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RAPID COMMUNICATION



# Safety of Sotrovimab use in children with COVID-19: an Italian experience

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**ABSTRACT**

Sotrovimab is a monoclonal antibody approved in adult and adolescents at high risk for COVID-19. Thirty-three children evaluated in five Italian paediatric centres received Sotrovimab infusion and were retrospectively enrolled from December 2021 to April 2022. In more than half of cases (19/33, 57.6%) Sotrovimab was prescribed off-label. Overall, the infusion was well tolerated with no significative differences in those receiving an off-label prescription. All children had a complete recovery. Data on the safety of Sotrovimab should be investigated in a larger paediatric cohort, considering the continuous selection of new SARS CoV-2 variants which may be more or less susceptible to the effects of the Sotrovimab.

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## Introduction

Since November 2021 the B.1.1.529 (Omicron) variant of SARS-CoV-2, has rapidly spread becoming the most prevalent variant [1]. Among the monoclonal antibodies (mAbs), Sotrovimab has been approved by US Food and Drug Administration (FDA) for emergency use in adults or adolescents with mild to moderate coronavirus disease 2019 (COVID-19), who do not require supplemental oxygen, with risk factors for progression to severe COVID-19 [2]. Although Sotrovimab preserves its anti-viral activity against Omicron BA.1 and BA.1.1 variant, its efficacy in Omicron BA.2, BA.4 and BA.5 appears to be limited [3–5]. So far, no serious side effects have been reported in literature, but data on efficacy and safety of Sotrovimab in paediatric age are still lacking [6]. At present, only a few case studies on children are available which confirm a favourable outcome after the treatment [7–9]. The aim of this multicentre study is to describe the safety of Sotrovimab and the clinical and virologic outcome in paediatric patients. This is crucial because, the continuous selection of new variants of concern (VOC) could lead to the diffusion of new variants for which Sotrovimab could also be effective.

## Methods

Children with SARS-CoV-2 infection at risk of severe COVID-19according to the European Medicines Agency (EMA) and the Italian Medicines Agency (AIFA) criteria [4,10], seen in five Italian paediatric referral centres, were retrospectively enrolled from December 2021 to April 2022.

In accordance with the local ethical committee, all parents had signed, at the time of their first hospital access, an informed consent for the inclusion of children's data in observational studies with anonymised data extraction. SARS-CoV-2 infection was confirmed by Polymerase Chain Reaction (PCR) on nasopharyngeal swab. Moreover, confirmation of Omicron variant was obtained based on local laboratory availabilities.

Sotrovimab was prescribed in line with EMA) and AIFA indications in children over 12 years and weighing more than 40 kg [4,10]. In selected cases of children under 12 years and weighing less than 40 kg Sotrovimab was prescribed off-label, subject to parental consent, according to the local hospitals' procedure.

Clinical history and demographic data were collected, and any possible side effect after administration of the drug was registered. Clinical outcome was also evaluated, through the analysis of symptoms 7 days after Sotrovimab administration and defined as

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**Table 1.** Population characteristic according to on-label and off-label Sotrovimab administration.

| *Clinical and demographic features* | ***ALL (n = 33)*** | ***ON-LABEL (n = 14)*** | ***OFF-LABEL (n = 19)*** | *p* |
|---|---|---|---|---|
| Sex (male), n (%) | 17 (51.5%) | 5 (35.7%) | 12 (63.2%) | 0.118 |
| Age (years), median (IQR) | 11.9 (6.67-14.9) | 14.9 (13.3-16.3) | 7.4 (3.8-11.1) | **<0.001** |
| Malignant disease | 17 (51.5%) | 7 (50%) | 10 (52.6%) | 1 |
| Immunosuppressive conditions | 23 (69.7%) | 10 (71.4%) | 13 (68.4%) | 1 |
| Vaccinated for SARS-CoV-2 | 8 (24.2%) | 7 (50%) | 1 (5.3%) | **0.005** |
| Asymptomatic prior Sotrovimab infusion | 9 (27.3%) | 4 (28.6%) | 5 (26.3%) | 1 |
| Symptomatic 7 days after Sotrovimab | 4/30 (13.3%) | 3/13 (23.1%) | 1/17 (5.9%) | 0.29 |
| Negativization 7 days after Sotrovimab | 5/25 (20%) | 3/11 (27.2%) | 2/14 (14.2%) | 0.59 |
| Median time of negativization (days), median (IQR) | 23 (9.5-30)[a] | 17 (8-24)[b] | 23.5 (13.5-33)[c] | 0.31 |
| Sotrovimab side effects | 2 (6.1%) | 2 (14.3%) | 0 (0%) | 0.17 |
| COVID-19 complications | 4 (12.1%) | 2 (14.3%) | 2 (10.5%) | 1 |

[a]Calculated on 25 patients.
[b]Calculated on 11 patients.
[c]Calculated on 14 patients.

**Table 2.** Comorbidities reported in our cohort of children.

| Comorbidity | N |
|---|---|
| Lymphoma | 4 |
| Leukaemia | 9 |
| Systemic Lupus Erythematosus | 3 |
| Thalassemia Major | 1 |
| 22q11.2 deletion syndrome | 2 |
| Ewing sarcoma | 1 |
| Soft tissue sarcoma | 1 |
| Osteosarcoma | 1 |
| Glyoma | 1 |
| XIAP/BIRC4 mutation | 1 |
| Other primary immunodeficiencies | 2 |
| Kidney transplantation and Caroli disease | 1 |
| Barterr syndrome | 1 |
| Tetralogy of Fallot | 1 |
| Other cardiovascular disease | 1 |
| Ulcerative rectocolitis | 1 |
| Microvillus inclusion disease | 1 |
| Chronic intestinal pseudo-obstruction | 1 |

asymptomatic, pauci-symptomatic and symptomatic, according to the clinical picture. Virologic outcome was also evaluated 7 days after Sotrovimab administration and defined as cleared if the nasal swab was negative.

Patient's Data were analysed through SPSS.Statistics, 26.0 statistics software. Continuous variables were reported as mean and standard deviation (SD), or median and interquartile ranges (IQR), based on their distribution and compared using t-test or Mann-Whitney test, as appropriate. Categorical variables expressed as frequencies and percentages were compared using Fisher's exact test or $\chi 2$. $p < 0.05$ was considered statistically significant.

## Results

Thirty-three patients treated with Sotrovimab were enrolled. In more than half of cases (19/33, 57.6%) Sotrovimab was prescribed off-label. Omicron variant was confirmed in 75.7% of cases (25/33). Demographic and clinical characteristics of our cohort, according to on-label and off-label administration of Sotrovimab are reported in Table 1. Almost half of the patients suffered from malignant disease (17/33, 51.5%) and about two third of the children (23/33, 69.7%) received immunosuppressive therapies. Presence of comorbidities are summarized in Table 2. The most common signs/symptoms reported were fever in 15/33 (45.4%) children, followed by cough (12/33, 36.4%), gastrointestinal symptoms (5/33, 15.1%) and sore throat (4/33, 12.1%). Interestingly, nearly one third of patients (9/33, 27.3%) was asymptomatic. All patients received Sotrovimab within 5 days of a positive SARS-CoV-2 PCR nasopharyngeal swab. Interestingly, COVID-19 serology was negative in more than one third of the children (7/19, 36.8%) tested before infusion of mAbs (19/33 57.6%). The majority of patients received a single administration of Sotrovimab at standard dose of 500 mg, whereas 250 mg were administered in three children aged 6, 3 and 1 years and 125 mg in two children aged 5 and 11 months. Overall, Sotrovimab was well tolerated by all patients, and no serious side effects were recorded. Only 2 of 33 (6%) children reported an episode of vomiting and a peak of fever more than one hour after the end of infusion, both resolved within few hours. One week after the mAbs infusion the 86.7% (26/30) of children showed mild or no symptoms, while the remaining 13.3% (4/30) presented SARS-CoV-2 related interstitial pneumonitis. Of these, two children required oxygen supplementation, and another one was admitted to intensive care unit due to respiratory failure. About half of the patients (18/33, 54.5%) required hospital admission with a median time of hospital stay of 7 days (IQR: 3-19.5 days). For 7 children the length of hospitalization was not available. Notably only 4 patients, all with confirmed Omicron variant, were hospitalized due to SARS-CoV-2 interstitial pneumonia, developed after Sotrovimab administration, with a median length of hospitalization of 37.5 days (IQR: 35.25-54 days). The remnant was admitted due to their comorbidities. Overall, a week after infusion 26/33 (78.8%) children resulted to be asymptomatic or pauci-symptomatic. Notably, most of symptomatic patients

received an on-label prescription of Sotrovimab (23.1% vs 5.9%, $p = 0.29$). In this cohort, all patients had a complete recovery from SARS-CoV-2 infection, with no reports of death or sequelae. A week after the infusion only 5/25 patients (20%) had a negative SARS-CoV-2 PCR nasopharyngeal swab. Overall, the mean time to negativity was 23 days (IQR: 9.5-30 days) and it was longer in the group of children that received Sotrovimab off-label compared with the on-label one, though no statistically significant difference was reported between them (respectively 23.5 days, IQR 13.5-33 vs 17 days, IQR 8-24; $p = 0.31$).

## Discussion

This retrospective study reports safety data on the on-label and off-label Sotrovimab use in a cohort of 33 high-risk children. The study confirms the safety of Sotrovimab in children, as none of patients reported any serious side effect. This is remarkable considering that half of our patients received an off-label infusion, and there is a paucity of published data regarding off-label Sotrovimab administration [7–9,11]. A recent European study by Rau and colleagues on the off-label use of mAb in 53 high-risk children with COVID-19 confirmed the safety of using Sotrovimab [12]. In October 2022, Blind and colleagues published a study on a large cohort of 182 children treated with mAbs, of whom 48 children (26%) received Sotrovimab, confirming a good tolerability and reporting no adverse effects [13]. Consistent with our findings, all these reports confirmed that Sotrovimab is safe and well-tolerated even in high-risk and immunocompromised children.

Currently, the real efficacy of Sotrovimab in preventing severe forms of SARS-CoV2 is debated, due to the development of multiple mutations that led to the selection of variants capable of escaping the neutralization of many mAbs [14]. Therefore, further mutations of spike protein have caused the selection of subvariants for which Sotrovimab is ineffective *in-vitro* [15]. Since the diffusion of Omicron BA.2, in April 2022, FDA revoked the emergency use authorization for Sotrovimab [16]. However, a recent study conducted by Martin-Blondel on 190 high-risk patients (25% of whom with BA.2 infection) for SARS-CoV-2 complications, showed a similar favourable outcome after Sotrovimab administration in BA.1 infected compared to BA.2 [17].

The clinical outcome after infusion was favourable in the majority of patients, with 78.8% of patients being asymptomatic or pauci-symptomatic at 7-days. In any case, all patients went through a full recovery with no permanent outcomes. In the study by Blind and colleagues [13], 3/48 patients receiving Sotrovimab required a COVID-19 related medical examination within 30-days of infusion. In our study, the virological outcome a week after the infusion showed that only the 20% of children had a negative swab. This finding agrees with data from the literature, considering the high rate of immunosuppressed patients in our cohort. In fact, in a study on oncologic patients the median time of positive PCR was 16 days (range 1-70 days), but 12.7% of patients tested positive beyond day 20. Moreover, the risk of having a positive swab is estimated to be three times higher in immunosuppressed patients, suggesting a prolonged viral shedding in these patients [18]. These results confirm that the viral load on nasopharyngeal swab is unable to predict the efficacy of Sotrovimab, as SARS-Cov-2 PCR positivity may persist even without an active viral replication [19].

In conclusion, we confirm that Sotrovimab infusion is safe and well-tolerated in children, with no significative differences in those receiving an off-label prescription. Despite our study is one of the largest paediatric cohorts in literature, the limited number of patients enrolled doesn't allow to formulate certain conclusion. Stronger safety data should be obtained on larger paediatric cohort, considering the continuous selection of new SARS CoV-2 variants which may be more or less susceptible to the effects of the Sotrovimab.

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## Disclosure statement

No potential conflict of interest was reported by the authors.

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