Infect Dis Ther (2022) 11:629–633
https://doi.org/10.1007/s40121-021-00565-w

LETTER

Letter to the Editor Regarding Management of Adult Patients with COVID-19 Outside Intensive Care Units: Guidelines from the Italian Society of Anti-Infective Therapy (SITA) and the Italian Society of Pulmonology (SIP)

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Received: September 1, 2021 / Accepted: November 9, 2021 / Published online: December 10, 2021

ABSTRACT

Recently, the Italian Society of Anti-Infective Therapy (SITA) and the Italian Society of Pulmonology (SIP) published guidelines on the management of inpatients with COVID-19. The guidelines do not recommend the use of monoclonal antibodies (mAbs) in inpatients, pending results from clinical trials. However, recently the Italian Drug Agency (AIFA) has allowed for the use of casirivimab/imdevimab at higher doses in hospitalized seronegative patients with COVID-19. Furthermore, several other therapeutic options based on mAbs are about to become available for outpatients. Here we provide a brief summary of the future possibilities and summarize existing data.

Keywords: SARS-CoV-2; COVID-19; Monoclonal antibodies; Anti-viral therapy; Seronegative

Key Summary Points

Currently in Italy the use of monoclonal antibodies is reserved to outpatients with COVID-19.

High dose casirivimab/imdevimab has recently become available in Italy to treat hospitalized anti-S negative patients with COVID-19.

Monoclonal antibodies (mAbs) are complementary to other treatments such as remdesivir, steroids, and tocilizumab.

Other monoclonal antibodies are being tested for intramuscular use in the prevention of severe COVID-19.

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Dear Editor,

We read with great interest the recently published guidelines for the clinical management of adult patients with COVID-19 outside intensive care unit, jointly developed by the Italian Society of Anti-Infective Therapy (SITA) and the Italian Society of Pulmonology (SIP) [1].

Their work will definitely be an important tool for frontline clinicians dealing with

patients affected by COVID-19. The SITA/SIP guidelines are mostly in line with current recommendations issued by the National Institutes of Health (NIH) [2], as well as with recommendations endorsed by the National Institute for Health and Care Excellence (NICE) [3]. Regarding the use of antiviral drugs, SITA/SIP recommend the use of remdesivir in hospitalized patients in the early phases of COVID-19, while monoclonal antibodies (mAbs) are reserved for outpatients. The use of mAbs is not advised in hospitalized patients, pending further results from randomized trial [1].

In fact, so far, the main role of mAbs has been in outpatients: both the BLAZE-I trial for bamlanivimab/etesevimab and the COV-2066 study with casirivimab/imdevimab showed a reduction in hospitalizations when the two drugs were used intravenously. This led to the emergency use authorization of the two drugs in the USA and Europe [4, 5]. The same effect was noted with the subcutaneous administration of casirivimab/imdevimab, at lower dose than the one employed for intravenous use, suggesting that such a dose might be enough to attain clinical efficacy [6]. More recently, the use of sotrovimab has been authorized for emergency use in the and during the publication process of this paper, sotrovimab has also been granted authorization in Italy, where it became available for administration at the end of November [7, 8] and Europe [9], based on data from an interim analysis in the COMET-ICE trial. Recently, definitive results for the IV use of sotrovimab have been published, confirming findings from the interim analysis [10]. Moreover, casirivimab/imdevimab received the authorization for emergency use by the Food and Drug Administration (FDA) for post-exposure prophylaxis for individuals either not fully vaccinated or not able to mount adequate responses to the vaccine and is now recommended in this setting by the NIH guidelines [2].

During the summer the use of bamlanivimab/etesevimab has been partially limited, as a result of the risk of possible clinical failure in the presence of certain variants of concern (such as the Beta and the Gamma variants) [2]. Conversely, both casirivimab/imdevimab and sotrovimab seem to retain their activity against these variants [5, 9]. Studies on the use of intramuscular formulation of sotrovimab are ongoing (NCT04913675). Another trial, active in Italy, is now investigating the MAD0004J08 compound, a potent monoclonal antibody for intramuscular use, engineered to reduce the risk of antibody-dependent enhancement and prolonged half-life, capable of neutralizing the authentic wild-type virus and the emerging variants [11] (NCT04952805).

Recently, the National Italian Drug Agency (Agenzia Italiana del Farmaco, AIFA) reviewed the recommendation for the use of casirivimab/imdevimab, opening to the possibility to treat patients hospitalized for COVID-19 excluding those requiring high flow oxygen or mechanical ventilation, provided that they test negative for anti-S antibodies [12].

The decision made by AIFA was based on the results of the COV-2066 and COV-2067 studies, as well as the results of the RECOVERY trial arms on casirivimab/imdevimab [5]. In the latter study, a significant reduction in mortality (24% vs 30%) was noted when comparing casirivimab/imdevimab to standard care [13]. The cohort was largely made up of patients treated with low-flow oxygen. The same finding was noted in the COV-2067 study, whose data are presented in the emergency use authorization released by the European Medicines Agency (EMA) [5]. Likewise, although the NIH guidelines acknowledge the existence of data supporting this therapeutical option [2], they do not make a clear endorsement of this use.

The biological rationale for the use of mAbs in SARS-CoV-2 seronegative patients resides in conferring passive humoral immunity against SARS-CoV-2 to patients who failed to develop humoral immunity against the virus after vaccination, or after a first infection. Of note, in the COV-2067 study, seronegativity was defined as anti-N and anti-S negativity [5], while in the RECOVERY trial patients were tested only for anti-S antibodies [13]. AIFA preferred the latter approach.

A reduction in viral load, usually highest in the early phase of disease [14, 15], is consistent with the proposed mechanism of action of the mAbs and could help to prevent cases of

persisting viral replication which have been suggested to maintain the inflammatory phase of the disease [16, 17]. It should be noted that mAbs used for the treatment of COVID-19 have a low rate of serious adverse effects, without a statistical difference between placebo and treatment arms [5]. Moreover, dosages used in the RECOVERY trial were much higher than those approved for the therapy of outpatients with mild and moderate COVID (8 g vs 2.4 g). Such dosages could cause issues of drug access and supply, especially in the Italian scenario, where the prescription of casirivimab/imdevimab is restricted to infectious diseases specialists from selected centers and a registry for drug monitoring is active [12]. The 8g dosage was available in Italy until Nov 30th 2021, subsequently AIFA decided to reduce the dose needed to treat both inpatients and outpatients, bringing the former to 2.4 g and the latter to 1.2 g [18]. Current recommendations by AIFA on the use of casirivimab/imdevimab for hospitalized patient is limited to seronegative patients requiring low-flow oxygen [1, 12]. As a matter of fact, the majority of patients enrolled in the RECOVERY trial, where the benefit of casirivimab/imdevimab in hospitalized patients [13] has been documented, were on low-flow oxygen. Patients with more advanced disease are likely to have progressed to the inflammatory phase of the disease, where anti-inflammatory agents such as steroids or tocilizumab have been shown to be more effective [2].

Moreover, the enrollment of patients requiring high-flow oxygen or mechanical ventilation in the REGN-COV2 trial in hospitalized patients has been placed on hold pending collection and analysis of further data based on a potential safety signal and an unfavorable risk/benefit of casirivimab/imdevimab in this subset of patients. Enrollment of hospitalized patients requiring either no or low-flow oxygen is continuing [19]. The use of mAbs in patients treated with low-flow oxygen is not in contrast with other therapeutic options. In fact, patients in the RECOVERY trial were also treated with standard care treatments in similar proportions when comparing the two treatment arms. In detail, more than 90% received corticosteroids, one quarter with remdesivir and one-seventh with tocilizumab [13].

The emergence and proliferation of SARS-CoV-2 variants conferring resistance to some antibodies is of major concern. However, monoclonal antibodies with high barrier to resistance such as casirivimab/imdevimab and sotrovimab are currently available. The former binds noncompeting epitopes of the receptor-binding domain of the SARS-CoV-2 spike protein [20], while the latter neutralizes SARS-CoV-2 by targeting an evolutionarily conserved epitope that lies outside the rapidly evolving receptor-binding motif [21].

Despite the great potential shown by mAbs and their increasing use in some countries, in Italy this therapeutical option is still not used as often as it should be. In this perspective, the importance of the cooperation between hospital-based physicians and territorial services for the prompt detection of patients eligible for treatment with mAbs has been recently underlined by the Italian Society for General Medicine (SIMG) and by Italian Society for Infectious and Tropical Diseases (SIMIT) [22].

In conclusion, mAbs, when available, represent a valuable tool to treat mild or moderate COVID-19 in outpatients. In Italy, their use is also authorized for seronegative hospitalized patients with severe disease requiring low-flow oxygen.

These drugs can prevent COVID-19 infection and disease progression especially in patients who are not vaccinated, who have waning vaccine-mediated protection over time or because of the emergence of variants, or who are immunocompromised and cannot mount an antibody-mediated antiviral response. The potential use of mAbs as pre- or post-exposure prophylaxis to prevent SARS-CoV-2 infection and symptomatic disease is another promising option [6]. A wider adoption of these drugs could play a major role to prevent severe forms of disease and to reduce the pressure on hospitals. Data from the use of mAbs in a real-world setting, especially in different age classes or through alternative administration routes, should be gathered.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for the preparation and publication of this manuscript.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contribution. Writing—original draft preparation: Tommaso Manciulli and Lorenzo Zammarchi; Writing—review and editing: Michele Spinicci, Alessandro Bartoloni. Supervision: Alessandro Bartoloni. All authors read and approved the final version of the manuscript.

Disclosures. Tommaso Manciulli, Michele Spiniccci, Alessandro Bartoloni and Lorenzo Zammarchi have nothing to disclose.

Compliance with Ethics Guideline. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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