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LETTER TO THE EDITOR

Roxadustat for SARS-CoV-2 Infection: Old Signaling Raised New Hopes

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To the editor,

Roxadustat (RXT) (4-hydroxyl-1-methyl-7-phenoxyisoquinoline-3-caboxylic acid) (Fig. 1) is an orally active prolyl hydroxylase (PHD) inhibitor that increases production of endogenous erythropoietin with subsequent activation of bone marrow to produce red blood cells [1].

RXT is indicated in the management of anemia in chronic kidney disease (CKD) [1]. RXT was approved in China and Japan in 2018 and 2019, respectively, for the treatment of CKD-induced anemia [1]. RXT was approved by the European Union in 2021 for the treatment of anemia caused by CKD [2]. RXT has high bioavailability, high plasma protein binding, and is metabolized by P450 and excreted in the urine. RXT maximum plasma concentration is reached within 1 h. However, RXT bioavailability and plasma concentration are reduced by phosphate binders, which are commonly prescribed in patients with CKD to treat hyperphosphatemia [16].

PHD is responsible for the inactivation of hypoxia-inducible factor HIF-1α under normoxic conditions; however, under hypoxic conditions PHD is inhibited and HIF-1α is stabilized, activated, and transcriptionally energetic [3]. HIF-1α could be a protective mechanism against the pathogenesis of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection. HIF-1α inhibits the expression of angiotensin-converting enzyme 2 (ACE2) and transmembrane protein protease 2 (TMPRSS2), which

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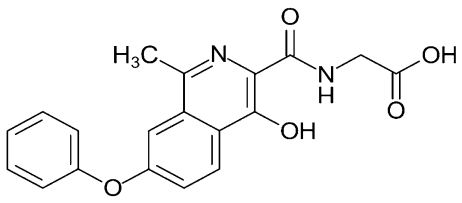

Fig. 1 Chemical structure of roxadustat

activates SARS-CoV-2 spike protein, decreasing the interaction between SARS-CoV-2 and ACE2/TMPRSS2 axis [4]. In addition, HIF-1α upsurges the shedding of membranous ACE2 through activation of disintegrin and metalloproteinase domain-containing protein 17 (ADAM17) [4]. Therefore, HIF-1α could be effective in reducing the pathogenesis of SARS-CoV-2 infection by inhibiting ACE2 and TMPRSS2 and activating the ADAM17 pathway. Increasing soluble ACE2 by ADAM17 decreases SARS-CoV-2 infectivity through neutralization of the SARS-CoV-2 spike protein [4]. Moreover, SARS-CoV-2 exploits other types of receptors including C-type lectin receptors (CLRs) like CD209/L-SIGN, CD209/DC-SIGN, and CLEC10A, as well as neuropilin-1 and CD147, which are highly expressed on epithelial and endothelial cells [14]. CD209/L-SIGN interacts with ACE2 to enhance its conformational changes during binding with SARS-CoV-2. However, soluble CD209L inhibits binding of SARS-CoV-2 with SARS-CoV-2 [14]. Remarkably, CD209/L-SIGN and CD209/DC-SIGN may act as alternative receptors for entry of SARS-CoV-2 in tissues where ACE2 has a low expression or is absent [14]. CLRs act in synergy with Toll-like receptors (TLRs) and contribute to immunoinflammatory response in myeloid cells of patients with Covid-19 [15, 20].

In Spartan SARS-CoV-2 infection both acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) developed as a result of the direct cytopathic effect of SARS-CoV-2 and related exaggerated immune response, with the propagation of a cytokine storm [5]. Various preclinical clinical studies have confirmed that HIF-1α promotes pulmonary epithelium repair and prevents the risk of ALI. HIF-1α activates the proliferation of alveolar epithelial type II and attenuates lipopolysaccharide-induced ALI in mice [6]. Also, HIF-1α may reduce ALI severity and prolong the patient's survival through activation of adenosine receptor type II, which has anti-inflammatory activity [7]. Thus, intensification of HIF-1α through inhibition of PHD could be effective in treating SARS-CoV-2 infection-mediated ALI and ARDS.

It has been shown that RXT alleviates ALI in septic mice by upregulating HIF-1α [8]. Therefore, augmentation of HIF-1α through inhibition of PHD might be of value in treating SARS-CoV-2 infection-mediated ALI and ARDS. Wing and colleagues showed that RXT inhibits SARS-CoV-2 replication as the viral post-entry life cycle is oxygen-sensitive [9]. RXT and other PHD inhibitors block replication of SARS-CoV-2 in a dose-dependent manner with maximal inhibition at 6 μM, which is in the range of reported plasma level (182 mIU/ml) in human individuals after oral administration of these agents in clinical doses [9]. Therefore, clinical administration of RXT in a dose range of 1–2 mg can achieve plasma concentrations that have antiviral effects.

Similarly, RXT and other PHD inhibitors are effective against ALI and acute kidney injury in patients with severe Covid-19 [9]. An in vitro study involving a human cell line showed that RXT reduced entry and replication of SARS-CoV-2 through intensification of the HIF-1α pathway [9]. To date, melatonin has been hypothesized to be a potent PHD inhibitor that regulates the expression of the ACE2/TMPRSS2 axis [13]. Of note, an evaluation of 11,672 patients revealed that melatonin decreases the risk for the development of SARS-CoV-2 infection by reducing the expression of ACE2 [13].

To our knowledge, there has been no clinical study evaluating the potential role of RXT in Covid-19. Thus, with the limitation of preclinical and clinical studies, RXT could be a possible helpful modality in the prevention and treatment of Covid-19.

Nevertheless, RXT and other PHD inhibitors may increase the expression of furin and cathepsin L, which increases the entry of SARS-CoV-2 to the host cells [10]. Hence, RXT and other PHD inhibitors are not recommended in the initial phase of SARS-CoV-2 infection due to activation of furin and cathepsin L by HIF-1α. In addition, PHD inhibitors may increase the risk of thrombosis by increasing the expression of coagulant factors [11]. Therefore, appropriate anticoagulant treatment is recommended when RXT and other PHD inhibitor therapies are initiated. However, a recent experimental study illustrated that RXT does not affect platelet production and activation in vitro or in vivo [12]. These observations proposed that RXT may have dual effects on SARS-CoV-2 infection (Fig. 2).

Thus, early administration of RXT in Covid-19 may augment the pathogenesis of SARS-CoV-2 infectivity by increasing expression of proteases like furin and cathepsin. Therefore, protease inhibitors like polyarginine [11] must be used with RXT when used in the early phase of Covid-19.

The most common adverse effects of RXT use are hypertension, pulmonary hypertension, thrombosis, hyperkalemia, and peripheral edema [16]. No evidence of cytotoxicity following administration of RXT 100 mg has been shown in an experimental study [19]. Of note, hypertension and thrombosis increase the risk for development of Covid-19 severity [11]. In addition, other co-morbidities like diabetes mellitus are commonly associated with Covid-19 severity [17]. It has been shown that RXT administration did not

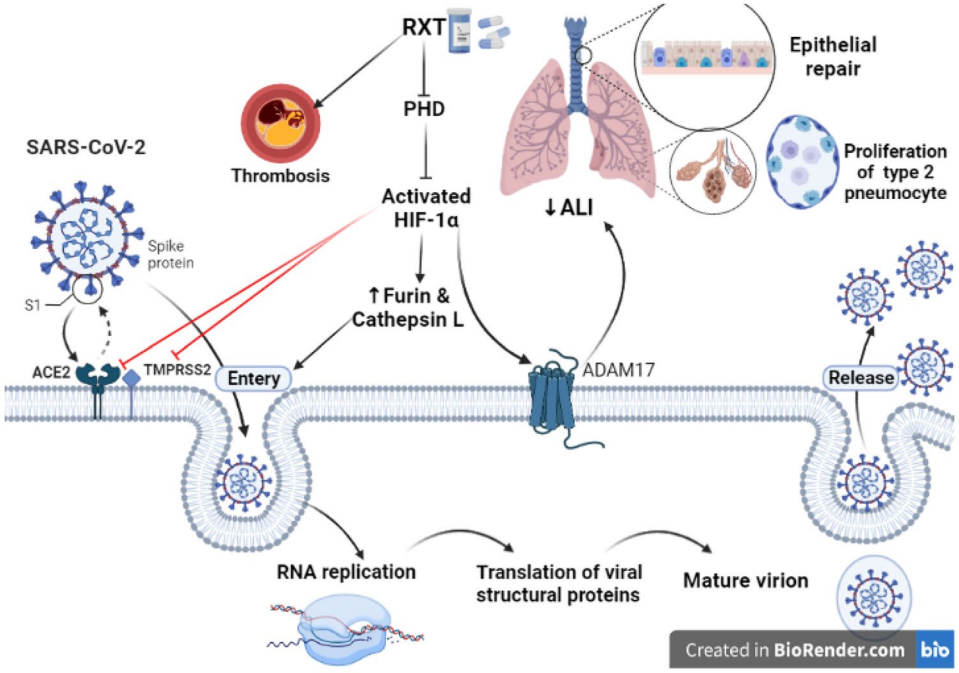

Fig. 2 Effects of roxadustat (RXT) on SARS-CoV-2 infection: RXT inhibits prolyl hydroxylase (PHD) thereby inducing stabilization of hypoxia-inducible factor 1 alpha (HIF-1α) leading to inhibition of SARS-CoV-2 proliferation and suppression expression of angiotensin-converting enzyme 2 (ACE2) and transmembrane protein protease 2 (TMPRSS2). RXT may increase the risk of SARS-CoV-2 pathogenesis by activating furin and cathepsin L

affect the outcomes of diabetic patients [18, 21]. Therefore, precautions are recommended with RXT administration in Covid-19 patients with pre-existing hypertension and risk of thrombosis.

Thus, experimental, preclinical, and clinical studies are recommended to confirm and substantiate the possible role of RXT in Covid-19 management. In conclusion, we suggest that RXT may be a new avenue in the management of Covid-19.

Declarations

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