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Case Report

Successful Treatment of SARS-CoV2 Delta Variant Infected Patient with a Monoclonal Antibody Cocktail

Maria Grazia Cusi[1,2*], Danilo Tacconi[3], Gianni Gori Savellini[1], Gabriele Anichini[1], Beatrice Valoriani[3], Claudia Gandolfo[1]

[1]Virology Unit, Department of Medical Biotechnologies, University of Siena, Italy

[2]Microbiology and Virology Unit, 'S. Maria alle Scotte' Hospital, Italy

[3]Infectious Diseases Unit, S. Donato Hospital, Italy

[*]**Corresponding author:** Maria Grazia Cusi, Virology Unit, Department of Medical Biotechnologies, University of Siena, Siena, Italy

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Abstract

We report the successful effect of mAbs therapy against SARS-CoV-2 Delta variant (also known as B.1.617.2) in a woman aged 59, affected by secondary immunodepression due to a rheumatoid arthritis currently treated with biological drugs.

Keywords: Delta variant; Monoclonal antibodies; SARS-CoV-2

Introduction

The COVID-19 pandemic is still ongoing and a variety of prophylactic and therapeutic interventions has been developed. Monoclonal Antibodies (mAbs), able to block the virus in the infected host, are becoming more important in treating specific categories of subjects infected by SARS CoV-2 and within a context of viral variants' emergency. Being biological drugs, monoclonal antibodies have lately become an important class of drugs treating multiple conditions in infectious diseases. However, an important limit when using these mAbs is antibody escape, due to the virus mutation in the region responsible for antibody binding, making the antibody unarmed. Several companies have developed antibody therapeutics for Covid-19, including Lilly with etesevimab and bamlanivamab [1] and Regeneron with casirivimab and imdevimab [2,3]; other new mAbs are on clinical trials [4]. These antibodies bind two distinct and non-overlapping sites on the Receptor Binding Domain (RBD). The rationale for this antibody combination is that it is unlikely that a mutation in the S protein of SAR-CoV-2 simultaneously renders both antibodies ineffective.

First identified in India and already spread in many countries, the Delta variant represents a new source of risk and a new challenge for humans, because of the mutations in the spike gene. These mutations found in the Receptor Binding Domain (RBD), which is the neutralizing antibodies major target, can impair the monoclonal antibody efficacy in COVID-19 therapy. The Delta variant, also known as B.1.617.2, is considered a 'variant of concern' by the Center for Disease Control and Prevention (CDC) [5]. This variant has four mutations of interest in the Spike protein: L452R, T478K, D614G, P681R; in particular, the substitution at position 452 confers a stronger affinity of the spike protein to the ACE2 receptor and seems to decrease the recognition capability of the immune system, while the substitution at position 681, near the furin cleavage, may facilitate the cleavage of S precursor protein into the active S1/S2 subunits, resulting in better transmissibility [6].

B.1.617.2 shows increased transmissibility, potential reduction in neutralization by some monoclonal antibody treatments under emergency authorization and potential reduction in neutralization in sera after vaccination in lab tests [7]. Here, we report the successful effect of mAbs therapy in a woman aged 59, affected by secondary immunodepression due to a rheumatoid arthritis currently treated with biological drugs.

Materials and methods

Prior to participating in this study, the subject, living in Arezzo area (Tuscany, Italy), signed a written informed consent. This research was crried out according to the principles of Helsinki declaration.

Nasopharyngeal swab was collected in viral transport media on May 25th, 2021. Then, RT-PCR targeting *N1* and N2 genes

(Cepheid GeneExpert, Sunnyvale, CA, USA) was performed for SARS-CoV-2 detection. Viral RNA was extracted using the EZ1 Advanced XL system (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Moreover, amplification through molecular PCR was done. Finally, Sanger sequencing of the entire Spike protein (Table 1) was performed using the following primers and the sequence was uploaded on Gisaid (EPI_ISL_2550732):

Position	Gene	Ref /TUS-Siena-33 (nt)	Ref/TUS-Siena-33 (aa)
21618	S	C/G	Thr/Arg
21987	S	G/A	Gly/Asp
22029-22034	S	AGTTCA/del	Phe, Arg/del
22227	S	C/T	Ala/Val
22917	S	T/G	Leu/Arg
22995	S	C/A	Thr/Lys
23403	S	A/G	Asp/Gly
23604	S	C/G	Pro/Arg
24410	S	G/A	Asp/Asn

1) 1173 bp, nt 21289-22461

SARS-S-F3 5' TATCTTGGCAAACCACGCGAACAA 3'

SARS-S-R7 5' TTTGTTTCTGAGAGAGGGTC 3'

2) 1326 bp, nt 22342-23668

SARS-S-F7 5' TGGTGCTGCAGCTTATTAT 3'

SARS-S-R6 5' TTCTGCACCAAGTGACATAGTGTAGGCA 3'

3) 1140 bp, nt 23398-24537

SARS-S-F6 5' TCAGGATGTTAACTGCACAGAAGTCC 3'

SARS-S-R8 5' TGCACTTCAGCCTCAACTT 3'

4) 1156 bp, nt 24465-23310

SARS-S-F8 5' CCAATTTTGGTGCAATTT 3'

SARS-S-R3 5' ACCCTTGGAGAGTGCTAGTTGCCATCTC 3'

Table 1: Genetic variations of hCoV-19/Italy/TUS-Siena-33/2021 isolate compared to the SARS-CoV-2 reference genome isolated in Wuhan (NC_045512.2).

Moreover, to test subject's seronegativity for SARS-CoV-2 before the treatment with monoclonal cocktail, serum was analyzed using the Abbott SARS-CoV-2 IgG/IgM Chemiluminescent Microparticle Immunoassay (CMIA) (Abbott Laboratories, Chicago, IL) on an Abbott Architect i2000 (Abbott Diagnostics) according to the manufacturer's instructions. This method is a qualitative assay that detects IgG/IgM binding to an undisclosed epitope of the SARS-CoV-2 nucleocapsid protein, with the results expressed as Relative Light Units (RLU). The final interpretation of positivity was determined by the ratio above a threshold value, with positive ratio ³1.4 or negative ratio <1.4.

Results

On May 20th, 2021 she presented fever (39°C), arthralgia, headache; thus, the day after, her family doctor recommended her to do a swab for SARS-CoV-2, which was positive by molecular real-time PCR (Ct 28), (Cepheid GeneeXpert, Sunnyvale, CA, USA).

The Sanger sequence limited to the viral spike protein revealed the presence of SARS-CoV-2 Delta variant (B.1.617.2) (GISAID EPI_ISL_2550732).

The woman had a mild disease and normal oxygen saturation without lung involvement.

She was, however, treated with monoclonal cocktail considering her chronic assumption of biological drugs for rheumatoid arthritis, therapies related whit high risk of developing a severe form of COVID-19 and hospitalization. She had received no SARS-CoV-2 vaccine and was seronegative (Abbott Laboratories, Chicago, IL). On May 25th, in the morning, she was treated with a cocktail of monoclonal antibodies (casirivimab 1200 mg + imdevimab 1200 mg; Regeneron, Tarrytown, NY, USA). On the infusion day, vital parameters were stable with Sp02: 98%, BP: 120/80, HR: 85. During the night, the high fever, that was present for four days, disappeared. She turned negative to SARS-CoV-2 after a control swab on June 5th. The patient recovered from Covid-19, reporting persistence of a moderate asthenia.

Discussion

This is the first reported case of a patient infected by the Delta variant, treated with the combination of casirivimab and imdevimab in the early stage of COVID-19 and recovered after 12 days, suggesting the therapeutic role of these mAbs against this emergent SARS-CoV-2 variant. Because of high incidence of B.1.1.7 and P.01 variants in the area, she was suggested to be treated with Regeneron mAbs, based on the observation of Hoffmann et all. that found the casirivimab/imdevimab combination efficient in inhibiting viral entry into cells for all variants, while bamlanivimab failed to inhibit B.1.351 and P.1 variants [8]. Although this analysis only includes one patient, this is an *in vivo* confirmation that this mAbs cocktail was successful in hindering the Delta variant.

Authors' Contributions

M.G.C. conceptualized the work and wrote the first draft of the manuscript. G.G.S., G.A. and C.G. performed the experiments. D.T. and B.V. provided the study samples.

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