interleuki trophoblasts. Moreover, it has been shown to act as an antioxidant in TNF-α-induced treatment of disseminated intravascular coagulation (DIC) and acute respiratory distres as an anticoagulant in extracorporeal circulation such as continuous renal replacement failure in Asian countries.

Recently, Nafamostat mesylate as a serine protease inhibitor prevents the fusion of the surface membranes by inhibiting transmembrane serine protease 2(TMPRSS2), a hum mesylate might have a potential antiviral activity.

Here we review recent studies that showed possible roles of Nafamostat mesylate Nafamostat mesylate in relation to the pathogenesis of COVID-19 are also discussed. It basis for the use of Nafamostat mesylate as a potential therapeutic for COVID-19 in hum for COVID-19 established.

Keywords: Nafamostat mesylate, COVID-19, SARS-CoV-2, Anti-inflammation, An

Introduction

Coronavirus disease 2019 (COVID-19), which started in Wuhan in December 2019, is a pandemic caused by the newly emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (genus Betacoronavirus, family Coronaviridae). This virus has been reported in 227 countries with more than 21,866,088 confirmed cases and 773,726 deaths as of August 18, 2020 [1].SARS-CoV-2 is transmitted primarily via the respiratory route in the form of droplets, and also by contact with fomites in the proximity of infected patients.

The clinical spectrum of COVID-19 encompasses asymptomatic infection, mild upper respiratory tract illness, pneumonia that may result in respiratory failure, multi-organ failure, and death.

Depending on recommends the in whom oxygen anticoagulant, if the United States guideline. Howev treatments so far.

Currently, there new infectious di are looking for d on COVID-19. Re on the life cycle of COVID-19, alc mesylate, which COVID-19 among

J Cell Immunol. 2021
Volume 3, Issue 1

Received: 10 March 2021 | Revised: 10 June 2021 | Accepted: 22 June 2021

DOI: 10.1002/nano.202100023

RESEARCH ARTICLE

Nano WILEY

Broad antiviral and anti-inflammatory efficacy of nafamostat against SARS-CoV-2 and seasonal coronaviruses in primary human bronchiolar epithelia

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Funding information
National Institutes of Health, Grant/Award Numbers: U01EB029085, R41ES031639; U.S. Department of Defense Congressionally Directed Medical Research Programs Discovery Award, Grant/Award Number: W81XWH2010035; Gordon and Betty Moore Foundation

Abstract

Antiviral strategies that target host systems needed for SARS-CoV-2 replication and pathogenesis may have therapeutic potential and help mitigate resistance development. Here, we evaluate nafamostat mesylate, a potent broad-spectrum serine protease inhibitor that blocks host protease activation of the viral spike protein. SARS-CoV-2 is used to infect human polarized mucociliated primary bronchiolar epithelia reconstituted with cells derived from healthy donors, smokers and subjects with chronic obstructive pulmonary disease. Nafamostat markedly inhibits apical shedding of SARS-CoV-2 from all donors ($\log_{10}$ reduction). We also observe, for the first-time, anti-inflammatory effects of nafamostat on airway epithelia independent of its antiviral effects, suggesting a dual therapeutic advantage in the treatment of COVID-19. Nafamostat also exhibits antiviral properties against the seasonal human coronaviruses 229E and NL6. These findings suggest therapeutic promise for nafamostat in treating SARS-CoV-2 and other human coronaviruses.

KEYWORDS
SARS-CoV-2, Nafamostat, antiviral, anti-inflammatory, airway epithelium

1 | INTRODUCTION

Emerging coronaviruses pose substantial threats to public health and global economic well-being. Over the past 2 decades, new strains of highly pathogenic coronaviruses have emerged by zoonotic transmission to humans, namely severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002, Middle East respiratory

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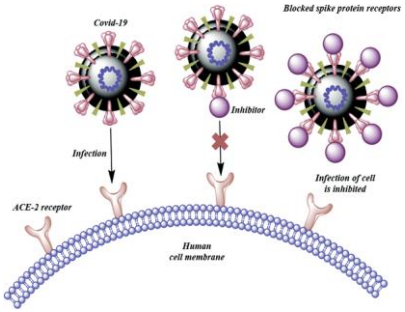
Nano Select 2021;1–13. wileyonlinelibrary.com/journal/nano 1

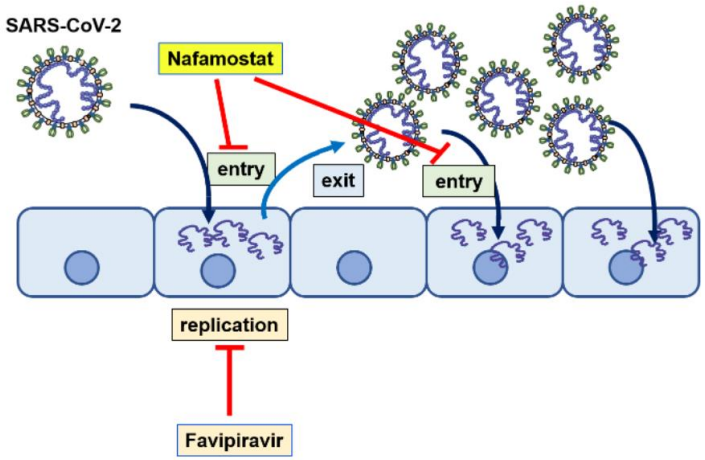


Publications support a potential COVID treatment by inhibiting TMPRSS2

1. B. F. Niemeyer, C. M.Miller, C. Ledesma-Feliciano, J. H. Morrison, R.Jimenez-Valdes,C.Clifton,E.M.Poeschla,K.H.Benam, Nano Select ????,

Combination Therapy will be the Future of COVID Treatment

- Nafamostat inhibits viral entry into cells while other agents, such as inhibitors of viral RNA polymerase, inhibit replication



- Recent Phase 2 study demonstrated sickest COVID patients had higher recovery rate with nafamostat + SOC (61%) compared to SOC alone (11%)

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Research paper

Nafamostat in hospitalized patients with moderate to severe COVID-19 pneumonia: a randomised Phase II clinical trial

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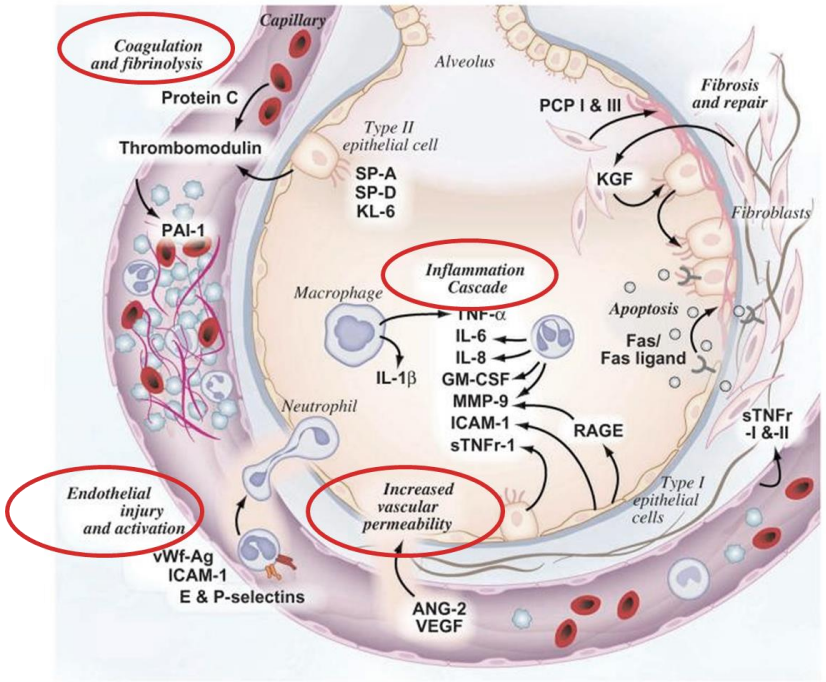
Acute Respiratory Distress Syndrome (ARDS) Overview

ARDS is a life-threatening lung injury that allows fluid to leak into the lungs

- ARDS typically occurs as a result of another condition, such as bacterial pneumonia, sepsis, systemic infections, aspiration, or trauma. Recently, COVID-19 has become a large-scale cause of ARDS
- The goal of current ARDS treatment is primarily to **keep the patient alive until the underlying etiology can be resolved**, and secondarily to prevent medium-or long-term damage to the lungs

Key pathways and proteomic changes involved in ARDS pathogenesis



Levitt 2016

Nafamostat modes of action in ARDS

- Anticoagulation
- Anti-inflammation
- Sustaining endothelial barrier function/preventing vascular leak

Final Q & A Session