# ALPHA 1 ADRENERGIC RECEPTOR ANTAGONISTS

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## Introduction

Catecholamines, epinephrine (Epi) and norepinephrine (NE) are critical for initiating the "fight or flight" response of the sympathetic nervous system.

The sympathetic nervous system regulates human immune system functions through (Epi) and (NE) activation of adrenergic receptors (AR) expressed on immunocompetent cell populations.[1,2] which brings to light the possible immunomodulation is catecholamine blockade.

## Mechanism of action

The AR family has three types, $\alpha_1$, $\alpha_2$, and β- and each further characterized into nine subtypes. All three AR types are expressed in the immune system and are considered immuno reactive (able to mount an immune response to haptens or antigens) when activated by Epi or NE.

AR activation serves many functions in the immune system including modification of depth and breadth of immune response.[1,2,3,4,5] Hence, theory is that administration of selective alpha 1 receptor antagonists may provide an immunodulatory response in human subjects.[4,5,6,7]

Several murine studies have shown that administration of AR antagonists decreased expression of monocyte intracellular adhesion molecules and CD40 expression.[7] Migration of immature Langerhan cells, skin dendritic cells to the lymph nodes[8] were also diminished. The investigators were able to show that pharmacologic blockade of catecholamine with metyrosine protected mice from lethal complication of cytokine release syndrome resulting from infections and biotherapeutic agents.[9] Two studies, one in 2002 and another in 2009, showed that mice pre-treated with prazosin prior to LPS injection had increased levels of anti-inflammatory cytokines (IL-10).[10, 11]

In humans however, adrenergic receptors blockade diminished monocyte migration[12], and modulated complement component C2, particularly prazosin and phentolamine.[13,14]

Taking into consideration these findings, it is noteworthy to establish if they should translate into similar clinical consequences in humans.

## Clinical Studies

Konig and colleagues[14] in a preprint article, examined the possible role of cathecholamine blockade in clinical outcomes of patients with COVID-19. A retrospective analysis was made, looking at two cohorts of hospitalized patients. The retrospective analysis included 45 to 64 year old male patients who filled an $\alpha$1-AR antagonist prescription (doxazosin, prazosin, silodosin, terazosin, or tamsulosin) for more than an aggregate of 180 days in the year preceding the event.

The first cohort consisted of patients with pneumonia. Results showed that those patients with prior use of α1-AR antagonists had 12.9% lower incidence of invasive mechanical ventilation compared to non-users (OR = 0.86, 95% CI 0.78-0.95, p = 0.002; AOR = 0.83, 95% CI 0.75-0.92, p < 0.001). Further, those patients had a 16.0% lower incidence of both being ventilated and dying in the hospital (OR = 0.84, 95% CI 0.68-1.02, p = 0.044; AOR = 0.77, 95% CI 0.62-0.94, p = 0.007).

The second cohort consisted of patients with acute respiratory failure including ARDS. Their findings showed that patients with prior use of α1-AR antagonists had 22.2% lower incidence of invasive mechanical ventilation compared to non-users (OR = 0.75, 95% CI 0.59-0.94, p = 0.008; AOR = 0.75, 95% CI 0.59-0.95, p = 0.009).

Perhaps more importantly, those patients had a 36.0% lower incidence of both being ventilated and dying in the hospital (OR = 0.63, 95% CI 0.37-1.01, p = 0.037; AOR = 0.59, 95% CI 0.34-0.95, p = 0.021). The authors concluded that their findings mirrored those of pre-clinical models. These may support the use of alpha 1 receptor antagonists in the preventing severe complications of pneumonia, ARDS in COVID-19.

Currently, Johns Hopkins University will be spearheading an open label randomized study on the role of prazosin in 220 Covid19 positive patients. Prazosin shall be given at incremental doses and outcome measures to be determined will include hospitalization requiring mechanical ventilation or supplemental oxygen and incidence of grade 3 and 4 adverse events.[15] (Appendix 5)

**Recommended Dose**

Prazosin at an initial dose of 1 mg every 8 hours will be administered to patients included in the study. The dose shall be adjusted accordingly according to possible blood pressure changes every three days. The maximum dose to be used will be 5 mg q8.[15]

As of May 10, 2020, there are no specific studies addressing the use of alpha-1 adrenergic receptor antagonists for treatment in the pediatric population.

**Adverse Effects**

The most common side effect is postural hypotension. All of the alpha-1 adrenergic receptor antagonists are associated with a minimal rate of serum hepatic enzyme elevations during chronic therapy (0.2% to 2%). These elevations are almost always mild-to-moderate in severity, self-limited, and do not require dose modification or drug discontinuation.[16]

## Conclusion

The complete and extensive role of this receptor in modulating immune responses is still in its infancy. Hence, future studies are still required to further elucidate the depth and breadth of its involvement and therapeutic potential in human subjects with COVID-19.

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