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OPINION
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Opinion: An Existing Drug to Assess *In Vivo* for Potential Adjunctive Therapy of Ebola Virus Disease and Post-Ebola Syndrome

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We currently have no approved drugs for the treatment of Ebola virus disease (EVD) or post-Ebola syndrome (PES). A substantial proportion of patients presenting for treatment die, including healthcare workers (HCWs) with hospital-acquired infections. More than 28,000 people were suspected or confirmed with EVD and 11,000 died in the West Africa outbreak during 2014–2016. A new EVD epicenter developed in the Democratic Republic of Congo in mid-2018, and it is likely that new outbreaks will occur in the future. The low survival rate discourages patients from presenting for treatment, and the occupational risk discourages HCWs from caring for highly infectious patients. A substantial proportion of survivors complain of chronic symptoms, such as eye problems (47%) and arthralgias (64%)—a condition that has been termed PES (Wilson et al., 2018). Inflammation may play a role in both the uveitis, which can result in blindness (Shantha et al., 2017) and in arthritis (Amissah-Arthur et al., 2017). Availability of an efficacious adjunctive treatment drug would save lives, increase the number of people presenting for treatment, and increase the willingness of HCWs to care for patients. An efficacious drug for adjunctive treatment of PES could decrease morbidity suffered by survivors. To date, most research efforts have focused on vaccine for prevention and either antivirals or antibody preparations for treatment. However, given the extensive inflammatory component of EVD, adjunctive therapy to decrease inflammation —but not globally downregulate the host immune response in a manner that could be detrimental (e.g., steroids)—may hold promise for better outcomes for those infected. Although drugs such as acetylsalicylic acid, ibuprofen, indomethacin, and celecoxib are also broadly anti-inflammatory, they all inhibit cyclooxygenase and can interfere with platelet aggregation—a characteristic that would be disqualifying for use with hemorrhagic fevers.

"Cytokine storm," a burst in production of inflammatory cytokines, is thought by many to be integral to EVD pathogenesis, and high levels of tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-10, IL-1β, macrophage inflammatory protein (MIP)-1α, MIP-1β, and macrophage chemoattractant protein (MCP)-1 are associated with fatal infections (Ruibal et al., 2016;

TABLE 1 | Comparison of the Effect of Ebola Virus and Minocycline on Selected Biomarkers.

Biological Marker	Ebola Virus			Minocycline Effect on Physical or Infectious Challenge	
	Nonsurvivors	Survivors	Animal Model[§]	*In Vivo*	*In Vitro*
TNF-α	↑ (Baize et al., 2002)	↑ (Baize et al., 2002)	↑ (Geisbert et al., 2003; Mahanty et al., 2003; Rubins et al., 2007)	↓ (Ledeboer et al., 2005; Masocha et al., 2006; Suzuki et al., 2010; Wu et al., 2012; Hou et al., 2013; Ashraf et al., 2014)	↓ (Szeto et al., 2010; Tai et al., 2013)
IL-6	↑ (Baize et al., 2002; Hutchinson and Rollin, 2007; Wauquier et al., 2010)	↑ (Baize et al., 2002; Wauquier et al., 2010)	↑ (Geisbert et al., 2003; Rubins et al., 2007)	↓ (Ledeboer et al., 2005; Masocha et al., 2006; Suzuki et al., 2010)	↓ (Tai et al., 2013)
IFN-α	↑ (Villinger et al., 1999; Gupta et al., 2012)	↑ (Villinger et al., 1999; Gupta et al., 2012)	↑ (Geisbert et al., 2003; Mahanty et al., 2003)		↓ (Drewes et al., 2014)
MIP-1α	↑ (Wauquier et al., 2010)	↑ (Wauquier et al., 2010)	↑ (Geisbert et al., 2003; Rubins et al., 2007)	↓ (Suzuki et al., 2010)	↓ (Tai et al., 2013)
MIP-1β	↑ (Baize et al., 2002; Hutchinson and Rollin, 2007; Wauquier et al., 2010)	↑ (Wauquier et al., 2010)	↑ (Geisbert et al., 2003; Rubins et al., 2007)		↓ (Tai et al., 2013)
MCP-1			↑ (Geisbert et al., 2003; Mahanty et al., 2003; Rubins et al., 2007)	↓ (Suzuki et al., 2010)	↓ (Tai et al., 2013)
MMP-3			↑ (Cilloniz et al., 2011)	↓ (Masocha et al., 2006)	↓ (Fortier et al., 2010)
Markers of oxidative stress[¶]	↑ (Sanchez et al., 2004)		↑ (Hensley et al., 2002; Geisbert et al., 2003)	↓ (Suzuki et al., 2010; Huang et al., 2012; Ashraf et al., 2014)	
Pro-apoptotic factors/ markers[Ψ]	↑ (Hutchinson and Rollin, 2007; Wauquier et al., 2010)	↑ (Hutchinson and Rollin, 2007)	↑ (Rubins et al., 2007)	↓ (Chu et al., 2005; Czerny et al., 2012; Drewes et al., 2014)	↓ (Yang et al., 2007; Tai et al., 2013)
Anti-apoptotic marker (bcl-2)			↓ (Gupta et al., 2012) *(in vitro)*		↑ (Tang et al., 2007)
Liver function	↑ (Rollin et al., 2007)	↑ (Rollin et al., 2007)	↑ (Geisbert et al., 2003)	↓ (Chu et al., 2005; Czerny et al., 2012)	↓ (Szeto et al., 2010; Schwartz et al., 2013)

[§]*In vitro data for Ebola can be found in references.*

[¶]*iNOS (inducible nitric oxide synthase), NO (nitric oxide), nitrate, SOD (superoxide dismutase).*

[Ψ]*TACE (tumor necrosis factor-α converting enzyme), TRAIL (tumor necrosis factor [TNF]-related apoptosis-inducing ligand), RANTES (regulated upon activation, normal T cell expressed and secreted), Eotaxin, Fas (Fas antigen), FasL (Fas antigen ligand), caspase-3, annexin.*

IL, interleukin; MIP, macrophage inflammatory protein; MCP, macrophage chemoattractant protein; MMP, matrix metalloproteinase. ↑, significantly increased; ↓, significantly decreased.

Vernet et al., 2017). Nuclear factor of activated T cells (NFAT) is thought to be *the* key transcriptional regulator of inflammatory mediators (Madelain et al., 2018). Knock-out mice with dampened cytokine response (Tim-1 -/-) are considerably more likely to survive Ebola virus challenge than their wild-type counterparts, despite a limited impact on viremia (Younan et al., 2017).

We questioned whether the inflammation associated with cytokine storm could be countered pharmaceutically—and having some familiarity with one antimicrobial (minocycline) with significant anti-inflammatory properties as well as documented antiviral activity—we searched PubMed for articles describing cytokine activity during EVD and during minocycline use.

Minocycline is an FDA-approved semisynthetic tetracycline with an established safety profile that has been used for 40 years in the treatment of acne and rosacea (Cullen and Cohan, 1976; Hersle and Gisslen, 1976), and more recently, for multidrug resistant *Acinetobacter* (Lashinsky et al., 2017). It appears to have activity against certain viral pathogens: It inhibits H7N9 replication *in vitro* (Josset et al., 2014), attenuates stimulation of interferon-related gene and TRAIL[Ψ] in human dendritic cells and PBMCs exposed to HIV or influenza virus (Drewes et al., 2014), reduces West Nile Virus titers in brain-derived cell types in a dose-dependent manner (Michaelis et al., 2007), reduces Japanese encephalitis-induced damage in neuronal cell cultures (Mishra et al., 2009), and, based on molecular dynamics, may possibly inhibit the binding of Congo Crimean hemorrhagic fever virus to host nucleoprotein during cell infection—a host protein that is believed to be pivotal to viral replication (Sharifi et al., 2017). In a randomized controlled trial of patients with dengue hemorrhagic fever, compared to patients who received standard-of-care supportive treatment, those who also received the related tetracycline class antibiotic—doxycycline—had significantly lower mortality [20.9% vs 11.2% ($p < 0.05$)] and lower TNF and IL6 levels on days 3, 5, and 7 ($p < 0.05$ for all)

(Fredeking et al., 2015). **Table 1** compares the effects of Ebola virus and minocycline on selected biomarkers including important cytokines and chemokines.

As shown in our table, the anti-inflammatory activity of minocycline opposes those of many gene products of Ebola virus. It also selectively impairs NFAT-mediated transcriptional activation (Szeto et al., 2011). Due to its small size and lipophilic nature, minocycline may reach potentially therapeutic concentrations in tissue compartments for which antibiotic penetration is typically difficult, such as the eye (Abcouwer et al., 2013; Scholz et al., 2015) and joints (McEvoy, 2016). Such spaces appear to be capable of harboring Ebola virus (Varkey et al., 2015; Steptoe et al., 2017; Subissi et al., 2018) and are thought to contribute to the chronic sequelae seen in PES (Shantha et al., 2017; PREVAIL III Study Group, 2019; Heydari-Kamjani et al., 2019). However, pharmacokinetic/pharmacodynamic (PK/PD) data are lacking that would confirm minocycline penetration into such spaces. As previously mentioned, inflammation may play a role in both the potentially blinding uveitis and arthritis of PES. Although there are animal data to suggest that minocycline may have anti-inflammatory effects in the eye (Scholz et al., 2015) and human data to suggest anti-inflammatory activity in joints (Pradier et al., 2018), it is not known whether it has direct antiviral activity against Ebola virus.

Given minocycline's broad anti-inflammatory activity against cytokines/chemokines that appear to be pathologically upregulated by Ebola virus and the safety history, relative availability, and affordability of minocycline, we feel it should be investigated as an adjunctive therapy in animal models of acute EVD. Given that it appears to cross into protected spaces where it may have anti-inflammatory activity, we feel it should also be investigated as adjunctive therapy for chronic sequelae of EVD (i.e., PES). It is likely that the anti-inflammatory benefit would be greater in certain infected populations (starting treatment early vs late in the infection), and it is also possible that, for some, downregulation of inflammation in general could impair host clearance of the virus. These important issues are amenable to investigation in animal models.

AUTHOR CONTRIBUTIONS

KH performed the literature review and drafted the table and text. MP helped to synthesize the tabular data and edited the text. JB reviewed the information and edited the text.

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Disclaimers: Use of trade names and commercial sources is for identification only and does not imply endorsement. This is an opinion piece based on literature review. No experiments have been conducted or data collected at this time for the potential adjunct treatment of Ebola virus disease or post-Ebola syndrome.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.