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tied to their clinical productivity) and thereby decrease adoption? Will the added data collection be actionable in terms of clinical management [13], or merely potentially valuable in the future? Who should order and interpret a novel assay – a consulting sub-specialist (perhaps board-certified in Laboratory Medicine or Clinical Genetics) or the treating clinician, who may be best positioned to interpret results in the context of the patient's presentation and pre-test probability, perhaps aided by machine learning or artificial intelligence?

Early multi-stakeholder collaborative partnerships can directly consider the financial models that sustain the innovation (assuming it is adopted at scale) and related decisions about initial use cases (including which research questions, disease indications, or reimbursement models). Uncertain reimbursement is frequently cited as a systemic barrier to the use of genetic testing, for instance [14]. Given the broader shifts occurring in healthcare reimbursement, it is possible that certain clinical innovations (such as a novel phenotype that improves risk stratification) would engender better stakeholder financial alignment under a value-based (as opposed to a fee-for-service) reimbursement model.

Finally, healthcare services are increasingly delivered away from hospitals and clinics and in some cases, marketed directly to consumers (in a reverse of the shift from the early 20th century). Future innovations should evaluate how their adoption might enable, or benefit from, these trends in healthcare delivery. Digital platforms may be particularly useful in this context, as they can facilitate both data acquisition and clinical care in the home, and in a more continuous and less obtrusive manner.

Concluding Remarks

The SARS-CoV-2 pandemic has highlighted the myriad connections between scientific discovery, healthcare delivery, the healthcare industry, and society at large. In this interconnected environment, widespread adoption of a scientifically-validated technology requires understanding stakeholder perspectives and their conceptions of the technology's value. Efforts to efficiently incorporate novel genomic or phenotypic insights into a learning health system (and ultimately to change clinical practice) would benefit from a more systematic, holistic assessment of the ecosystem into which these innovations must take root.

Acknowledgments

C.A.M., R.C.D., and S.Y.S. have received research support from the American Heart Association (One Brave Idea, with support from Verily, AstraZeneca, and Quest). S.Y.S. declares support from NHLBI/NIH (R01 5R01HL131015).

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https://doi.org/10.1016/j.molmed.2020.11.007

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Forum

CGRP Receptor Antagonism in COVID-19: Potential Cardiopulmonary Adverse Effects

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Recently, the US FDA has authorized a drug repurposing trial with calcitonin gene-related peptide (CGRP) receptor antagonists to reduce lung inflammation in coronavirus 2019 (COVID-19). However, the well-established cardiopulmonary protective effects of CGRP raise concerns about the safety of antagonizing CGRP in COVID-19. Awareness regarding potential cardiopulmonary adverse effects may enable their early detection and prevent illness from worsening.

Antagonizing Vasodilatory and Nociceptive Signaling via CGRP Antagonists for Migraine Prophylaxis

In migraine, CGRP release by trigeminal nerves is increased and causes dural and pial meningeal vessel dilation. Moreover, CGRP enhances the central relay of pain

Table 1. Calcitonin Gene-Related Peptide (CGRP) in Related Diseases

Effect	Mechanism	Disease	Refs
Pathological	Dural and pial vessel dilation	Migraine	i
	Central sensitization	Migraine	
Protective	Suppression of elevated systemic blood pressure	Systemic arterial hypertension	[3]
	Suppression of myocardial fibrosis	Systemic arterial hypertension	[1]
	Inotropy	Heart failure	Discussion in [1,3]
	Suppression of elevated pulmonary arterial pressure	Pulmonary hypertension	[13,14]
	Suppression of right ventricular remodeling	Pulmonary hypertension	
	Prevention of airway hyper-responsiveness	Lung inflammation in allergy and respiratory virus infection	[10], discussion in [10]
Conflicting	Inflammatory cytokine production	Local and systemic inflammation	[7–9,11], discussion in [7]

signals from the trigeminal nerves to the caudal trigeminal nucleus (Table 1). Therefore, antagonizing the vasodilatory and nociceptive signaling activated by the neurotransmitter CGRP is a very potent therapeutic concept. Small molecule receptor antagonists (gepants) or monoclonal antibodies directed against the CGRP receptor, and the ligand CGRP, have recently been approved as migraine prophylactic therapy[i]. However, all clinical trials evaluating the efficiency of anti-CGRP therapy were conducted in migraineurs without any pre-existing cardiovascular diseases such as systemic hypertension or stroke. This has raised concerns about the potential adverse effects of long term anti-CGRP therapy in hypertension and stroke because inhibition of endogenous CGRP worsens ischemic stroke and causes heart failure in systemic hypertension in preclinical models [1,2]. Accordingly, pharmacotherapy by a systemically administered long-lasting αCGRP-analog reduced elevated systemic blood pressure and consequently improved cardiac function in murine models of hypertension and heart failure [3]. In humans, αCGRP administration delays the onset of myocardial ischemia upon exercise in patients with stable angina pectoris and enhances cardiac function in patients with congestive heart failure (Table 1) (*cf.* discussions in [1,3]).

Repurposing CGRP Receptor Antagonists for COVID-19 Treatment

Apart from the clinical use of CGRP antagonists in migraine prophylaxis, most recently, the FDA has provided authorization for initiating a Phase II, randomized trial of a small molecule CGRP receptor antagonist, originally advancing to Phase III development for acute treatment of migraine, to reduce severe lung inflammation, impending oxygen desaturation, acute respiratory distress syndrome, need for supplemental oxygenation, artificial ventilation, or death in hospitalized COVID-19 patients[ii].

Rationale Supporting the Repurposing of CGRP Receptor Antagonists

The rationale supporting the repurposing of a small molecule CGRP receptor antagonist in COVID-19 treatment seems to be the stimulatory effects of CGRP on production of proinflammatory cytokines, including IL-6, and polarization of T cell response towards T helper (Th)17-based responses in various types of cultured cells and animal models studied in the absence of viral infection [4]. Inhibiting endogenous CGRP signaling has been shown to attenuate respiratory malfunction in ovine models of burn and smoke inhalation and mice models of acid-induced lung injury [5,6]. Severe alveolar and interstitial inflammation, along with increased plasma inflammatory cytokine (IL-6, IL-1β) concentrations and skewing toward the Th17 phenotype are detected in hospitalized COVID-19 patients.

Rationale against the Repurposing of CGRP Receptor Antagonists

However, several arguments speak against the use of small molecule CGRP receptor antagonists to treat COVID-19 patients. Conflicting results exist for the role of CGRP in enhancing IL-6 production, explained by a concentration-dependent stimulation or no effect of exogenous CGRP and modulation of cAMP bioavailability by the presence of additional pharmacological agents [7–9]. Further, CGRP expression is decreased in airway neuroepithelial bodies and submucosal nerve plexuses in mice models of allergy and respiratory syncytial virus (RSV) infection. CGRP administration restores normal airway responsiveness during persistent allergic and RSV airway inflammation, suggesting that endogenous CGRP does not induce airway hyper-responsiveness; rather, it can even have beneficial effects [10]. Moreover, CGRP suppresses type 2 cytokine synthesis and type 2 innate lymphoid cell proliferation (Table 1) [11]. It is particularly important to further stress that the hypothesis that CGRP release is enhanced in COVID-19 and that its release is stimulated by upregulation of transient receptor potential channels is not yet supported by direct evidence. A non-peer reviewed paper suggests that circulating CGRP concentrations are actually decreased in COVID-19 patients, negatively affecting disease outcome. These findings suggest restoring CGRP levels as a therapeutic approach [12].

A critical factor, still completely ignored, which may predict a life-threatening adverse effect of this effort is the consistent preclinical finding that endogenous CGRP is protective in pulmonary hypertension (PH) by suppressing pulmonary artery remodeling, elevation of total pulmonary resistance, and, thus, right ventricular (RV) remodeling in chronic hypoxia (Table 1) [13,14]. Increasing evidences indicate PH and resulting RV impairment in hospitalized COVID-19 patients, including even those with nonadvanced disease [15]. Moreover, preliminary survey results show that the incidence of COVID-19 infection is 2.1 cases per 1000 patients and 30% of PH patients infected with COVID-19 had to be hospitalized [16]. A crucial role for endogenous CGRP and its receptors in attenuating hypoxia-induced PH becomes evident from previous studies, which showed that infusion of CGRP neutralizing antibody, CGRP receptor antagonist, or antisense oligodeoxyribonucleotides targeting CGRP and the CGRP receptor component RAMP1 mRNA in lungs exacerbates pulmonary artery pressure and RV hypertrophy in chronic hypoxic rats [13,14]. Additionally, circulating CGRP concentrations are reduced in pulmonary hypertensive patients and rats with hypoxia-induced PH, in correlation with the rise in pulmonary artery pressure. Reduced CGRP concentration may permit unopposed action of vasoconstrictors such as endothelin-1. Although cells attempt to simultaneously upregulate CGRP receptor expression and thus increase CGRP binding to counteract the effects of decreased peptide bioavailability, this adaptive mechanism is not effective in restoring the dilatory potential of CGRP in pulmonary vasculature [14]. Rather, increasing endogenous CGRP concentrations by infusion of CGRP analogs and gene therapy (intratracheal administration of adenoviral vector encoding CGRP) are capable of inducing pulmonary vasodilation, reducing elevated total pulmonary resistance, and preventing PH and RV remodeling in chronic hypoxic rats. Furthermore, CGRP protects also against pulmonary vasoconstriction induced by endothelin-1, angiotensin II, and the nitric oxide synthase inhibitor N^{G}-nitro-L-arginine methyl ester [13]. In addition, the well-established positive inotropic effect of CGRP [3] alone may enhance pulmonary hemodynamics by regulating RV function.

Concluding Remarks

What do these studies tell us about the potential cardiopulmonary risks associated with the use of CGRP receptor antagonists in COVID-19 patients? In COVID-19 patients with PH, CGRP receptor antagonist therapy may exacerbate: (i) existing PH and RV remodeling, thus accelerating the transition to RV heart failure; and (ii) vasoconstriction that may further amplify intravascular coagulopathy and lung infarcts. Moreover, it generates the question whether there exists a correlation between circulating CGRP concentrations and PH, which may predict such adverse effects? If yes, those who have been receiving CGRP antagonists for migraine prophylaxis may have increased risk of developing cardiopulmonary complications upon COVID-19 infection and therefore require a specific clinical assessment program to detect earlier signs of such complications and termination of anti-CGRP therapy. Currently, subjects with chronic diseases are considered to be much more susceptible to fatal complications of COVID-19. Migraineurs receiving CGRP antagonists should also be considered in this category if cardiopulmonary adverse effects of CGRP antagonists become evident in COVID-19 patients. We suggest that considering these adverse effects, predicted on the basis of consistent preclinical findings and provided in this report, may further improve design of the proposed clinical trial to detect these adverse effects with adequate statistical power.

In conclusion, endogenous CGRP protects against pulmonary vascular remodeling and hypertension and subsequent right heart failure in preclinical models of chronic hypoxia. Therefore, CGRP receptor antagonism may be associated with cardiopulmonary adverse effects, including exacerbation of hypoxia-preceded PH and RV dysfunction in COVID-19 patients. Appropriate safety considerations should be made to enable their early detection during the investigational CGRP receptor antagonist therapy in COVID-19 patients.

Resources

[i] https://clinicaltrials.gov/ct2/show/NCT02066415

[ii] https://clinicaltrials.gov/ct2/show/NCT04346615

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https://doi.org/10.1016/j.molmed.2020.10.005

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