Research & Reviews: Journal of Microbiology and Biotechnology

e-ISSN: 2320-3528
p-ISSN: 2347-2286

Possible Role for Heparin/Heparinoid Antithrombotics in the Management of COVID-19 Infection

Magnani HN*

Aspen Pharma, Schoutstraa, The Netherlands

Short Communication

Received date: 01/04/2021
Accepted date: 14/04/2021
Published date: 21/04/2021

***For Correspondence**

Magnani HN, Clinical Consultant, Aspen Pharma, Schoutstraa, The Netherlands

E-mail: harry.magnani@hetnet.nl

INTRODUCTION

Depending upon the SARS-CoV-2 viral load and the susceptibility of the patient, cellular invasion in COVID-19 infection can quickly lead to dysregulation of the normal cross-talk between the immune/complement [1,2] and haemostasis systems [3,4] that co-ordinates their ability to control and/or kill invading pathogens. Viral induced cell death attracts and activates leucocytes and platelets to release a mixture of cytokines, mitogens, and proteins that promote thrombosis or prevent thrombolysis to limit viral spread. By disrupting this co-ordination the virus induces a hyper-inflammatory response with complement activation, cell damage and death, local oedema (in the lungs to pneumonia and respiratory failure) as infected and dying endothelial cells [5] lose their tight junctions, and accelerated thrombin generation producing fibrin deposition in the tissues and microvascular and systemic thromboses. As the invasion proceeds hypoxia and hypoxaemia cause more tissue destruction, amplifying the damage and allowing the virus to spread further.

As a result of the procoagulant state prophylactic antithrombotics [6] have been used with some success to prevent some of the serious sequelae of the infection. However in the body, the ubiquitous natural GlycosAminoGlycans (GAGs) [7] Heparin (HP) and Heparan Sulphates (HS) are closely linked with the immune system control suggesting that treatment with their commercial antithrombotic counterparts, i.e. Unfractionated Heparin Sulphate (UFH), Low Molecular Weight Heparin (LMWH) and heparinoids (sulodexide and danaparoid sodium) might provide similar benefits, especially if the actions are independent of their antithrombotic activity [8,9].

ABOUT THE STUDY

The currently available antithrombotics are heterogeneous mixtures of either a single or mixed groups of negatively charged GAGs extracted and purified from animal tissues. The GAG groups are mainly defined by their content of HP, Heparan Sulphate (HS) and Dermatan Sulphate (DS). Unfractionated Heparin (UFH) and the LMWHs consist of HP with traces of DS, Sulodexide contains 80% HP and 20% DS and Danaparoid is about 85% HS with about 12% DS. The macro and micro chemical structures of their linear hexose chains determine specific binding to many proteins and hence their participation in many physiological activities, e.g. angiogenesis regulation, vascular permeability, cell-cell interactions, cancer spread, lipoprotein processing, antithrombotic activity etc.

Differences in overall negative charge density (HP>LMWH>sulodexide>danaparoid) and chain length (UFH>sulodexide>LMWHs=danaparoid) also influence protein binding which is highest for UFH and lowest for danaparoid. All products inhibit thrombin generation by catalysing the inactivation of Factor Xa by Antithrombin (AT) and similarly inhibit thrombin activity via AT or Heparin Cofactor II. Danaparoid also directly inhibits thrombin mediated Factor IX activation, an important positive feedback loop in states of high thrombin generation. Despite different modes of action the overall effects of UFH, LMWHs, sulodexide and danaparoid on thrombus inhibition are similar.

However other interactions of the heparins and heparinoids produce different effects on bleeding (heparin>LMWH>sulodexide>danaparoid) and their ability to influence immune reactions. Subtle differences in their molecular size shape and charge influence the extent of their participation in immune mediated reactions such as control of glycocalyx/basement membrane permeability, tumour cell growth and metastasis, cell proliferation, angiogenesis, anti-inflammatory activity, reperfusion injury and endotoxin induced injury. These actions have been demonstrated in animal and in vitro experiments but some have been confirmed in volunteer and patient studies. Hence the possibility that the results may translate into a useful therapeutic effect for COVID-19 infection is intriguing.

Is there a preferred candidate for testing in a clinical trial? Many of the immune-modulatory actions occur optimally at therapeutic dosing levels which for the heparins could increase the risk of bleeding [10], especially in severe COVID-19 infection.

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High PF4 levels can result in heparin resistance and the added risk of developing immune Heparin-induced Thrombocytopenia (HIT). Sulodexide and danaparoid have a low bleeding potential even at therapeutic dosing levels and both products have shown immune-modulatory activity [11]. Danaparoid does not interact with PF4, has a unique ability to interfere with the interactions of the HIT antibody with heparin and platelets [12], preserves antithrombotic APC levels that may be important for inhibiting PAI-1 activity and preventing rebound thrombosis, remains effective at moderate to low AT concentrations, and is also approved for the treatment of disseminated intravascular coagulation (including a hyperfibrinolytic variant similar to that seen in COVID-19 infection) and is safe in patients with renal or hepatic failure, children and in pregnancy. Thus would danaparoid or sulodexide [13] be more useful at therapeutic dosing in the management of COVID-19 infection?

CONCLUSION

At which stage of the disease might either be most useful (if at all), since the balance between disruption of inflammatory/immune factors and vascular/haemostatic factors might favour one GAG antithrombotic over the others? If efficacy in restoring the disruption between the immune and haemostasis systems can be established in suitably designed clinical trials, then it would provide a relatively cheap alternative to some of the more expensive drugs currently included in the management of COVID-19 infection. As such it would be more affordable for poorer nations and poorer patients within countries without adequate health care.

CONFLICT of INTEREST

The author led the clinical development of danaparoid sodium until his retirement in 1999 and has since worked as an independent clinical consultant with an interest in anticoagulants.

REFERENCES

1. Java A, et al. The complement system in COVID-19: friend and foe? JCI Insight. 2020;5: e140711.
2. Magro C, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. Translational Res. 2020;220:1-13
3. Levi M, et al. Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet. 2020;7: e438-440.
4. Tang N, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18:844-847.
5. Varga Z, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020;395:1417-1418.
6. Connors J M, et.al.COVID-19 and its implications for thrombosis and anticoagulation. Blood. 2020;135:2033-2040.
7. Lindahl U, et al. Proteoglycans and Sulfated Glycosaminoglycans. Chapt 17 in Essentials of Glycobiology.2015.
8. Cassellini G, et.al. Old and new applications of non-anticoagulant heparin. Int J Cardiol.2016:212; S14-S21.
9. Bikdeli B, et al. Pharmacological Agents Targeting Thrombo-inflammation in COVID-19: Review and Implications for Future Research. Thromb Haemost. 2020;120:1004-1024.
10. Sadeghipour P, et al. Effect of Intermediate-Dose vs. Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality Among Patients With COVID-19 Admitted to the Intensive Care Unit. The INSPIRATION Randomized Clinical Trial. JAMA.2021.
11. Dou H, et al. Heparinoids sulodexide and danaparoid as clinically useful drugs. Prog Mol Biol Translational Sci.2019;163:55-74.
12. Krauel K ,et al. Heparin-induced thrombocytopenia – therapeutic concentrations of danaparoid, unlike fondaparinux and direct thrombin inhibitors, inhibit formation of platelet factor 4-complexes. J Thromb Haemost.2008;6:2160-2167.
13. Magnani HN. Rationale for the Role of Heparin and Related GAG Antithrombotics in COVID-19 infection. Clin Appl Thromb Hemost. 2021;27:1-26.