Monoclonal Antibodies in COVID-19 Treatment

Subjects: Infectious Diseases
Contributor: Anabel Torrente

Therapeutic monoclonal antibodies (mAbs) have been the subject of widespread investigation focusing on two target-based groups, i.e., non-SARS-CoV-2 specific mAbs, that target immune system responses, and SARS-CoV-2 specific mAbs, designed to neutralize the virus protein structure.

Keywords: COVID-19 treatment ; clinical trials ; monoclonal antibodies ; non-SARS-CoV-2 specific ; SARS-CoV-2 specific

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has emerged as a new infectious disease which has reached pandemic proportions. This coronavirus belongs to the *Betacoronavirus* genus in the Coronaviridae family, together with other previously identified coronaviruses, such as SARS-CoV and MERS-CoV. These viruses have a positive-sense RNA genome which encodes structural and non-structural proteins [1]. SARS-CoV-2 transmission is mainly mediated by respiratory droplets and aerosols and most infected patients are asymptomatic or present mild symptoms, such as fever, cough, dyspnoea, diarrhoea, muscle pain, sore throat, headache, and loss of smell and/or taste. However, about 20% of patients undergo a serious illness with dyspnoea, pneumonia, and supplemental oxygen requirements. The most seriously ill patients can suffer respiratory failure and cardiopulmonary collapse or shock that can lead to death [2]. In response to this global emergency, a wide range of therapeutic agents such as chloroquine, hydroxychloroquine, antivirals, antibodies, corticosteroids, or convalescent plasma among others have been or are currently being evaluated for the treatment of COVID-19 [3], in addition to the development of vaccines. Unfortunately, not all these agents have proved successful and some, such as chloroquine, hydroxychloroquine and several antivirals, have already been discarded as possible treatments [4][5][6].

One of the strategies considered for defeating COVID-19 is passive immunotherapy (Figure 1). There are two ways to guarantee passive immunization: (i) via natural antibodies using convalescent plasma therapy (CPT) in which plasma is extracted from a hyperimmune patient and transfused into a COVID-19 patient; or (ii) via antibodies that are biotechnologically designed, i.e., therapeutic monoclonal antibodies (mAbs) or a cocktail of polyclonal antibodies (pAbs) [7]. Of these two passive immunization strategies, the use of mAbs offer the most innovative approach to the prevention and treatment of infectious diseases, such as COVID-19, where current research aims at developing treatments based on specific mAbs to block and/or neutralize SARS-CoV-2 in infected patients [8]. In addition, already available mAbs have been used off-label based on the knowledge acquired during the pandemic regarding the pathogenesis of the disease. Therefore, the characteristic of mAbs made them perfectly suitable for the treatment of COVID-19 [9].

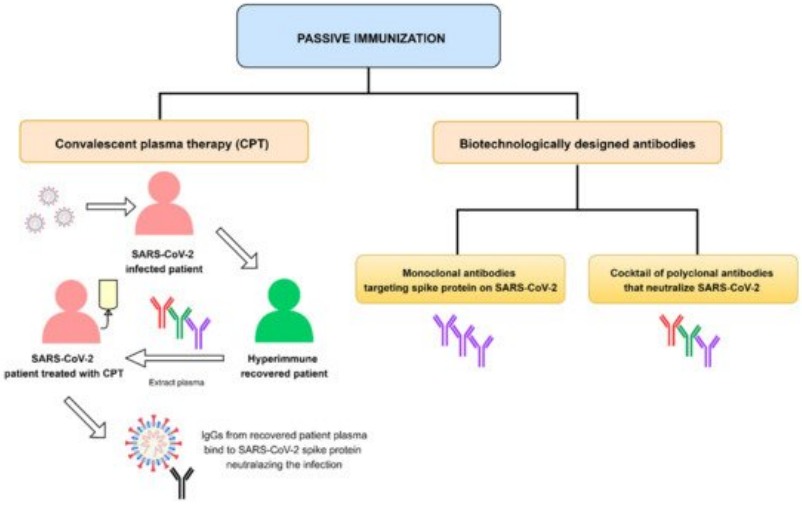

Figure 1. Different strategies to guarantee passive immunization using antibodies.

The off-label use of drugs can be defined as their use for a non-officially approved condition. It also refers to the use of drugs with an unapproved dosage, route of administration, or in an unlicensed combination regimen [10]. Off-label administration of drugs to treat COVID-19 is an extensive practice. However, this is not the first time that mAbs have been prescribed off-label. Several mAbs have proven safe and effective for treatments not indicated in their respective Summary of Product Characteristics (SPC). One example is bevacizumab: an anti-cancer biotherapeutic which is currently widely administered intravitreally to treat age-related macular degeneration (AMD) instead of the approved drug, ranibizumab [11]. Although both biotherapeutics have similar efficacy and safety, bevacizumab is now preferred due to its better cost–benefit ratio.

Several clinical trials are currently being conducted to test the efficacy and safety of different mAbs for the treatment of COVID-19, some of which are already being administered in hospitals while others are under evaluation [12]. Many of them target immune system responses (non-SARS-CoV-2 specific mAbs) while others are designed to neutralize the SARS-CoV-2 protein structure (SARS-CoV-2 specific mAbs) (Figure 2) [7].

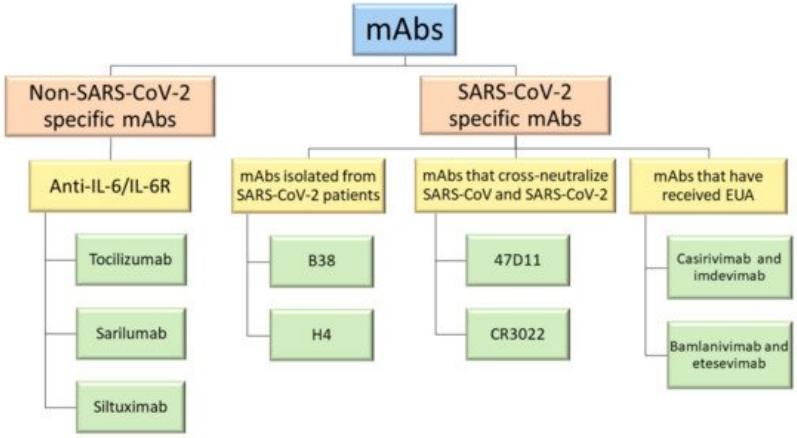

Figure 2. Relevant mAbs used to treat COVID-19 deeper discussed in this review.

2. Non-SARS-CoV-2 Specific Monoclonal Antibodies

The mAbs that are currently being used in hospitals to treat COVID-19 focus on the immune responses provoked by the virus, which can affect the severity of COVID-19 disease [7]. One of these immune responses involves the sudden release of large numbers of certain cytokines into circulation, in what is known as a ‘cytokine storm’, a life-threatening systemic inflammatory syndrome [13]. IL-6 is one of the key pro-inflammatory cytokines found in COVID-19 patients, which is why anti-IL-6/IL-6R biological drugs have been used for the treatment of this disease from the beginning. The mAbs selected to treat COVID-19 patients with high IL-6 levels include tocilizumab, sarilumab, and siltuximab. Several clinical trials are currently underway to test their efficacy, which has yet to be fully proven [2].

Clinical trials are also ongoing with other non-SARS-CoV-2 specific mAbs whose therapeutic targets are not IL-6/IL-6R, such as bevacizumab, clazakizumab, eculizumab, emapalumab, gimsilumab, itolizumab, mavrilimumab, meplazumab, nivolumab, pembrolizumab, etc. [2][12][14]. The therapeutic, anti-IL-1R protein, anakinra, has also been used [15]. No conclusive results have been obtained with any of them as yet. Due to their widespread use, in this paper we will be focusing specifically on the anti-IL-6/IL-6R mAbs and their use in the treatment of the COVID-19-associated cytokine storm.

3. SARS-CoV-2 Specific Monoclonal Antibodies

Phylogenetic analysis has shown that SARS-CoV and SARS-CoV-2 are very similar in genetic and structural terms. This helped scientists understand the pathogenesis of COVID-19 and provided a basis for initial research. Indeed, the glycosylated spike (S) proteins from both coronaviruses have a primary amino acid sequence homology of 77.5% [7][8]. The S proteins are located on the surface of these coronaviruses and are a key component in infection. They mediate viral host cell entry by binding to the host cell receptor angiotensin-converting enzyme 2 (ACE2). The SARS-CoV-2 S protein is composed of 1273 amino acids (aa) and consists of three segments: an extracellular N-terminus, a transmembrane (TM), and a short intracellular C-terminal segment. A signal peptide is located at the N-terminus domain which consists of a few aa (1–13 residues). The rest of the protein is divided into two large regions: S1 and S2 subunits. The S1 subunit (14–685 aa) is responsible for receptor binding and consists of an N-terminal domain (NTD) and a receptor-binding domain (RBD). The S2 subunit (686–1273 aa) comprises the fusion peptide (FP), heptapeptide repeat

sequence 1 (HR1), HR2, TM domain, and cytoplasm domain, and is involved in the fusion of the viral and host cell membranes and the consequent release of the viral genome into the host cell (Figure 3a). The RBD region is considered a critical target for neutralizing antibodies (nAbs) since it allows the spike protein to bind to the cell receptor ACE2. A deeper knowledge about the structure and configuration of the SARS-CoV-2 S protein can be found in references [16][17].

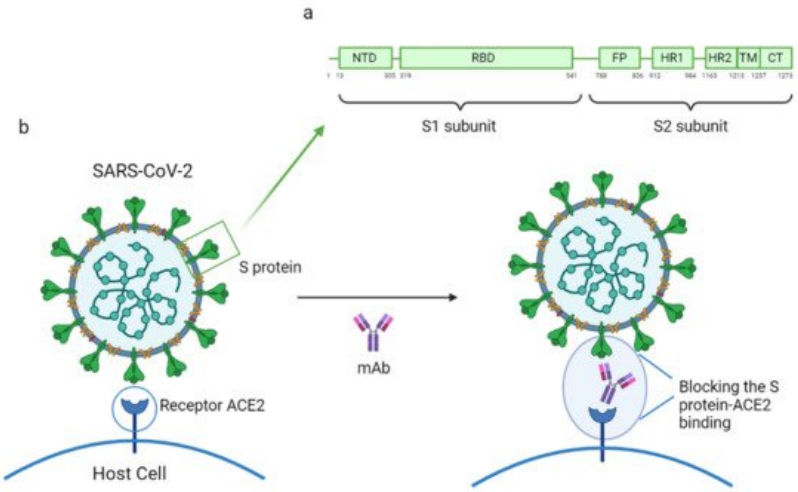

Figure 3. (**a**) Mechanism of action of a mAb by blocking the SARS-CoV-2 S protein and human ACE2 receptor binding; (**b**) structure of the SARS-CoV-2 S protein. This figure was composed using BioRender (available at: https://biorender.com/. Accessed on 12 May 2021).

The mAbs specifically designed to combat SARS-CoV-2 can be classified into three groups based on their respective objectives: (1) inhibiting virus attachment and entry by targeting either the virus structure or host receptors; (2) interfering with virus replication and transcription; and (3) hindering various stages of the immune system response [7]. Most of the mAbs currently under development target the S protein, which the virus uses to enter host cells [18]. Some reports highlighting the efficacy of specific mAbs against COVID-19 have already been published. These reports propose B38, H4, 47D11, and CR3022 as potential SARS-CoV-2 specific mAbs as they have demonstrated significant capacity to prevent infection by the virus. All these mAbs act by binding to the receptor-binding domain (RBD), therefore inhibiting the union between the virus and the human-ACE2 receptor (Figure 3b). It was also noted that B38 and H4, which had been isolated from a convalescent patient, bind exclusively to SARS-CoV-2 RBD, while 47D11 and CR3022 were tested against SARS-CoV and have demonstrated their ability to cross-neutralize SARS-CoV and SARS-CoV-2 [7][8][19]. In Table 1 are shown the binding site and the mechanism of action of the SARS-CoV-2 specific mAbs discussed in this review.

Table 1. Binding site and mechanism of action of SARS-CoV-2 specific mAbs discussed here.

Groups of Specific mAbs	Name	Binding Site and Mechanism of Action
MAbs isolated from SARS-CoV-2 patients	B5	SARS-CoV-2 RBD; partial competition with ACE2
	B38	SARS-CoV-2 RBD; complete competition with ACE2
	H2	SARS-CoV-2 RBD; no competition with ACE2
	H4	SARS-CoV-2 RBD; complete competition with ACE2
	EY6A	SARS-CoV-2 RBD and SARS-CoV RBD with lower affinity; site spatially separate from that of ACE2

Groups of Specific mAbs	Name	Binding Site and Mechanism of Action
MAbs that cross-neutralize SARS-CoV and SARS-CoV-2	47D11	SARS-CoV-2 and SARS-CoV RBD; conserved epitope in the RBD
	CR3022	SARS-CoV RBD and SARS-CoV-2 RBD with lower affinity; conserved epitope in the RBD. Do not neutralize SARS-CoV-2
MAbs that have received Emergency Use Authorization (EUA)	Bamlanivimab (LY-CoV555)	SARS-CoV-2 RBD; EUA revoked
	Casirivimab (REGN10933) and imdevimab (REGN10987) in a combined therapy	Non-overlapping epitopes of the SARS-CoV-2 RBD
	Bamlanivimab (LY-CoV555) and etesevimab (LY-CoV016) in a combined therapy	Different, but overlapping, epitopes of the SARS-CoV-2 RBD

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