Fighting Bacteria With Its Own Weaponry?

To the Editor:

For many years, intrapleural administration of fibrinolytics and deoxyribonuclease (DNase) was a controversial issue in the management of complicated parapneumonic effusion and empyema.\(^1\) Their effectiveness was assessed in a large clinical trial (the second Multicenter Intrapleural Sepsis Trial).\(^2\) Coadministration of tissue plasminogen activator and DNase was beneficial in terms of radiographic progression, days of hospitalization, and surgical referral. Instead, DNase alone increased the need for surgery.\(^2\) The rationale behind DNase use was to facilitate effusion drainage via chest tube. So why did DNase monotherapy lead to an unfavorable outcome?

First, the main pathogens detected in pleural infections (the Streptococcus milleri group, Staphylococcus aureus, Streptococcus pneumoniae) encode DNases in their genomes. Those nucleases are emerging as potential virulence factors, due to their ability to degrade neutrophil extracellular traps (NETs).\(^3\) Released from neutrophils, NETs, composed mainly of chromatin and certain proteins, entrap and kill bacteria extracellularly. Furthermore, those weblike structures are in abundance in pus,\(^4\) thus, their disassembly may explain the appreciable viscosity reduction after DNase treatment. Another issue is the DNases’ biofilm-dispersing activity. Indeed, DNases have been reported to degrade biofilms,\(^5\) but their role in acute infections is an open question. To refine our therapeutic strategies, the exact nature of the tissue plasminogen activator-DNase synergism and NETs disruption impact on clinical course are areas in which further insight must be gained.

Dimitrios Ntelios, MD
Volos, Greece

AFFILIATIONS: From the Volos General Hospital, Department of Internal Medicine.

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CORRESPONDENCE TO: Dimitrios Ntelios, MD, Volos General Hospital, Department of Internal Medicine, Polymeri 134, 38222, Volos, Greece; e-mail: ntdimitris@yahoo.gr

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References


Response

To the Editor:

We would like to thank Dr Ntelios for his letter regarding the point/counterpoint editorial discussion on the treatment in pleural infection.\(^1\) Dr Ntelios discusses the potential mechanisms of combined intrapleural fibrinolytics and deoxyribonuclease (DNase) therapy in improving drainage in pleural infection and the potential causes of DNase monotherapy in increasing the need for surgical referral.

The second Multicenter Intrapleural Sepsis Trial (MIST2) study results demonstrated efficacy for improving radiographically measured pleural drainage with the combination of intrapleural tissue plasminogen activator (tPA) and DNase, whereas the agents given alone had no significant effect over placebo for the primary outcome measure.\(^2\) In the first MIST Study, fibrinolytics alone were shown to have no significant effect over placebo.\(^3\) We assume that this is related to a combination of septation disruption and a DNase effect that could be related to either viscosity changes or treatment of intrapleural biofilms, although the exact mechanism is unclear.

DNase alone had negative effects on pleural infection, and this may be a clue about the mechanism of action. In MIST2, the need for surgical intervention was increased with DNase alone, and in parallel, there was a nonsignificant trend toward increased fever in the DNase-alone group.\(^2\) This is in contrast to the result seen...
with combination tPA and DNase in which there was a statistically significant reduction in the need for surgery and a statistically significant reduction in the odds of fever by day 3 compared with placebo. Although these were secondary outcome measures and should, therefore, be treated with some caution, one possible explanation for this result is that DNase alone liberated bacteria (eg, from biofilms), but in the absence of an agent to improve pleural drainage (ie, a fibrinolytic), this resulted in increased systemic sepsis. The effect of DNase alone on neutrophil extracellular traps would also be a reasonable potential mechanism. Within the MIST2 study, we specified that surgical intervention should occur in response to both ongoing pleural collection and markers of systemic sepsis after treatment (eg, raised inflammatory markers and fever), and this might explain the negative effects of DNase alone on the surgical outcome. We agree that further translational work is now required to elucidate the interactions of tPA, DNase, and the pleural infection microenvironment, which create the significant clinical results seen in MIST2.

John P. Corcoran, MD
Najib M. Rahman, DPhil
Oxford, England

AFFILIATIONS: From the Oxford Centre for Respiratory Medicine (Drs Corcoran and Rahman), Oxford University Hospitals; Oxford Respiratory Trials Unit (Drs Corcoran and Rahman), University of Oxford; and NIHR Oxford Biomedical Research Centre (Dr Rahman).

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CORRESPONDENCE TO: Najib M. Rahman, DPhil, Oxford Respiratory Trials Unit, Oxford University Hospitals, Old Rd, Oxford, OX3 7LE, England; e-mail: najib.rahman@ndm.ox.ac.uk

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