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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Immediate hypersensitivity reactions to anti-SARS-CoV-2 neutralizing monoclonal antibodies: A real-life experience

To the Editor,

Several neutralizing mAbs directed against the spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) have been developed and evaluated in clinical trials to prevent progression to severe disease in high-risk individuals. The combination of bamlanivimab/etesevimab, casirivimab/imdevimab, and sotrovimab alone received emergency use authorization from the Food and Drug Administration and the European Medicines Agency to treat non-hospitalized patients (12 years of age and older, weighing at least 40 kg) with mild-to-moderate COVID-19 that did not require oxygen therapy (or an increase in baseline oxygen flow rate in those on chronic oxygen therapy), but at high risk of progression to severe COVID-19 disease.

In randomized clinical trials, therapy with mAbs for COVID-19 was well tolerated and overall, a low incidence of infusion-related or hypersensitivity reactions was reported.¹⁻⁴ Gottlieb et al.¹ reported, in a trial including 577 patients randomized to bamlanivimab or bamlanivimab/etesevimab treatment or placebo, nine cases (eight in treated groups and one in the placebo group) of mild hypersensitivity reactions, mostly occurring during infusion that was, however, completed in all instances. Two different trials using casirivimab/imdevimab reported, respectively, three allergic reactions in 4839 hospitalized patients treated with mAbs plus usual care,² and the same

percentage of hypersensitivity reactions in 275 non-hospitalized patients treated with casirivimab/imdevimab and in the placebo group.³ Likewise, in a clinical trial with sotrovimab, the percentage of patients with infusion-related reactions was the same (1%) in the group (291 patients) treated with sotrovimab and in the placebo group (292 patients).⁴ However, all these reported adverse events were no further characterized and/or classified from an allergological point of view.

Both clinical trials and real-life experiences are needed to establish robust data on the true incidence of adverse reactions, but currently, to our knowledge, no evidence of immediate hypersensitivity reactions (IHRs)⁵ to these biologics in real-world settings has been reported.

Starting in May 2021, we treated with intravenous (i.v.) mAbs 281 non-hospitalized patients, including eight patients with primary immunodeficiency and 31 with a secondary immunodeficiency, with mild-to-moderate COVID-19 at high risk of progression to severe disease and/or hospitalization: 134 females (F) and 144 males (M), with ages ranging from 22 to 90 years (mean, 71.4 years). Bamlanivimab/etesevimab (700/1400 mg) was administered in 123 patients (56 F; 67 M), casirivimab/imdevimab (1200/1200 mg or 600/600 mg) in 86 (44 F; 42 M) and sotrovimab (500 mg) in 72 (34 F; 38 M). In the treated population, 16 patients

TABLE 1 Incidence of immediate hypersensitivity reactions from 281 anti-SARS-CoV-2 mAbs treated patients.

	Bamlanivimab/etesevimab	Casirivimab/imdevimab	Sotrovimab
Patients treated (female/male)	123 (56 F/67 M)	86 (44 F/42 M)	72 (34 F/38 M)
Total number (%) of IHRs	2 (1.62%)	0	1 (1.38%)
Number (%) grade 1 (mild)	1 (0.81%)	0	1 (1.38%)
Number (%) grade 2 (moderate)	1 (0.81%)	0	0
Number (%) grade 3–4 (severe)	0	0	0

Abbreviation: IHRs, immediate hypersensitivity reactions.

reported an adverse reaction to at least one drug and 14 had a positive history of asthma.

During infusion, IHRs occurred in three female patients (1.06%). According to the grading system for generalized hypersensitivity reactions,⁶ clinical manifestations were classified as grade 1 (mild reaction), only urticarial rash, in two patients (one bamlanivimab/etesevimab and one sotrovimab), and grade 2 (moderate reaction), urticarial rash associated with rhinorrhea, eye itching, throat tightness, and mild dyspnea in the third patient (bamlanivimab/etesevimab). No severe hypersensitivity reactions (grades 3 and 4), including hypoxia, hypotension, or neurologic compromise, occurred (Table 1). Delayed hypersensitivity reactions within the first 72 h after mAbs administration were not reported.

The infusion was stopped in two patients (both bamlanivimab/etesevimab) and the adverse reaction was treated with i.v. administration of corticosteroid and antihistamine, whereas in one patient (sotrovimab) the infusion was completed reducing the infusion rate and no treatment was needed. None of the three patients had allergy and/or anaphylaxis history.

Our data confirm the low incidence of IHRs during i.v. infusion of anti-SARS-CoV-2 mAbs observed in clinical trials. The main strength of our experience is that anamnestic data collection, mAbs administration, and IHRs evaluation have been managed by an allergist-immunologist expert in recognizing signs or symptoms of hypersensitivity reactions.

One limitation of this study is that we did not perform any confirmatory test at that time because of the COVID-19 pandemic that affected our ability to make the necessary investigations and we are now conducting these investigations.

To the best of our knowledge, this is the first report concerning IHRs to anti-SARS-CoV-2 mAbs administered in outpatients with mild/moderate COVID-19 in real-life experience.

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CONFLICT OF INTEREST

Laura Franceschini and Alessandro Farsi declare no conflict of interest in relation to this work.

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