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COMMENTARY

Telmisartan and losartan: The marked differences between their chemical and pharmacological properties may explain the difference in therapeutic efficacy in hospitalized patients with COVID-19

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At the beginning of the COVID-19 pandemic, Gurwitz,[1] taking into account that SARS-CoV-2 virus enters cells after binding to ACE2 (Angiotensin Converting Enzyme 2), proposed the hypothesis of the involvement of the RAS (Renin Angiotensin System) in the pathophysiology of this disease. Our adherence to the hypothesis led to the design of a clinical trial selecting telmisartan among the angiotensin AT1 receptor blockers (ARBs) at a dose of 80 mg twice a day, orally, for 14 days, for the treatment of hospitalized patients with COVID-19.[2] On the contrary, also starting in April 2020, a clinical trial with losartan, another ARB, was designed in hospitalized patients with COVID-19, administering doses of 50 mg orally twice daily for 10 days (NCT04312009). Recently, Liu et al.[3] published the results obtained after analyzing 54 randomized controlled trials (RCTs) that compared 13 drugs for the treatment of patients with COVID-19 against placebo or standard care. Among the drugs selected for the analysis, they included two ARBs, telmisartan, and losartan. To evaluate the efficacy of the drugs included, covered all causes of mortality at 5–8, 14/15, 21-, 25-, 28/30, 35-, 45-, 60-, 70, and 90-days.

Compared with the control group, only four drugs showed statistically significant efficacy in reducing mortality.

Among these four drugs, the angiotensin II AT1 receptor blocker telmisartan stands out, which showed an 81% reduction in the risk of mortality at 30 days after oral administration in doses of 80 mg twice/day for 14 days and in hospitalized patients with COVID-19 not admitted to an intensive care unit and from no more than 4 days after the onset of symptoms.[4] Conversely, losartan did not show oral efficacy at a dose of 50 mg twice daily for 10 days in hospitalized patients with COVID-19.[5]

On the contrary, a recent article[6] reported the results of an RCT of telmisartan treatment in COVID-19 patients. This study was conducted largely in India (99% of all subjects) during the period from May 3, 2020, to November 13 when the delta variant of SARS-CoV-2 was present. Telmisartan (40 mg daily) failed to reduce mortality.

Only 24% of all subjects were > 60 years of age (median age 49 years) and only 3% had underlying cardiovascular disease. The trial was halted after 14 days because of futility. Overall mortality rates were only 10/368 (2.72%) in the telmisartan group and 6/378 (1.58%) in the placebo group. The results of the trial are of low impact both for clinical practice and evaluation of the role of RAS blockade in COVID-19 taking into account that the study participants were relatively young, the disease severity and mortality were low, and the telmisartan dose used was four times lower than previously described effective doses in hospitalized COVID-19 patients.[4] In line with the lack of clinical effectiveness of telmisartan 40 mg/day, are the results obtained by Bähr et al.[7] where only high-dose treatment (160 mg/day) with telmisartan induces monocytic peroxisome proliferator-activated receptor gamma target genes in patients with the metabolic syndrome.

These results have raised a great question in the international scientific community as to why two drugs from the same pharmacological group (ARBs) used in equivalent antihypertensive doses, one of them (telmisartan) is effective, and the other (losartan) is not, in patients hospitalized with COVID-19.[8–11]

The objective of this manuscript was to compare the chemical and pharmacological properties of telmisartan and losartan, which, due to their marked differences, support the results obtained with the administration of both agents in patients hospitalized with COVID-19.

Table 1 shows the main chemical, pharmacokinetic, and pharmacodynamic properties of telmisartan, losartan, and their active metabolite EXP3174. In addition, a comparative analysis is made between these angiotensin II AT1 receptor blockers, indicating the most important differences between them that we consider to be related to the effectiveness of telmisartan on the one hand and the ineffectiveness of losartan on the other in hospitalized patients with COVID-9.

1 | SITE OF PHARMACOLOGICAL ACTION OF TELMISARTAN AND LOSARTAN

The main pharmacological action of both telmisartan and losartan is the blockade of angiotensin II AT1 receptors. AT1 receptors are cell membrane receptors with a structure of seven transmembrane domains. Therefore, in order to develop the aforementioned pharmacological action, each of the ARBs needs to reach the so-called site of pharmacological action or biophase, represented by the extracellular space in intimate contact with AT1 receptors.

To exert the antihypertensive effect, telmisartan and losartan reach concentrations in biophase (extracellular space in contact with arterial smooth muscle cells) pharmacologically effective to counteract the overstimulation of AT1 receptors caused by endogenous angiotensin II (Table 1 shows the Cmax of telmisartan and losartan at oral doses of 160 and 100 mg, respectively, which are higher than the pK_i or pIC_{50} values as AT1 receptor blockers).

The SARS-CoV-2 virus enters the airway and binds, by means of the S protein on its surface, to the membrane protein ACE2 in type 2 alveolar cells. The S protein-ACE2 complex is internalized by endocytosis facilitating the entry of each virion into the cytoplasm. The consequence is a partial or total loss of the function ACE2 in the alveolar cells of the lung in direct relation to the viral load of the air inoculum. The function of ACE2 is to catalyze the transformation of angiotensin II into its physiological antagonist angiotensin 1–7 (acting on Mas receptors causes vasodilatation and anti-inflammatory effects). Infection with the SARS-CoV-2 virus produces a deviation of the homeostatic balance of the renin–angiotensin system in favor of angiotensin II-AT1 receptor axis, promoting proinflammatory effects.[2]

On the contrary, it has been shown in neuro-2A cell culture (a murine neuroblastoma cell line) that the stimulation of the AT1 receptor can facilitate the internalization of ACE2 and lysosomal degradation, probably due to the co-endocytosis of both proteins during the internalization of the receptor AT1 mediated by Angiotensin II. Furthermore, this effect was inhibited by the AT1 receptor blocker losartan.[20] Thus, the administration of an AT1 receptor blocker in patients with COVID-19 may hamper ACE2-related internalization of SARS-CoV-2 into infected cells, an additive effect to blockade of AT1 receptors antagonizing the proinflammatory effects of Angiotensin II.[21]

In addition, recently Piplani et al.,[22] based on the results obtained with telmisartan using a validated in silico docking and molecular dynamics protocol effective at identifying SARS-CoV-2 drugs able to bind to the spike, speculate whether the clinical effectiveness of telmisartan in our clinical trial in patients with COVID-19 may be due to its blocking action on the conformational switch required for spike to bind to ACE-2.

There is ample scientific evidence that pulmonary macrophages possess all the components of a cellular RAS.[23,24]

There is also solid pathophysiological information that involves pulmonary alveolar macrophages in the development of the inflammatory process of COVID-19 after significant amounts of SARS-CoV-2 reach the alveoli and their uptake by these cells induces proinflammatory phenotypes.[25]

Therefore, the site of pharmacological action of both ARBs, to obtain a pulmonary anti-inflammatory effect in patients with COVID-19, is the extracellular space that surrounds pulmonary macrophages in intimate contact with AT1 receptors.

2 | CONCLUSION

If the inflammatory process at the pulmonary level suffered by patients with COVID-19 is significantly dependent on overstimulation of the AT1 receptors of pulmonary macrophages, the clinical effectiveness that can be obtained with the administration of an ARB such as telmisartan or losartan requires that they reach effective concentrations in biophase (in the extracellular space in intimate contact with the AT1 receptors). The comparative analysis

TABLE 1 Comparison of chemical and pharmacological properties between telmisartan, losartan, and EXP3174.

Properties	Telmisartan	Losartan	EXP3174	Comparative analysis
Chemical				
Molecular weight	514.61	422.91	436.90	The molar equivalences between these agents and telmisartan are: losartan: 1.217; EXP3174: 1178
Molecular structure	Bis-benzimidazole	Tetrazolo-biphenyl	Tetrazolo-biphenyl	There is consensus that the dissimilarity in molecular structure of telmisartan (bis-benzimidazole derivative) and losartan and its active metabolite EXP3174 (tetrazolo-biphenyl derivatives) is the cause of the differences in lipid solubility, oral bioavailability, metabolism, plasma half-life, residence time, elimination, and affinity for the angiotensin II AT1 receptor.[12]
Lipophilicity Partition coefficient: (log P octanol/ Buffer pH 7.4)	3.2	1.19	−2.45	Telmisartan is the most lipophilic of all ARBs. High lipophilicity facilitates and allows tissue and cell penetration. Conversely, losartan, and its active metabolite EXP3174 are water soluble and do not cross cell membranes.[12,13]
Pharmacokinetic				
Oral bioavailability	58%	33%	14%*	
Volume of distribution (V_d)	500 L	34 L	10 L	The high lipophilicity of telmisartan results in its high V_d and extensive tissue binding.[12,13] Conversely, due to its marked hydrophilicity, both losartan and its active metabolite EXP3174 have very low volumes of distribution values indicating poor tissue penetration.[12]
Plasma half-life ($t½$)	24 h	24 h	6–9 h	The relatively long plasma half-life of telmisartan and its first-order elimination kinetics cause a self-limited process of accumulation in blood and tissues in the first 4–5 days of administration every 12 h, reaching a theoretical plateau (at 4–5 $t_{1/2}$) of 3.41 times of the respective concentrations obtained with the first dose. With an administration every 12 h of losartan this accumulation phenomenon does not exist for the mother drug and is not significant for its active metabolite EXP3174.[14]
Accumulation	Yes	No	No	
Plasma C_{max} (ng/mL)	1520	799	—	Plasma C_{max} values are presented after administration of telmisartan 160 mg/day orally[15] or losartan 100 mg orally single dose.[16] The accumulation observed with telmisartan, based on its $t_{1/2}$ of 24 h, practically determines to reach twice the initial concentration in a stable state.
Steady-state C_{max} (ng/mL)	2871	—	—	
Blood–brain barrier (BBB) permeability	Yes	Practically none	No	There is abundant scientific information indicating telmisartan as the ARB with the strongest evidence for crossing the BBB.[12,13,17,18]
Pharmacodynamic				
Competitive antagonism on the AT1 receptor: pKi o pIC50	8.33	7.71	8.17	Telmisartan is an AT1 receptor blocker with an affinity (potency) greater than that observed for both losartan and its active metabolite EXP3174.[13]

(Continues)

TABLE 1 (Continued)

Properties	Telmisartan	Losartan	EXP3174	Comparative analysis
Unsurmountable antagonism: Dissociation half-lives from AT1 receptor	213 min	67 min	81 min	The disbinding of telmisartan from the AT1 receptor is very slow (greater than losartan and EXP3174). practically demonstrating an irreversible antagonism.[13]
Partial PPAR-γ agonism: EC50	5 μM	50 μM	Undetectable	In addition, telmisartan with the same plasmatic concentrations obtained in its antihypertensive use demonstrates to behave as a partial agonist of the PPAR-γ receptors, while losartan in antihypertensive doses practically lacks this effect. Taking into account that PPAR-γ receptors are located in the cell nucleus, the high lipophilicity of telmisartan allows it to cross the membranes and reach the site of pharmacological action (intranuclear space). Stimulation of PPAR-γ receptors antagonizes inflammatory responses by transrepression of nuclear factor Kappa B (NF-kB) target genes.[12,13,19]

*Only 14% of the orally administered dose of Losartan is converted to EXP3174.

of the main chemical and pharmacological properties of these two drugs (Table 1) allows us to predict that administered in equivalent antihypertensive doses, telmisartan, penetrating the lung interstitium, will reach effective pulmonary tissue concentrations that support the effectiveness obtained with telmisartan[4] and may explain the lack of effectiveness with losartan[5] in hospitalized patients with COVID-19.

Many studies have shown that ACE inhibitor/ARB use was associated with reduced mortality among COVID-19 patients.[26–33] Considering that telmisartan is a very safe ARB (even in high doses it presents placebo-like adverse effects), cheap and available practically throughout the planet, it can represent an adequate off-label therapeutic tool in patients with COVID-19, especially in countries with low resources, to face current and future waves of SARS-CoV-2.

AUTHOR CONTRIBUTION

Rodolfo Pedro Rothlin: Conception, writing and revision. Facundo Germán Pelorosso: Writing and revision. Mariano Duarte: Revision. Liliana Nicolosi: Revision. Fernandez Criado Ignacio: Revision. María Victoria Salgado: Revision. Héctor Vetulli: Revision.

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