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Review Article

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Biomarkers, Pandemics and Host Response Treatment

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Abstract

Biomarkers for the COVID-19 pandemic and other forms of severe critical illness are beneficially affected by generic drugs – statins, ACE inhibitors, angiotensin receptor blockers (ARBs) and metformin. These drugs are widely available and affordable in low- and middle-income-countries (LMICs). Considered together, they are the only practical way that poor people in these countries might be able to reduce pandemic mortality. Combination treatment with these drugs might not affect pandemic viruses but by modifying the host response to infection they might save lives. Sadly, WHO and major foundations have not been interested in testing this idea. If combination treatment could be shown to work, it could have a remarkable effect on LMIC mortality due to any pandemic virus.

Keywords: biomarkers, pandemics, host response treatment, COVID-19

The COVID pandemic has receded, but the virus has not disappeared. Its impact has been especially severe in low-and middle-income (LMIC) countries [1, 2]. Its cost in the first 2-3 years was nearly 30 trillion dollars. Almost half of these costs were generated in the US [3]. High levels of governmental intervention have been needed to control its impact [4]. Effective vaccines against the SARS-2 virus were developed in less than a year, but a WHO program to vaccinate everyone, especially those in LMICs, fell short [5]. Effective treatments have also been slow to appear. Widespread antiviral treatment, together with vaccination, would have been effective in reducing mortality, but in LMICs antivirals have been costly and largely unavailable [6].

Another approach to reducing mortality in LMICs might have been to modify the host response to infection [7, 8]. For more than a decade I have worked on this approach to emerging pandemic threats [9-12]. The idea has not attracted much attention , despite its practicality and the potential benefits of using certain generic drugs [statins, ACE inhibitors (ACEis), angiotensin receptor blockers (ARBs), and metformin] in LMICs. These drugs are widely available and should be affordable. One reason for considering them is their almost universal effect on biomarkers of critical diseases [13].

A biomarker (i.e., biological marker) is a naturally occurring molecule, gene, or characteristic that identifies a specific pathological or physiological process [13]. It captures what is happening in a cell or an organism at a given moment and serves as an early warning system for health, not on how an individual feels or functions. The FDA-NIH Biomarker Working Group on Biomarkers, EndpointS and other Tools (BEST) defines seven biomarker categories - susceptibility/risk, diagnostic, monitoring, prognostic, predictive, pharmacodynamic/response and safety - that can reflect an exposure or therapeutic intervention. Qualified biomarkers (not the biomarker measurement method) can reduce regulatory uncertainty during drug development. They have undergone a formal regulatory process so we can rely on them to have specific application in the development and regulatory review of a medical product.

There are many biomarkers for COVID, only some of which are listed in Table 1. The references for these biomarkers were obtained from PubMed [15-222]. Remarkably, almost all are beneficially influenced by generic drugs. (Some biomarkers (e.g., sox17, GDF15) have been developed only recently and have not been tested.) The table gives references for each generic drug that affects each biomarker. They are listed for statins, ACE inhibitors, ARBs and metformin. Several critical illnesses [sepsis, acute respiratory distress syndrome (ARDS), COVID-19] are also affected by these biomarkers. The references are a mix of in vitro and in vivo studies and cite mostly observational studies. Only articles that show the relationships between each biomarker and

each drug are listed. The articles are representative, not central to establishing the relationship between the two.

There are a great many reports of the effectiveness of individual generic drugs (monotherapies) in treating COVID patients. Many studies (mostly observational) have shown that outpatient (preadmission) statin treatments are associated with reduced mortality but not all studies have yielded similar results [223-225]. Studies of inpatient treatment are no different. Despite a recently published RCT showing beneficial results from inpatient statin treatment (226), not all RCTs of inpatient treatment have given similar results [227]. One reason for this discrepancy is failure to consider whether patients continued with statin treatment after hospital admission [228]. Outcomes (including mortality) can be different in patients whose preadmission statin treatment is not continued after hospital admission [229].

Outpatient treatment with ACE inhibitors or ARBs has sometimes been shown to be beneficial, but not all reports have shown similar results [230-233]. One report showed that ACEi/ARB treatment had no effect on mortality [234]. Although outpatient treatment might not reduce COVID mortality, for patients with more severe disease, continuing ARB treatment after hospital admission can reduce mortality [235, 236]. For preadmission metformin treatment, three recent meta-analyses have come to different conclusions. Two showed reductions in mortality but the third one did not [237-239].

Given the confusing results of different reports of monotherapies, it might be worth considering combination treatment (a statin, an ARB, and metformin). Surprisingly, no one has yet undertaken such a study for COVID. Its benefits for poor people in LMICs are obvious; they can ill afford expensive antiviral or other treatments and vaccines remain too expensive and are inequitably distributed. It is not as though combination treatment hasn't been tried. In the pre-COVID era different drugs combinations were tested against hypertension and other cardiovascular diseases and diabetes mellitus [255-264]. In these reports and for the outcomes studied (some of which included biomarkers), combination treatment was, without exception, better than monotherapy [240-254].

Why no one has suggested testing combination generic drug treatments for COVID (or other forms of severe critical illness) is a question I cannot answer. Neither can I suggest a mechanism for how combination treatment might save lives. Generic drug treatment might affect overwhelming inflammation, mitochondrial dysfunction, or endothelial cell functioning. In all likelihood, COVID-related mortality (and all pandemic-related mortality) is multifactorial and combination treatment might affect only one of many mechanisms (sub phenotypes) [265, 266].

No one has stepped up to make a decision to test generic drugs for host response treatment – not the World Health Organization (WHO) nor major foundations that have been active in pandemic preparedness. Treating the host response is the only practical approach that might save the lives of poor people who live in LMICs because generic drugs are widely available and affordable in these countries. Efforts to produce a pandemic vaccine and specific treatments in LMICs will not succeed, if only because no one knows how to equitably distribute them. When the next pandemic strikes, poor people will die as a result.

Almost all biomarkers for COVID and other critical illnesses are beneficially affected by statins, ACE inhibitors, ARBs, and metformin. They need to be tested as combination treatment of COVID and future pandemics. This approach might save lives no matter what the next pandemic virus happens to be. It will do little or nothing to counter the virus itself. Instead, in modifying the host response to infection it would simply allow people to live. They can then be vaccinated or take treatment later on that specifically counters the new pandemic virus. The same approach might be taken to treat people with severe life-threatening illnesses (e.g., sepsis, ARDS).

There is no good reason not to test these drugs. The indifference of WHO and major foundations to testing generic drugs for combination treatment is difficult to understand. An agenda for this research has been published [12]. People in LMICs should insist this be done.

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tyrosine kinase (15-18)	TNF (91-94)	MCP-1 (165-168)
janus kinase (19-22)	FOXP3 (95-98)	eNOS/iNOS (169-172)
IL-1 (23-26)	Treg (99-102)	VCAM-1/ICAM-1 (173-176)
IL-4 (27-30)	NADPH oxidase (103-106)	VE-cadherin (177-180)
IL-6 (31-34)	IFN (107-110)	actin cytoskeleton (181-184)
IL-10 (35-38)	TGF-β1 (111-114)	VEGF (185-188)
IL-17 (39-42)	hs-CRP (115-118)	bradykinin (189-192)
lipoxinA4 (43-46)	mTOR (119-122)	CCR5 (193-196)
HMGB1 (47-50)	adiponectin (123-126)	CCL-11 (197,198,ACEis/ARBs - nd)
vWF (51-54)	PPARα (127-130)	FOXM1 (199,200,ARBs - nd, 201)
thrombomodulin (55-58)	PPARγ (131-134)	sirtuin1 (202-205)
thromboxane-A2 (59-62)	α nicotinic Ach receptor (135,136,ARBs – nd,137)	apelin (206-209) AhR (210-213)
t-PA (63-66)	RAGE (138-141)	ATF3 (214,215,ACEis/ARBs – nd)
P-selectin/E-selectin (67-70)	ferritin (142-145)	DAMP/alarmin (216-219)
PAI-1 (71-74)	mitochondria (146-149)	TREM-1 (220,221,ACEis/ARBs - nd)
β-arrestin (75-78)	HO-1 (150-153)	IFNλ (222,ACEis/ARBs/met – nd)
Inflammasome (79-82)	KLF4 (154-157)	
AMPK (83-86)	angpt2/Tie2 (158-161)	GDP15 (stat,ACEis/ARBs,met – nd)
MAPK/Akt (87-90)	ACE2 (162-164,met – nd)	sox17 (stat,ACEis/ARBs,met – nd)

Table 1: Beneficial effects of statin, ACE inhibitor or ARB treatment on biomarkers of inflammation, mitochondrial functioning and/or endothelial barrier integrity

Adapted from reference 12 and updated. The biomarkers in this table are representative and do not include all that affect inflammation, mitochondrial functioning or endothelial barrier integrity. Beneficial treatment by statins, ACE inhibitors (ACEis) or angiotensin receptor blockers (ARBs) is defined as either up regulation or down regulation in cell signaling pathways that reduce inflammation, improve mitochondrial functioning and/or improve endothelial barrier integrity. The literature for each agent on each biomarker is extensive and individual articles are cited. These selected citations are representative and are meant to indicate only the relationship between each generic drug and each biomarker.

Abbreviations. α7 nicotinic aCh receptor = alpha7 nicotinic acetylcholinesterase receptor; ACE2 = angiotensin converting enzyme-2; ACEis – ACE inhibitors; AhR = aryl hydrocarbon receptor; Akt = a serine/threonine kinase (also called protein kinase B) ; angpt = angiopoietin; AMPK= adenosine monophosphate kinase; ARBs = angiotensin receptor blockers; ATF3 = activating transcription factor 3; CCR5 = cysteine cysteine chemokine receptor 5; CCL-11 = C-C motif chemokine 11 (eotaxin-1); eNOS/iNOS = endothelial/inducible nitric oxide synthase; DAMP/alarmin = damage-associated molecular pattern/alarmin; FOXM1 = fork head box M1; FOXP3 = fork head box P3; HMGB1 = high mobility group box 1; hsCRP = highly sensitive C-reactive protein; HO-1 = heme oxygenase-1; IFN = interferon; IL-1 = interleukin 1; IL-4 = interleukin 4; IL-6 = interleukin 6; IL-10 = interleukin 10; IL-17 = interleukin 17; KLF4 = Kruppel-like factor 4; MAPK/Akt = mitogen-activated protein kinase/three members of the serine/threonine protein kinase family; MCP-1 = monocyte chemoattractant protein-1; mTOR = mechanistic target of rapamycin kinase; met = metformin; NADPH = nicotinamide adenine dinuelotide phosphate; nd = no data; PAF = platelet activating factor; PAI-1 = plasminogen activator inhibitor-1; PAR = protease activator receptor; PPARα = peroxisome proliferative activated receptor alpha; PPARγ = peroxisome proliferative activated receptor gamma; P-selectin/E-selectin = platelet and endothelial selectin; RAGE = receptor for advanced glycation end products; stat = statins; TGF-□1 = transforming growth factor-β1; tie-2 = an endothelial cell-specific tyrosine kinase; tPA = tissue plasminogen activator; TREM-1 = triggering receptor expressed on myeloid cells 1; Treg = regulatory T cells; TNF = tumor necrosis factor; VCAM-1/ICAM-1 = vascular/intercellular adhesion molecule-1; VE-cadherin = vascular endothelial-cadherin; VEGF = vascular endothelial growth factor; vWF = von Willebrand Factor