Treatment with ATYR1923 reduces biomarkers in COVID-19 pneumonia

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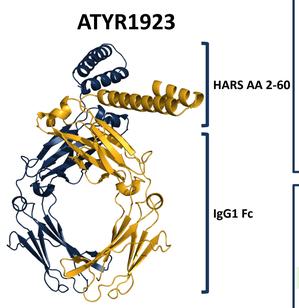
Overview

ATYR1923 is a novel immunomodulator that is in development for the treatment of severe inflammatory lung diseases, and was recently evaluated in a Phase 2 randomized double-blind placebo-controlled study in patients with severe pneumonia related to SARS-CoV2 infection (COVID-19). Patients with COVID-19 pneumonia often experience serious respiratory complications caused by excessive T-cell mediated inflammatory responses. ATYR1923 downregulates T-cell responses in models of immune-mediated acute lung injury. This study aimed to understand the role of ATYR1923 on circulating inflammatory serum biomarkers in patients hospitalized for COVID-19 pneumonia. Serum for biomarker analysis was collected before and after a single IV administration of placebo, 1mg/kg or 3mg/kg ATYR1923. Biomarker levels were examined to determine the effect of ATYR1923 to resolve systemic inflammation in COVID-19 patients.

Introduction

ATYR1923: A novel molecular entity that acts as an extracellular immunomodulator by downregulating innate and adaptive immune responses in inflammatory conditions. ATYR1923 comprises a human 59 amino acid protein fused to the Fc region of human immunoglobulin 1 (IgG1). The amino acid sequence of the 59 amino acid domain in ATYR1923 corresponds identically to the extracellularly active N-terminal domain of histidyl-tRNA synthetase (HARS). In solution, the ATYR1923 molecule forms a homodimer, similar to other Fc fusion proteins. ATYR1923 has been shown to decrease inflammatory cytokine production, including IL-2, TNF-α, and IL-13 from human T cells activated *in vitro* and has been shown to significantly reduce levels of IL-6, IFN-g and MCP-1 in animal models of ILD. Both *in vitro* and *in vivo* activities substantiate that ATYR1923 directly modulates T-cell responses.



Covid-19: Emergent data gathered from patients with COVID-19 infection indicate that significant inflammatory infiltration of the lungs and simultaneous elevations in pro-inflammatory cytokines/chemokines are prominent factors in severe cases that have progressed to acute respiratory distress syndrome (ARDS)[1]. Severely ill patients have significant increases in plasma concentrations of several pro-inflammatory cytokines[2]. The same pro-inflammatory markers are implicated in other severe inflammatory lung diseases that are a development focus for ATYR1923, such as pulmonary sarcoidosis.

Materials and Methods

Phase 2 Study Design & Baseline Demographics

Objective	• Evaluate safety and preliminary efficacy of ATYR1923 in subjects hospitalized with COVID-19-related severe respiratory complications
Design	• Randomized, double-blind, placebo controlled, single dose
Population	• Adult patients age 18-70 years • Severe respiratory complications related to COVID-19 infection • Hospitalized, requiring supplemental oxygen but not mechanically ventilated
Doses	• Randomized 1:1:1 - Single dose of 1.0 or 3.0 mg/kg ATYR1923 or Placebo

Dose Day 1 › Inpatient Intensive Monitoring Day 2 to Day 14/discharge › Follow-up through Day 60 (EOS)

Blood samples collected pre-dose on Day 1, and days 2, 3, 5, 7 & 14 post-dose.

		Placebo	ATYR1923 1 mg/kg	ATYR1923 3 mg/kg	Combined ATYR1923
Patients Dosed	N	**10**	**10**	**12**	**22**
Age (Years)	Median min, max ≥ 65 n(%)	51.5 36, 74 1 (10)	53.5 38, 73 3 (30)	56.5 27, 70 4 (33)	54.5 27, 73 7 (32)
Sex, n (%)	Male Female	7 (70) 3 (30)	5 (50) 5 (50)	6 (50) 6 (50)	11 (50) 11 (50)
Race, n (%)	Black/African American White Asian/Other	2 (20) 3 (30) 5 (50)	1 (10) 6 (60) 3 (30)	1 (8) 4 (33) 7 (58)	2 (9) 10 (45) 10 (45)
WHO Score, n (%)	4 Hospitalized, Mild 5 Hospitalized, Severe	7 (70) 3 (30)	7 (70) 3 (30)	9 (75) 3 (25)	16 (73) 6 (27)
Hospitalized Prior to D1	Median days (min, max)	3.5 (2, 7)	5.5 (2, 14)	3.5 (2, 7)	4.5 (2, 14)
COVID Meds, n (%)[1]	Dexamethasone[2] Remdesivir Convalescent plasma	9 (90) 8 (80) 1 (10)	10 (100) 6 (60) 0 (0)	11 (92) 5 (42) 0 (0)	21 (96) 11 (50) 0 (0)

[1] Prior and/or concomitant
[2] Dexamethasone, methylprednisolone, or equivalent

Materials

- **Human serum:** Serum samples were received frozen from a central laboratory. Samples were thawed at room temperature, aliquoted & tested in duplicate at recommended kit dilutions.
- **Biomarkers:** Serum ferritin and D-Dimer were analyzed at the clinical site per local standards. All other biomarkers were run using Meso Scale Diagnostics V-PLEX Human Biomarker 40-Plex Kit (Cat.# K15209D) according to the manufacturer's recommendations and analyzed on a MSD QuickPlex SQ 120.
- **Data analysis:** Biomarker results were analyzed using GraphPad Prism v7.02 and R v4.0.3

Methods

- Sample values were calculated using an interpolated standard curve, multiplied by dilution factors and reported as an average of the replicate values in nanograms or picograms per milliliter (ng/mL or pg/mL).
- Patient samples from pre-dose to day 5 were prioritized due to sample numbers and disease resolution.
- A random coefficient regression model was fitted to each biomarker to estimate the rate of change from day 1 to day 5 by treatment, referred to as slopes analysis.
- Key biomarkers were defined as those most relevant to COVID-19 disease progression or ATYR1923 mechanism of action.

Results

Selection & Characterization of Elevated Biomarkers

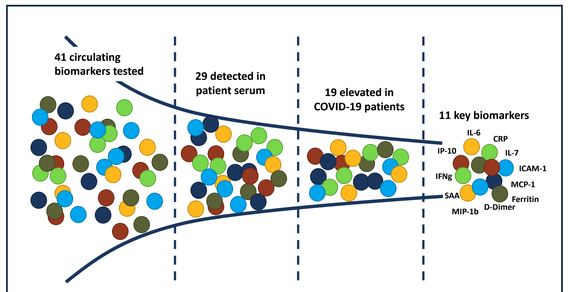


Figure 1: Serum biomarker characterization. Individual biomarkers were stratified based upon detection levels in patient serum samples and characterized as elevated compared to normal healthy serum controls (n=67) tested from internal & commercial sources.

bFGF	GM-CSF	IL-12p70	IL-1a
CRP	ICAM-1	IL-13	IL-1b
Eotaxin	IFNg	IL-15	IL-2
Eotaxin3	IL-10	IL-16	IL-4
Flt-1	IL-12p40	IL-17A	IL-5
IL-6	MCP-4	SAA	VCAM-1
IL-7	MDC	TARC	VEGF-A & C
IL-8	MIP-1a	Tie-2	VEGF-D
IP-10	MIP-1b	TNFa	Ferritin
MCP-1	PIGF	TNFb	D-Dimer
Undetectable	Detected: Not elevated	Detected: Elevated	Key

Figure 2: Biomarker classification. Individual biomarkers were grouped based on detection, elevation and relevance to COVID-19 pathogenesis and/or the mechanism of action for ATYR1923.

Inflammatory Biomarker Resolution

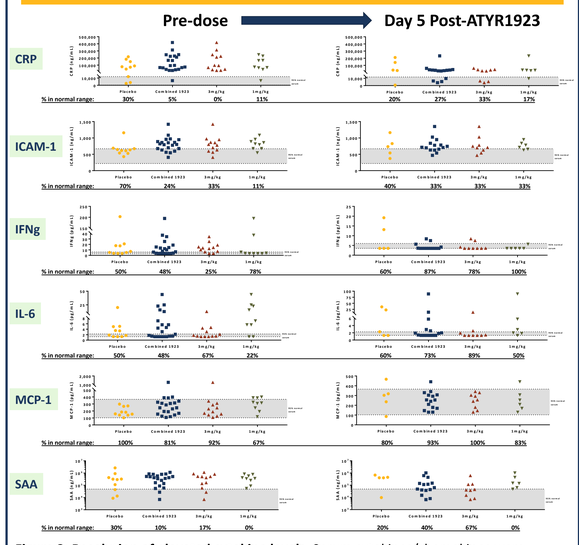


Figure 3: Resolution of elevated cytokine levels. Serum cytokines/chemokines were measured prior to ATYR1923 dosing and 5 days later. ATYR1923-treated subjects normalized to a greater extent than placebo-treated subjects. Gray zone = 95% of normal serum levels.

Inflammatory & COVID-19 Biomarker Slopes Analysis

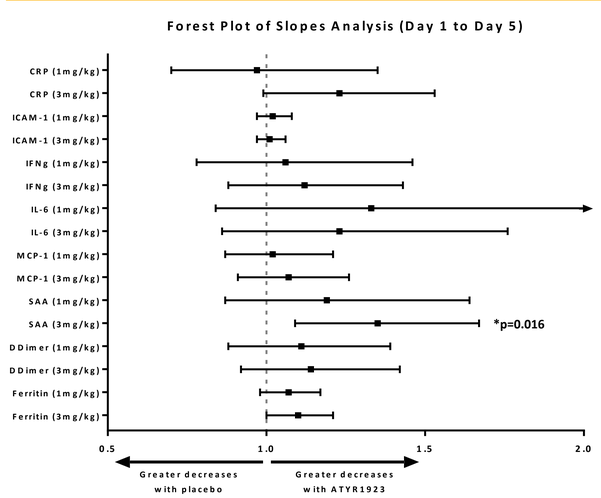


Figure 4: Improved slope of biomarker resolution. The slope of biomarker levels measured from pre-dose through day 5 showed a trend toward greater resolution with ATYR1923 treatment. Slopes were normalized to placebo resolution and values greater than 1.0 indicate a sharper decrease in elevated cytokine levels. Error bars = 95% confidence intervals.

Conclusions

The immunomodulatory activity of ATYR1923 was evaluated in patients with COVID-19 related severe pneumonia and changes in serum biomarkers was selected as an exploratory endpoint. Trial participants were enrolled while receiving current standard of care, including remdesivir and/or dexamethasone which are known to impact inflammatory biomarkers. Prior to initiation of this trial, treatment groups were randomized to placebo or ATYR1923. Post-hoc analysis of baseline characteristics and inflammatory biomarker levels suggested that ATYR1923 treatment groups contained more severe COVID-19 patients. In spite of this, ATYR1923 demonstrated a greater overall trend of reduction in inflammatory biomarkers as compared to placebo. Inflammatory cytokines and chemokines, including IFNg, IL-6 and MCP-1, showed improved normalization with ATYR1923 than observed in patients treated with placebo alone. In addition, ATYR1923 demonstrated a statistically significant rate of reduction in serum amyloid A (SAA) by day 5, a known marker of inflammation and fibrosis in target indications for ATYR1923. Patients treated with ATYR1923 demonstrated trends of overall improvement in 82% of biomarkers analyzed compared to placebo. While this study was not powered for statistical significance, there were clear signals that ATYR1923 treatment reduced systemic inflammatory biomarkers in an acutely inflamed patient population.

References

1. Zhou et al. National Science Review, Volume 7, Issue 6, June 2020, Pages 998–1002
2. Wang et al. Clinical Infectious Diseases, Volume 71, Issue 15, 1 August 2020, Pages 769–777

Acknowledgements

• aTyr would like to thank Liting Zhai and Yanyan Geng from Pangu BioPharma, a subsidiary of aTyr Pharma, for the ATYR1923 structure.