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REVIEW

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Perspective and update: intrapleural fibrinolytic therapy for pleural infections and other forms of pleural organization

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Abstract

Intrapleural fibrinolytic therapy (IPFT), also known as intrapleural enzymatic therapy (IET), has been utilized for decades to treat pleural infections by expediting drainage in patients with pleural organization. The successful MIST2 trial demonstrated that IPFT improves pleural opacification, reduces hospital stays, and decreases short-term surgical referrals. Despite significant progress, gaps remain in identification of the optimal fibrinolytic agents, dosing, and safety improvements. IPFT is generally recommended for patients with loculation and failed pleural drainage, with a consensus panel advocating for combined tissue plasminogen activator (tPA) and DNase therapy. How each agent may affect the activity or function of the other in the combination remains unclear. While IPFT can reduce the need for surgical intervention, there are relatively few comparative clinical trials to guide initial therapy. Emerging low-dose IPFT treatment approaches may benefit patients who are poor surgical candidates. Personalized IPFT candidate approaches, such as the Fibrinolytic Potential Assay (FPA), could refine dosing and improve outcomes. Additionally, biomarkers like pleural fluid PAI-1 and suPAR concentrations may predict clinical outcomes and guide treatment. New therapeutic agents, including PAI-1 inhibiting peptides and mesothelial profibrogenic targets, are under investigation to enhance IPFT efficacy. These advances hold promise for improving the management of pleural infections and other forms of pleural organization.

Introduction

Intrapleural fibrinolytic therapy (IPFT), sometimes now referred to as intrapleural enzymatic therapy (IET), had its inception for the treatment of pleural infection decades ago. It is designed to expedite drainage in patients with organization associated with pleural infections as well as those with retained hemothorax or loculation of malignant effusions (Fig. 1). Current use of IPFT for pleural infections was particularly buttressed by the successful MIST2 trial which showed improved pleural opacification, reduced hospital stay and reduced short-term surgical referral [1]. We last wrote about this topic seven years ago in this journal, at which point there were several unknowns about how IPFT should be used and what limitations existed. The key gaps included a lack of understanding about which fibrinolytic agents or combinations were optimal, empiric dosing of currently available agents and whether effectiveness and safety could be improved by better understanding of these important areas. Significant progress has been made in the interim but the partially addressed gaps remain. Their recognition is a catalyst for this update, which we hope may better inform expectations for clinicians who manage the complexities of treating patients with loculation and compromised drainage.

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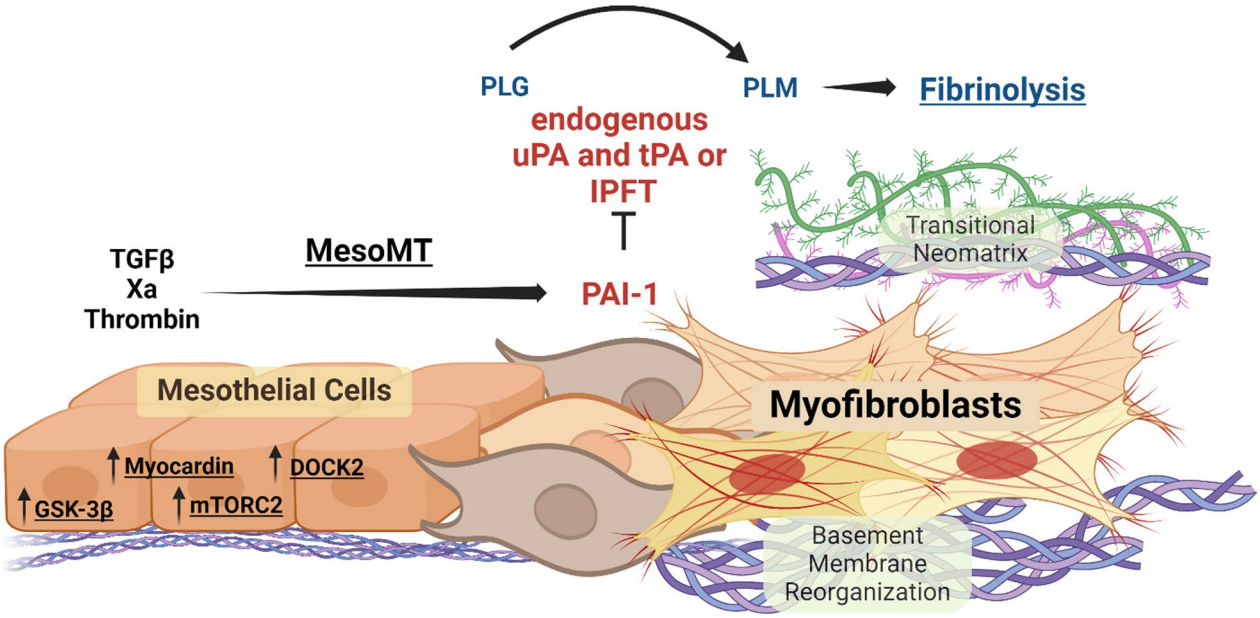

Fig. 1 Degradation of intrapleural organization by IPFT. IPFT (uPA or tPA ± DNase) or endogenous uPA and tPA degrade the transitional, extracellular fibrinous neomatrix in the pleural space. Intrapleural organization may accompany intrapleural infections, retained hemothoraces or organizing pleural malignancies. The process is regulated by mediators, such as TGFβ, coagulation factor Xa, and thrombin, which promote elaboration of neomatrix components by the mesothelium and cells of alternative lineage [3]. Pleural organization also involves transition of pleural mesothelial cells to myofibroblasts (MesoMT). Fibrinolysis is suppressed via upregulation of PAI-1 and inhibition of endogenous or exogenous plasminogen activator activity. Myofibroblasts also contribute to the reorganization of the pleural space by producing excess extracellular matrix proteins like collagen and fibronectin at the mesothelial surface and basement membrane. Targeting various aspects of this transition may offer therapeutic opportunities for treating fibrothorax. Potential targets include the inhibition of profibrogenic signaling pathways such as GSK-3β and mTORC2, as well as proteins like DOCK2 and myocardin [20]. Additionally, restoration of local fibrinolysis by administration of intrapleural tPA and uPA can counteract PAI-1-mediated inhibition, block further deposition of fibrin and clear loculation associated with relatively advanced intrapleural organization. Green Strands- Fibrin, Pink Strains- other extracellular matrix proteins including fibronectin, Purple strands- collagen strands

Current use of IPFT

IPFT is now generally advocated for use in patients with loculation and failed pleural drainage, although some of the patients in MIST2, for example, had free flowing effusions and pleural infection [1]. Interestingly, a consensus panel stratified use of IPFT for pleural infections based on initial utilization at initial placement of the chest drain in selected patients and depending on the availability of surgical expertise[2]. In addition, the panel recommended combined tissue plasminogen activator (tPA) and DNase therapy given at a dose of 10 and 5 mg respectively, twice a day; the same dosing used in MIST2[1]. The use of concurrent administration of these agents was recommended although it was acknowledged that the effects of either agent on the other were unknown. In other centers, the use of single agent IPFT for pleural infections has been and is still reported, as in the past[3, 4]. A starting dose of 5mg of tPA with 5mg of DNase appears to be safe and effective [5, 6]. Reduced dosing of the tPA in the combination now derives from a limited number of dose de-escalation studies, such as the informative ADAPT2 trial. [6, 7] Bleeding remains a complication with such dose de-escalations and the authors acknowledge that additional trial testing of reduced dose tPA in the tPA/DNase combination IPFT are required.

IPFT vs. surgery for empyema

IPFT can mitigate the need for surgical intervention in pleural infections although there are relatively few comparative studies of the approaches in organizing pleural infection, as recently reviewed. [2], While debate continues about the roles of IPFT versus surgery for management of empyema, surgery in early-stage empyema may shorten the need for chest tube access and hospital length of stay, when compared with IPFT [8]. However, it is more invasive, requires a trained surgical team, results in frequent procedural complications, and has mortality. The MIST3 prospective study [9] compared patients who failed initial standard therapy with antibiotics or tube thoracostomy and concluded that while the standard treatment of patients with empyema may be less effective than early IPFT or VATS, there may have been a significant cohort (up to 50% of patients randomized to the VATS group), who did not appear to require surgical

treatment [9]. A recent prospective pilot comparison of surgery with MIST2 tPA/DNase IPFT in patients with failed chest tube drainage demonstrated trends towards shorter chest tube use and hospital length of stay in the surgical group [10]. While further prospective clinical trials are needed to compare efficacy of early surgery and IPFT/IET for, novel low-dose IPFT/IET treatments emerging from preclinical studies [3] may benefit patients who poor surgical candidates or who decline surgery.

Monotherapy vs. combination therapy

Whether tPA/DNase IPFT affects the activity of either agent remains unclear and could be tested in vitro or in the presence of a range of pleural fluids from patients with pleural infections, retained hemothorax or loculated malignant pleural effusion, but to our knowledge these analyses have yet to be done. While currently available combination with tPA offers advantages[1], monotherapy with an intrapleural fibrinolytic agent appears to be safe and effective in pediatric pleural infections, and DNase appeared to offer little advantage to use of a fibrinolytic agent in children [11]. Single agent; fibrinolysin IPFT also appears to be effective and safe when administered in patients with retained hemothorax [3, 4] and possibly organizing pleural malignancies with loculation. Whether single agent therapy could be of benefit in subsets of adults with pleural infections and failed pleural drainage is also now unclear. At present, trials of this type would predictably be challenging given the uncertainties of dosing and best timing of such interventions.

All things considered, the use of tPA (10mg) and DNase (5mg) has been advocated [1, 2] and currently has the best evidentiary foundation for use in adult patients with pleural infections. It is important to remember that this dosing was empirically selected rather than predicated on preclinical dose response and toxicology studies. Would doses of more; 12 or 15 mg of tPA for example (or slightly less) be well-tolerated and more effective? Is the dosing schedule really optimal or can that be modified to advantage better clinical outcomes? Is the dose of the DNase adjunct optimal or even needed if the dose of tPA was optimized? These considerations derive from the off-label use of the tPA/DNase combination and remain to be examined in patients with loculated organizing pleural infection and compromised drainage.

Lower doses of tPA may be effective in infectious pleural loculation with failed drainage, but more clinical trial evidence is needed. [7] Whether such dosing could be effective and mitigate clinical bleeding could be tested by determining the ability of the different forms of IPFT to generate fibrinolytic and plasminogen activator (PA) activity in pleural fluids of patients with empyema exposed to the different regimens. These effects were measured in pleural fluids of patients receiving escalating doses of single chain urokinase PA (scuPA), a novel candidate for treatment of loculated pleural infections with failed drainage [12]. scuPA is relatively resistant to inactivation by plasminogen activator inhibitor-1 (PAI-1), the major PA inhibitor within pleural fluids[3, 12]. A phase 1 clinical trial demonstrated that this agent was well-tolerated and did not cause bleeding in a cohort of patient exposed to a range of doses of scuPA [12]. Antigenic and active PAs and PAI-1 as well as PA and fibrinolytic activities within pleural fluids were measured to assess the effects of the various intrapleural scuPA dose regimens over time and their relationship to clinical outcomes. While we are unaware of any other studies in which the relationship of the effects on IPFT on aberrant pleural fibrinolysis and outcomes was assessed, this approach could aid in the interpretation of the effects of different forms of IPFT in individual patients and could provide new insights to optimize or personalize IPFT.

Personalized IPFT approaches

The personalized approach to IPFT/IET now relies on dosage adjustments of currently used forms of IPFT in individual cases. A stratified approach to dosing of tPA as part of the tPA/DNase regimen has been suggested for the treatment of organizing pleural infections, for example [7]. Apart from these dosing iterations, a paucity of reliably safe and effective personalized IPFT care now exists. A candidate diagnostic, measurement of the ability of IPFT to overcome endogenous PA inhibitors in pleural fluids, called the Fibrinolytic Potential Assay (FPA), could be used to refine or personalize the dosing of IPFT [4]. The FPA represents the amount of fibrinolytic activity that is detectable within pleural fluid after supplementation by a relatively large dose of a fibrinolysin. The concept is that the measured fibrinolytic activity could be a guide to treatment or dosing of IPFT/IET. A close iteration of this assay was measured in the recent scuPA phase 1 trial [12], but the test needs to be validated for clinical use, and future investigation is warranted.

Biomarkers and predictive factors

Recently, it has been recognized that components of the fibrinolytic system within pleural fluids not only regulate fibrinolytic agents and IPFT but relate to outcomes of pleural infection. Pleural fluid PAI-1 was found to relate to the formation of intrapleural septations, their severity, length of hospital stay and 12-month mortality [13]. While increasing concentrations of PAI-1 antigen were associated with the severity of septations, their presence did not relate to clinical outcomes. PAI-1 rapidly inhibits tPA and the two chain active form of urokinase and lesser amounts of PAI-1 activity are detectable

in pleural fluids of empyema patients than total PAI-1 antigen. [12]. While PAI-1 activity was not measured in this study, it likely contributes to both pleural septation/loculation severity and may better reflect clinical outcomes. At present, this issue remains to be further clarified in future clinical trial testing. IPFT was used in a minority of these patients [13] as the samples were collected some time ago, before IPFT became more commonly used. Prospective future analyses will be needed to assess the contribution of PAI-1 to clinical outcomes and to the effectiveness of IPFT and its safety. In a related vein, increased soluble urokinase receptor (suPAR) concentrations in pleural fluids of patients with pleural infections were recently found to occur in loculated versus non-loculated parapneumonic pleural effusions and predict the need for more invasive chest tube management [14]. While this is a another promising biomarker, its validation and clinical utility awaits further rigorous clinical trial testing. The potential role of pleural fluid suPAR as a repository for uPA or scuPA, and its influence on uPA-based forms of intrapleural fibrinolytic therapy (IPFT), remains uncertain at this time.

Recently, it was reported that a deficiency of plasminogen occurred in pleural fluids of patients with pleural infections attributable to proteolytic degradation of plasminogen, mainly by neutrophil elastase and that in vitro supplementation with plasminogen could restore the fibrinolytic activity of the pleural fluids [15]. The study was small, including analyses of 10 patients who received either tPA/DNase over 3 days or were allocated to video-assisted thoracoscopy. It was not clear precisely when PAI-1 activity was measured after these treatments, but the PAI-1 deficiency that was seen could have been related to proximate delivery of the IPFT and collection of the pleural fluid samples. In time course studies, the deficiency of PAI-1 activity is transient and largely resolves when samples were collected prior to IPFT with scuPA [12]. If actionable decrements of plasminogen consistently occur in patients with pleural infections, it is likely that it and dynamic levels of PAI-1 levels may both contribute to failed IET/IPFT. Nevertheless, the authors acknowledge that further preclinical or clinical studies of plasminogen supplementation to tPA/DNase IFT/IET are needed. We believe that preclinical testing is prudent to assess safety and efficacy of plasminogen supplementation and dose-ranging estimates in anticipation of clinical trial testing. How pleural fluid plasminogen concentrations are regulated in organizing pleural conditions and by IPFT with plasminogen supplementation needs to be better understood. These remain additional areas requiring further scrutiny.

Future directions and research

New advancements might result in new developments in IPFT techniques. These could stem from new treatments for intrapleural fibrinolysis, pleural organization, and loculation with unsuccessful drainage (Fig. 1). These include intrapleural administration of PAI-1 inhibiting peptides or antibody adjuncts, which remain under active investigation [3]. New forms of packaging, including liposomal delivery designed to reduce the dose of effective IPFT and reduce bleeding are likewise being explored [3]. In a different but complimentary approach, new mesothelial profibrogenic targets are being studied to identify new interventional candidates that interrupt intrapleural organization and scarification. Thes include glycogen synthetase kinase 3β, a multi-functional regulator of apoptosis (GSK-3β)[16]; myocardin, a protein gene regulator [17] and mTOR complex 2 (mTORC2)[18], a protein complex that regulates cellular differentiation. DOCK2 (Dedicator of cytokinesis 2) is likewise implicated in MesoMT and pleural fibrosis[19] (Fig. 1). Whether these targets will ultimately yield new interventions that work independently or with IPFT remains to be determined but the leads are promising and are being aggressively pursued.

Abbreviations

IPFT	Intrapleural fibrinolytic therapy
IET	Intrapleural enzymatic therapy
tPA	Tissue plasminogen activator
scuPA	Single chain urokinase plasminogen activator

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SI, TAT and AAK wrote the main manuscript text. TAT prepared the Figure All authors reviewed the manuscript.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interest

Drs. Tucker and Komissarov declare no COI related to this work and Dr. Idell has a COI Management Plans from the University of Texas at Tyler. Dr. Idell has equity in Aileron Therapeutics Inc., which is commercializing single chain urokinase for pleural loculation and failed drainage in empyema among other products. He founded Lung Therapeutics, Inc which was acquired by Aileron, now called Rein; a publicly traded company. The authors declare no competing interests.

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