GAP·f
Global Accelerator for Paediatric formulations
WHO Hosted Network

World Health Organization

Paediatric drug optimization for COVID-19

Meeting report

6 SEPTEMBER 2022

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ISBN 978-92-4-006819-3 (electronic version)
ISBN 978-92-4-006820-9 (print version)

Design and layout by 400 Communications Limited.

Contents

Acknowledgements

The writing of this meeting report was led by Brian Jonat, with contributions from Tiziana Masini, Martina Penazzato, Janet Victoria Diaz John Adabie Appiah and Wilson Were.

The WHO's Science Division and Health Emergencies Programme acknowledge all speakers and participants who joined and contributed to the paediatric drug optimization COVID-19 meeting.

Background

Since the COVID-19 pandemic began, fewer cases of and deaths from COVID-19 have been reported for children and adolescents than for adults. In addition, the severity of COVID-19 infection and presentations differ between children and adolescents versus adults.

Of age-disaggregated cases reported to WHO from 30 December 2019 to 13 September 2021, children younger than five years represented 1.8% (1,695,265) of global cases and 0.1% (1721) of global deaths. Older children and younger adolescents (5–14 years old) comprised 6.3% (6, 020,084) of global cases and 0.1% (1245) of global deaths, and older adolescents and young adults (15–24 years old) comprised 14.5% (13,647,211) of global cases and 0.4% (6436) of global deaths *(1)*.

Children's initial course of COVID-19 is similar to that of adults, but progression to severe disease is much less frequent. Hypotheses for the less severe phenotype of COVID-19 in children include decreased expression of SARS-CoV-2 binding receptors, improved mucosal innate immune response and a less severe inflammatory response to infection *(2)*.

Although children are in general less affected by COVID-19, they still stand to benefit from safe, effective COVID-19 treatments and thus, accelerating COVID-19 therapeutic research and development for children is of utmost importance.

However, small but meaningful proportions of children require intensive care, and certain subgroups of children, including neonates and children with chronic conditions, have a higher risk of severe disease and death *(3)*. Children and adolescents also have a delayed hyperinflammatory syndrome known as multisystem inflammatory syndrome, which frequently results in severe disease and is rare among adults. Additionally, chronic symptoms after COVID-19 (long COVID) have been reported among children, causing significant morbidity.

Although children are in general less affected by COVID-19, they still stand to benefit from safe, effective COVID-19 treatments and thus, accelerating COVID-19 therapeutic research and development for children is of utmost importance *(4)*. This is especially true in low- and middle-income countries, where optimized supportive measures are not consistently available and where the most child deaths have been reported *(5)*.

Additionally, treatments for children may play an important role in breaking the chain of transmission, especially with evidence indicating that children are major drivers of viral spread. The importance of treating children is heightened as more transmissible variants spread in the population and more concerns are raised for post-COVID conditions. Timely and appropriate consideration of children in the development of COVID-19 therapeutics must therefore be ensured.

Despite several efforts to accelerate the investigation and development of new therapeutics for COVID-19 for children, important research gaps remain. Few trials have been specifically designed for children, and the extreme heterogeneity of these trials in terms of products, design, inclusion criteria, clinical endpoints and sample sizes will not contribute to the robust evidence needed to prompt any recommendation for this population. In fact, studies that are unable to yield reliable and consistent therapeutic information put their subjects at risk without an accompanying benefit. Extrapolating pharmacokinetic and safety data from adult studies to make recommendations for children is similarly challenging. Several of the treatments studied for COVID-19 for adults have been studied for other conditions for children and may be good candidates for accelerated development of therapeutics for children with COVID-19. However, additional studies are required to verify the efficacy of these therapeutics in treating COVID-19. Real-world data collection on medications that are already in use to monitor effectiveness and safety may be a complementary component of drug evaluation to expedite development. Collecting data to ensure appropriate, safe and effective use of therapeutic products for children and designing trials enrolling children should ensure that relevant, actionable outcomes for children – pharmacokinetics, dosing, safety and effectiveness – can be achieved.

To address the remaining research gaps that hinder the availability of appropriate therapeutics for children with COVID-19, WHO's Health Emergencies Programme and Science Division convened and facilitated PAediatric drug optimization (PADO) for COVID-19 exercise to ensure that research and development efforts in this field target a priority list of therapeutics and ensure that children with COVID-19 can also rapidly benefit from safe, effective and accessible treatment options.

THE NEED FOR PAEDIATRIC DRUG OPTIMIZATION EXERCISES

The development of medicines for children lags unacceptably behind that for adults by nearly a decade. Following the resolution at the 69th World Health Assembly on promoting innovation and access to quality, safe, efficacious and affordable medicines for children, WHO and partners have increased their efforts to deliver on this global commitment and scaled up activities to ensure that age-appropriate formulations are available for children *(1)*.

The Global Accelerator for Paediatric Formulations Network (GAP-f), a WHO-hosted network, works across the life cycle of drug development to give priority to, evaluate, develop and deliver optimal formulations for children *(2)*. Setting priorities is a necessary first step to enable a targeted approach to research and development. Developing a prioritized drug portfolio of the most needed formulations for children is essential to streamline researchers' and suppliers' efforts and resources around specific dosage forms and formulations that address the most urgent needs for children. This is particularly important given that the market for medicines for children is often small and/or fragmented, resulting in limited volumes with potential market failures.

PAediatric drug optimization (PADO) exercises to identify key priority products for research and development led by WHO technical departments, have been successfully undertaken for HIV, hepatitis C and tuberculosis, demonstrating their potential and impact to accelerate access to optimal formulations in the context of fragmented, small markets for medicines for children. To provide further guidance to support similar processes for optimizing drugs for children in other disease areas, GAP-f has published a guidance document that is intended for all WHO technical units and all stakeholders involved and describes how to undertake a PADO process and adapt it to the specific needs of each disease area *(3)*.

Developing a prioritized drug portfolio of the most needed formulations for children is essential to streamline researchers' and suppliers' efforts and resources

The PADO-COVID-19 exercise will enable alignment between funders, procurers, market-coordination entities, researchers, innovators, generics, product development partnerships and regulators on priority products to be investigated and developed.

Objectives

The purpose of the paediatric drug optimization COVID-19 founding meeting was:

- To review drugs and formulations currently recommended by WHO for adults and their approval status and indications for children; or
- To identify priority therapeutics to be further investigated and developed for children and adolescents; and
- To develop a clear research agenda to support and enable future drug optimization work for children, with the goal of ensuring that the unique needs of children are effectively addressed.

Methods

The PADO-COVID-19 meeting was held virtually on 6 September 2022 and brought together academic researchers, clinical experts, paediatricians, regulators, funders and other key stakeholders involved in research on and development of COVID-19 therapeutics. The process was supported by a review of current WHO guidelines for COVID-19 therapeutics for adults, a review of the WHO Global Clinical Platform for COVID-19 and a scoping review on the use of COVID-19 therapeutics for children and adolescents.

Following a first plenary session at which these aspects was presented, consensus on priority therapeutics to be further investigated for children and adolescents were reached through guided working group discussions, and at a last plenary session, the PADO-COVID-19 list and corresponding research agenda were developed.

To facilitate the priority setting, a dedicated framework was developed with the input of meeting participants before the meeting who were invited to rank the relative importance of the clinical scenarios to consider each one of the attributes to examine during the priority setting.

The attributes included were:

- efficacy
- safety and toxicity
- drug–drug interactions
- required screening
- window for treatment initiation
- patient acceptability
- need for monitoring
- specific subgroup indications
- known resistance.

Based on the information gathered, each attribute received a score of 0 to 5, with 5 being the most favourable.

The score adjusted based on the relative importance assigned by the group to each attribute, helped the group to set priorities with 5 being the most favourable. The total score helped the group to set priorities for specific drugs based on the full assessment of the attributes. The groups were invited to state the rationale for drug choice and list research gaps to inform the development and use of the prioritized formulations. Finally, opportunities to accelerate research were considered and discussed.

Participants' conflicts of interest were collected for all participants and closely reviewed, and if perceived or objective conflicts of interest were detected, participants were asked to join the meeting as an observer and asked to abstained from voting.

Summary of discussion

OVERVIEW OF CLINICAL MANAGEMENT AND THERAPEUTIC LANDSCAPE

In preparation for the PADO discussion, the group reviewed the epidemiology and clinical presentation for COVID-19 that continues to be prevalent throughout the world. Adults and especially older adults comprise the majority of cases of and deaths from COVID-19, but the number of children hospitalized or dying from COVID-19 is noteworthy. In particular, children with comorbidities such as immunocompromise, asthma or cancer have a higher risk for severe disease. Severe symptoms include pulmonary manifestations and rare nervous system or cardiac manifestations. The common clinical presentations of these patients were reviewed as well as WHO global clinical data on treatment choices by clinicians for children.

The group then considered off-label use of COVID-19 drugs based on published literature and a survey of clinicians undertaken by GAP-f partners. The available literature was reviewed, and it was noted that high-quality research available for treating children with COVID-19 is severely limited, with remdesivir being the most studied drug. Studies of corticosteroids were limited to multisystem inflammatory syndrome, and no relevant studies were identified for other immunomodulators included within WHO guidelines. Despite this limited availability of literature to guide therapy, clinicians must make decisions on medication choices for their patients. A survey of global clinicians was presented regarding treatment choices for COVID-19. Most clinicians had used antiviral agents and corticosteroids to treat children with COVID-19 without common or major side-effects. However, the results were heterogeneous overall, indicating practice variation from clinician to clinician (data submitted for publication).

After concluding the review of off-label use of medications for COVID-19, the group reviewed the therapeutic regulatory landscape in the United States of America and Europe to understand the rationale behind regulatory decisions related to COVID-19 therapeutics. The United States Coronavirus Treatment Acceleration Plan and the European paediatric investigation plans were reviewed, and the roles of emergency use authorization and marketing authorization were clarified. This framework was applied to the current therapeutics approved by the United States Food and Drug Administration and European Medicines Agency as well as current treatment guidelines. It was noted that most decisions on COVID-19 therapeutics for children were extrapolated from adult data, considering the different risk versus benefit profile of infection and treatment among children. In addition, studies involving children routinely take several years after marketing authorization to conclude, with some of the most vulnerable children being the last to be studied (infants and neonates). Overall, more studies involving children are required to delineate the role of COVID-19 therapeutics for children.

The group noted the current scenarios for introducing and rolling out medications. This discussion illustrated the importance of mode of administration, stability requirements and cost in identifying a successful therapeutic candidate. A clear alignment of policy around a small number of medications and consistent messaging to suppliers were recommended to address the challenges in implementing drug supply and distribution.

SETTING PRIORITIES

The priority-setting process was conducted for both medications whose mechanism of action is direct antiviral activity against SARS-CoV-2 and medications that primarily function as immunomodulators to regulate the harmful inflammatory response in moderate and severe COVID-19. The meeting participants were divided into two subgroups as described above (see methods). One group reviewed evidence to generate recommendations for antiviral medications, and the second group reviewed evidence for immunomodulatory medications. All reviewed medications were recommended by the WHO living guideline for treating people with COVID-19 at the time of the meeting.

The antiviral medications reviewed included:

- remdesivir
- nirmatrelvir-ritonavir
- molnupiravir
- sotrovimab
- casirivimab-imdevimab

The immunomodulatory medications reviewed included:

- tocilizumab
- sarilumab
- baricitinib.

PRIORITY DRUG CHOICE – ANTIVIRAL AGENTS

The priority drug of choice among antiviral agents was nirmatrelvir-ritonavir. The rationale behind this recommendation included:

- robust efficacy data for adults
- oral formulation, ideal for outpatient and inpatient use
- short duration of treatment
- potential use in mild or moderate COVID-19
- potential use among high-risk groups.

The major downside of this medication is the potential for drug–drug interactions, although this is potentially manageable. Although remdesivir is the most studied drug for children under consideration, the overall efficacy of remdesivir was considered weak. An intravenous formulation and lab monitoring make administration challenging as well. Molnupinavir had a mixed efficacy profile for adults, with a likely contraindication for children because of genotoxicity. Monoclonal antibodies (sotrovimab and casirivimab-imdevimab) were not retained as treatment options because they lack efficacy against circulating SARS-CoV-2 variants.

Recommended research gaps to be given priority for nirmatrelvir-ritonavir included:

- drug–drug interactions for children
- duration of treatment
- acceptability of oral formulation
- dosing and side–effects
- effect of vaccination or prior infection on efficacy
- incorporation of real-world data and post-marketing surveillance.

The group also noted an opportunity to accelerate research on using antiviral agents and preventing long COVID. Overall, there was consensus among group members about this prioritization.

PRIORITIZATION DRUG CHOICE – IMMUNOMODULATORS

The priority drugs of choice for immunomodulators were tocilizumab and baricitinib. The rationale behind these recommendations included:

- high levels of efficacy for adults
- favourable overall safety profile
- potential use in moderate, severe, and critical COVID-19.

Additional positive attributes of tocilizumab include single-dose treatment and frequent and longstanding clinical use for other conditions among children, reflecting a more reassuring safety profile. Concerns related to baricitinib include the limited safety data for children and the accessibility of oral formulations for critically ill children. Concerns related to tocilizumab include long drug half-life, drug–drug interactions and logistical requirements of refrigeration and storage. Sarilumab was not selected due to weaker efficacy data and lack of safety data for children.

Recommended research gaps to be given priority for tocilizumab and baricitinib included:

- safety and efficacy for children
- understanding variability in immunomodulation based on age
- frequency of contraindication of immunomodulators because of organ injury.

FIG.1. PADO-COVID-19 LIST OF PRIORITY PRODUCTS FOR RESEARCH AND DEVELOPMENT

Nirmatrelvir-ritonavir

- Robust efficacy data in preventing COVID-19 progression
- Oral formulation
- Short duration of treatment
- Ideal for high-risk children

Tocilizumab

- Strong efficacy data in moderate and severe COVID-19
- Reassuring and robust safety data for children
- Single dose treatment

Baricitinib

- Strong efficacy data in moderate and severe COVID-19
- Safety has been studied among children (non-COVID)
- Short half-life and oral formulation

Following the priority-setting exercise, the group considered some of the research gaps for treating children with COVID-19 (Box 1).

BOX.1. RESEARCH PRIORITIES IDENTIFIED BY THE PADO-COVID-19 EXPERT GROUP

RESEARCH GAPS TO INFORM THE DEVELOPMENT AND USE OF PRIORITY THERAPEUTICS FOR COVID-19
Pharmacokinetic and clinical effects of nirmatrelvir-ritonavir in combination with common medications for children (drug–drug interactions)
Effect of duration of treatment of nirmatrelvir-ritonavir on disease resolution, rebound symptoms and viral resistance among children
Tolerability and stability of various oral formulations of nirmatrelvir-ritonavir for children
Pharmacokinetics, clinical safety and efficacy of nirmatrelvir-ritonavir at escalating doses for children
Presence of rebound symptoms and/or infection among children after treatment with nirmatrelvir-ritonavir
Correlation of virological data and clinical outcomes in the context of nirmatrelvir-ritonavir treatment of children
Use of observational cohort and epidemiological data to identify safety and efficacy of nirmatrelvir-ritonavir for COVID-19 among children
Effect of prior infection with or vaccination for SARS-CoV-2 on the efficacy of nirmatrelvir-ritonavir for COVID-19 among children
Differing inflammosome and cytokine profiles based on age and severity of inflammation and associated response to tocilizumab and/or baricitinib therapy
Pharmacokinetic, safety and efficacy of baricitinib (and to a lesser extent tocilizumab) among children with COVID-19
Frequency of contraindication to tocilizumab based on organ injury among critically ill children with COVID-19
Benefits and downsides to oral versus intravenous formulations among critically ill children in resource-limited settings

Moving forward and next steps

Paediatric drug optimization COVID-19 outcomes will be shared with GAP-f partners, which will explore and move forward with targeted actions to ensure acceleration through the product life cycle of the products given priority. To ensure appropriate dissemination and promote alignment of key stakeholders, a policy brief and a peer-reviewed manuscript will be developed. Future development of a PADO watch list that may include pipeline products will be considered in conjunction with research and development work led by the R&D Blueprint team.

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Annex 1. Meeting agenda

PADO-COVID-19, 6 SEPTEMBER 2022

INTRODUCTION

TOPIC	SPEAKER	TIME
Welcome, introduction and meeting objectives	Janet Victoria Diaz and Martina Penazzato (WHO)	13:00 – 13:10

SESSION 1. BACKGROUND TO INFORM PADO-COV19

TOPIC	SPEAKER	TIME
The epidemiology of COVID-19 disease in children	Wilson Were and John Adabie Appiah (WHO)	13:10–13:20
Clinical experience with off-label use of COVID-19 therapeutics in children	Brian Jonat (WHO) and Daniele Donà (WHO)	13:20 – 13:30
Regulators' perspective	Laura Fregonese (European Medicines Agency) and Prabha Viswanathan (United States Food and Drug Administration)	13:30 – 13:50
Ensuring prioritization with an access lens	Sean Regan (Clinton Health Access Initiative)	13:50 – 14:00
Q&A	All (moderated by Janet Diaz)	14:00–14:10

SESSION 2. WORKING GROUP DISCUSSION

TOPIC	SPEAKER	TIME
Method for prioritization and group discussion	Tiziana Masini (WHO)	14:10 – 14:20
Group discussions (Prioritization, research questions and implementation considerations) · **Group 1: Antivirals and monoclonal antivirals** (facilitated by Martina Penazzato and John Adabie Appiah) · **Group 2: Monoclonal immunomodulators** (facilitated by Janet Diaz and Wilson Were)	All	14:20 – 15:30

BREAK **15:30-15:45**

SESSION 3. CONSENSUS DECISION-MAKING AND NEXT STEPS

TOPIC	SPEAKER	TIME
Report back from working groups	All (moderated by Martina Penazzato)	15:45 – 16:05
Plenary discussion – development of the PADO-COVID-19 list and related research questions	Wilson Were (WHO)	16:05 – 17:20
Wrap-up and next steps	Janet Diaz and Martina Penazzato (WHO)	17:20 – 17:30

Annex 2.
List of participants

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Marie Valentin	GAP-f Regulatory Lead, Regulation and Prequalification Department
Wilson Milton Were	Medical Officer, WHO Department of Maternal, Newborn, Child and Adolescent Health and Ageing

Annex 3. Summary of characteristics for therapeutics considered

THERAPEUTIC COMPOUND SUMMARY – ANTIVIRAL AGENTS

REMDESIVIR

Remdesivir is a nucleotide analogue that inhibits RNA transcription *(1)*.[6] It is manufactured by Gilead Sciences. The compound is activated intracellularly to nucleoside triphosphate GS-443902, leading to impaired viral RNA transcription. It is renally and hepatically metabolized with an elimination half-life of 1 hour. Its formulation is lyophilized powder for reconstitution and intravenous administration over 3–5 days (3 days recommended by WHO). Select adverse events associated with remdesivir include: hypersensitivity, transaminitis, renal injury, nausea and risk of toxicity in renal impairment. It is conditionally recommended by WHO for adults and adolescents with non-severe COVID-19 at highest risk of hospitalization. The United States Food and Drug Administration recommends remdesivir for adults and children ≥28 days old and ≥3 kg for COVID-19 requiring hospitalization or who are at risk of progression to severe COVID-19. The European Medicines Agency recommends its use for adults and adolescents with COVID-19 pneumonia requiring oxygen or who are at increased risk of progressing to severe COVID-19. The data to support these recommendations comes largely from multinational randomized controlled trials, many of which showed no effect on mortality *(2,3)*. One study (PINETREE) did show risk reduction in disease progression for high-risk nonhospitalized patients, and one study (ACTT-1) showed improved time to recovery for patients hospitalized with COVID pneumonia *(4,5)*. Some limited safety data for children have been reported from an ongoing trial *(6)*.

NIRMATRELVIR-RITONAVIR

Nirmatrelvir-ritonavir is a combination of nirmatrelvir, a viral protease inhibitor, and ritonavir, a CYP450 inhibitor *(7,8)*. It is manufactured by Pfizer Inc. Nirmatrelvir acts by directly binding and inhibiting chymotrypsin-like cysteine protease enzyme (Mpro). Ritonavir augments the metabolism of nirmatrelvir, leading to improved therapeutic drug levels. Nirmatrelvir (when given with ritonavir) has an elimination half-life of 6 hours and 69% protein binding. It is hepatically metabolized by CYP3A4 (inhibited by ritonavir), with renal excretion of metabolites. Its current formulation is a 150-mg tablet of nirmatrelvir (300-mg dose) and a 100-mg tablet of ritonavir (200-mg dose), with a recommended course of 5 days. Select adverse events associated with Nirmatrelvir-ritonavir include: drug–drug interactions, risk of toxicity with renal impairment, risk of toxicity with hepatic impairment, dysgeusia, diarrhoea, hypertension, myalgia and rebound symptoms. It is strongly recommended by WHO for adults with non-severe COVID-19 at highest risk of hospitalization. The United States Food and Drug Administration has authorized emergency use of Nirmatrelvir-ritonavir for adults and adolescents with COVID-19 with risk of progression to severe disease. The European Medicines Agency has granted conditional authorization for use for adults with COVID-19 who do not require oxygen therapy and who are at risk of progression to severe disease. The data to support these recommendations come from a multinational randomized controlled trial demonstrating reduction in hospitalization or death among adults with COVID-19 at risk of progression to severe disease *(9)*. Although there are no published efficacy or safety data for children, an ongoing clinical trial with children is currently enrolling patients (Clinicaltrials.gov, NCT05261139).

THERAPEUTIC COMPOUND SUMMARY – ANTIVIRAL AGENTS

MOLNUPIRAVIR

Molnupiravir is a ribonucleoside prodrug that causes lethal mutagenesis and therefore inhibits viral replication *(10)*. It is manufactured by Merck & Co. and Ridgeback Biotherapeutics. Molnupiravir is metabolized to NHC and intracellularly phosphorylated to its active form NHC-TP. It has an elimination half-life of 3.3 hours, no protein binding and is metabolized and excreted as pyrimidines. Its formulation and treatment recommendations are a 200-mg capsule (800-mg dose, twice daily) for 5 days. Select adverse events associated with molnupiravir include: diarrhoea, nausea, dizziness and risk of bone and cartilage growth toxicity. It is conditionally recommended by WHO for adults with non-severe COVID-19 at highest risk of hospitalization. The United States Food and Drug Administration has authorized emergency use of molnupiravir for adults with COVID-19 and risk of progression to severe disease. The European Medicines Agency is currently reviewing molnupiravir for marketing authorization but states that it can be used to treat adults with COVID-19 who do not require oxygen but are at risk of disease progression. The data to support these recommendations come from a multinational randomized controlled trial demonstrating a relative reduction in hospitalization and death among adults with COVID-19 at risk of progression to severe disease *(11)*. There are no data available for use of molnupiravir for children and no ongoing paediatric studies.

SOTROVIMAB

Sotrovimab is a recombinant human monoclonal antibody *(12,13)*. It binds to the SARS-CoV-2 spike protein and interferes after viral attachment, disrupting fusion of viral and cell membranes. It is manufactured by GSK plc. It has a slow elimination half-life, with peak serum concentration of 143 µg/mL and concentration at day 29 of 40.7 µg/mL after one dose. Its formulation is 500-mg/8-mL solution for single-dose intravenous administration. Select adverse events associated with sotrovimab include: hypersensitivity reaction, rash and diarrhoea. WHO conditionally recommends sotrovimab for people with non-severe COVID-19 at highest risk of hospitalization. The United States Food and Drug Administration authorized emergency use of sotrovimab for adults and adolescents with mild to moderate COVID-19 and high risk of progression to severe disease. The European Medicines Agency authorized sotrovimab for use for adults and adolescents with mild to moderate COVID-19 and high risk of progression to severe disease. The data to support these recommendations comes from a multinational randomized controlled trial demonstrating reduced incidence of all-cause hospitalization and death among nonhospitalized adults with COVID-19 at high risk of disease progression *(14)*. However, in vitro studies strongly suggest likely ineffectiveness of sotrovimab against the BA.2 Omicron variant *(15,16)*. Although there are no published efficacy or safety data in children, an ongoing clinical trial in children is currently enrolling patients (Clinicaltrials.gov, NCT05124210).

CASIRIVIMAB-IMDEVIMAB

Casirivimab-imdevimab is a combination of two different recombinant human monoclonal antibodies *(17)*. These antibodies bind to nonoverlapping receptor binding domains of the SARS-CoV-2 spike protein and block interaction with human ACE-2 receptors, preventing viral entry to cells. It is manufactured by Regeneron Pharmaceuticals. It has an elimination half-life of 26–32 days. Its formulation is 600 mg of casirivimab and 600 mg of imdevimab administered together as a single intravenous infusion or by subcutaneous injection. A select adverse event associated with casirivimab-imdevimab includes hypersensitivity reaction. WHO conditionally recommends casirivimab-imdevimab for people with non-severe COVID-19 at highest risk of hospitalization or for people with severe or critical COVID-19, for whom viral genotyping can confirm a susceptible SARS-CoV-2 variant. The United States Food and Drug Administration has authorized emergency use of casirivimab-imdevimab for adults and adolescents with mild to moderate COVID-19 and high risk of progression to severe disease as well as for post-exposure prophylaxis for these same high-risk people. The European Medicines Agency authorized casirivimab-imdevimab for adults and adolescents with COVID-19 who do not require oxygen and are at high risk of progression to severe disease as well as for post-exposure prophylaxis for these same high-risk patients. The data to support these recommendations come from one multinational randomized controlled trial demonstrating reduced incidence of symptomatic COVID-19 among adolescents and adults who had household contacts with COVID-19 but were asymptomatic and seronegative *(18)*. Another open-label multinational randomized controlled trial showed reduced 28-day mortality among seronegative people hospitalized with COVID-19 *(19)*. However, in vitro studies strongly suggest likely ineffectiveness of casirivimab-imdevimab against SARS-CoV-2 Omicron variants *(15,20)*. There are no data available for use of casirivimab-imdevimab for children younger than 12 years old and no ongoing paediatric studies for children younger than 12 years old.

THERAPEUTIC COMPOUND SUMMARY – ANTIVIRAL AGENTS

THERAPEUTIC COMPOUND SUMMARY – IMMUNOMODULATORS

TOCILIZUMAB

Tocilizumab is an interleukin-6 (IL-6) receptor inhibitor monoclonal antibody *(21)*. It has dose-dependent IL-6 receptor antagonism, leading to downstream anti-inflammatory effects through innate and adaptive immune system modulation. It is manufactured by Genentech Inc. Elimination half-life is concentration-dependent, ranging from 16 to 23 days for children, with 80% bioavailability. Its formulation for treatment of COVID-19 is 20 mg/mL vials for dilution (dose 8 mg/kg up to 800 mg) as a single intravenous infusion. A 162-mg/0.9-mL formulation for subcutaneous administration is also available. Select adverse events associated with tocilizumab include: transaminitis, secondary or serious infections, bowel perforation, infusion reactions, neutropaenia, thrombocytopaenia and possible increased metabolism of CYP substrates. WHO strongly recommends tocilizumab or sarilumab in conjunction with corticosteroids for severe COVID-19 among adults (use for children is neither recommended nor discouraged). The United States Food and Drug Administration authorized emergency use of tocilizumab for adults and children ≥2 years old with COVID-19 who are hospitalized and require supplemental oxygen or more invasive respiratory support (in combination with corticosteroids). The European Medicines Agency approved tocilizumab for adults with COVID-19 who are receiving steroids and who require supplemental oxygen or mechanical ventilation. Both the United States Food and Drug Administration and European Medicines Agency approve tocilizumab for children for other conditions. The data to support these recommendations come from several multinational randomized controlled trials that showed improvement in important clinical outcomes such as mortality and progression to mechanical ventilation for adults hospitalized with COVID-19 (some inclusion criteria only critically ill people) *(22–24)*. Some studies showed no difference in these outcomes, but in some of these studies corticosteroid use was low *(25,26)*. One study included adolescents. Although there are no published efficacy or safety data for children with COVID-19, an ongoing clinical trial with children is currently enrolling patients (Clinicaltrials.gov, NCT05164133). In addition, multiple studies have been conducted for use of tocilizumab for children with other illnesses, including juvenile idiopathic arthritis and cytokine release syndrome after CAR-T cell treatment *(27,28)*.

SARILUMAB

Similar to tocilizumab, sarilumab is an interleukin-6 (IL-6) receptor inhibitor monoclonal antibody *(29)*. Its IL-6 receptor antagonism leads to downstream anti-inflammatory effects through innate and adaptive immune system modulation. It is manufactured by Regeneron Pharmaceuticals and Sanofi S.A. Elimination half-life is concentration-dependent, ranging from 8 to 10 days for adults, with a volume of distribution of 7.3 L. Its formulation for COVID-19 is 200 mg/1.14 mL (400-mg dose) for a single-dose intravenous infusion. A 150-mg/1.14-mL formulation for subcutaneous administration is also available. Select adverse events associated with sarilumab include: transaminitis, secondary or serious infections, bowel perforation, infusion reactions, neutropaenia, thrombocytopaenia, lipid abnormalities and possible increased metabolism of CYP substrates. WHO strongly recommends sarilumab or tocilizumab in conjunction with corticosteroids for severe COVID-19 among adults (tocilizumab is preferred for children over sarilumab, although neither are directly recommended). The United States Food and Drug Administration has not authorized sarilumab for treatment of COVID-19, but it has authorized sarilumab for treatment of adults with moderate to severe rheumatoid arthritis. Similarly, the European Medicines Agency approved sarilumab for adults with moderate to severe rheumatoid arthritis but not for treatment of COVID-19. The data to support the WHO recommendations come from a multinational randomized controlled trial that showed improvement in organ-support free days and in-hospital mortality for adults with COVID-19 admitted to the intensive care unit and requiring respiratory or cardiovascular support *(23)*. Several studies showed no difference in key outcomes for adults hospitalized with moderate to severe COVID-19, and one study was stopped early due to safety concerns of the intervention group *(30–33)*. Although there are no published efficacy or safety data for children with COVID-19, an ongoing clinical trial with children for juvenile rheumatoid arthritis is currently enrolling patients (Clinicaltrials.gov, NCT02991469). There are no current data available for the safety or efficacy of sarilumab for children.

THERAPEUTIC COMPOUND SUMMARY – ANTIVIRAL AGENTS

BARICITINIB

Baricitinib is a JAK1/JAK2 inhibitor *(34)*. It modulates intracellular signalling pathways to promote immune modulation. Specifically, baricitinib inhibits IL-6 STAT3 phosphorylation, resulting in a reduction in immunoglobulin concentration and C-reactive protein. It is manufactured by Eli Lilly and Company. Elimination half-life is 12 hours for adults, with 80% bioavailability and 45–50% protein binding (Vd 76 L). It is metabolized through the CYP3A4 pathway and excreted renally. Its formulation is tablet form in 4-mg, 2-mg and 1-mg strengths (4-mg dose daily), with a recommended duration of treatment of 14 days. Select adverse events associated with baricitinib include: secondary or serious infections, bowel perforation, hypersensitivity, transaminitis, CPK increase, thrombocytosis, neutropaenia, venous thrombosis, pulmonary embolism, lymphoma and potential toxicity in renal impairment. WHO strongly recommends baricitinib in conjunction with corticosteroids for severe COVID-19 for adults (use for children is uncertain). The United States Food and Drug Administration authorized emergency use of baricitinib for children ≥2 years old with COVID-19 who are hospitalized and require supplemental oxygen or more invasive respiratory support (in combination with corticosteroids). The United States Food and Drug Administration granted full approval for use among adults with the same COVID-19 specifications. The European Medicines Agency has not approved baricitinib for treatment of COVID-19, but marketing authorization is under review. Both the United States Food and Drug Administration and European Medicines Agency approve baricitinib for adults for other conditions. The data to support these recommendations come from two multinational randomized controlled trials that showed improvement in mortality among adults hospitalized with moderate or severe COVID-19 *(35,36)*. One study showed no difference in mortality, but in this study corticosteroid use was low *(37)*. Although there are no published efficacy or safety data for children with COVID-19, an ongoing clinical trial with children is currently enrolling patients (Clinicaltrials.gov, NCT05074420). In addition, one study has released interim safety and pharmacokinetic data for use of baricitinib for children with atopic dermatitis (Clinicaltrials.gov, NCT05074420).

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