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VIEWPOINTS

Importance of Pediatric Inclusion in COVID-19 Therapeutic Trials

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Pediatric patients are excluded from most coronavirus disease 2019 (COVID-19) therapeutic trials. We outline a rationale for the inclusion of children in COVID-19 therapeutic trials, which enabled us to include children of all ages in a therapeutic COVID-19 trial at our institution.

Keywords. COVID-19; SARS-CoV-2; pediatrics; clinical trial; ethics.

Over 4.8 million people worldwide have been diagnosed with coronavirus disease 2019 (COVID-19), a disease caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), including over 1.5 million cases and over 90 000 attributable deaths in the United States [1]. Supportive care remains the mainstay of COVID-19 therapy, and the Infectious Diseases Society of America guidelines for COVID-19 treatment recommend use of antiviral and immunomodulatory medications suspected to have activity against COVID-19 only in the context of a clinical trial [2]. Unfortunately, children are not being given the opportunity to participate in most US-based COVID-19 clinical therapeutic trials. As of 6 May 2020, options to participate in antiviral clinical trials targeting SARS-CoV-2, aside from convalescent plasma trials, are limited to adolescents ages 12 or older (NCT04292730, NCT04292899, NCT04335552) with the exception of a hydroxychloroquine treatment study at our institution (NCT04369742) open to children of all ages. We advocate that pediatric patients should be given equal opportunities to enroll in COVID-19 therapeutic clinical trials and outline our rationale for inclusion of children in our hydroxychloroquine treatment trial.

Children are not simply small adults. They have inherent biological differences that evolve with age and can manifest as alterations in immunity, disease pathophysiology, drug metabolism, therapeutic effects, and drug-associated toxicities compared to adults. Infection with SARS-CoV-2 clearly demonstrates significant differences in clinical presentation and severity related to age [3]. Given these differences in COVID-19 manifestations, therapeutic data abstracted from adult treatment trials may not be reflective of the risks and benefits of therapeutic agents in children. Although most children infected with COVID-19 do not develop immediate severe illness, COVID-19 infection leading to hospitalization, intensive care admission, and death have been reported among children in the United States [4]. As a basic principle of justice, children significantly affected by COVID-19 should be given equal opportunities to receive potentially active therapeutic agents against COVID-19 in the safest manner possible: via structured clinical trials.

Well-designed therapeutic clinical trials incorporate routine, structured safety monitoring that maximizes the likelihood of detecting toxicities associated with therapeutic agents of unproven benefit beyond that offered in an off-label clinical context. Close monitoring for adverse events, integrating opportunities to monitor drug levels into the trial design if pediatric pharmacokinetics/pharmacodynamics of the investigational agent have not been established, and routine incorporation of criteria for halting the therapeutic agent in clinical trials make this the safest approach for use of an investigational or off-label therapeutic agent in children, particularly when the degree of direct benefit that the agent provides to the child in uncertain. For newly identified diseases, such as the COVID-19 pandemic, that immediately pose a direct threat to a large number of children worldwide, delays in initiation of pediatric clinical trials while awaiting adult data pose a potentially preventable safety issue for children and conflicts with the bioethical principle of beneficence. Not only do children and the medical community lose out on opportunities to gain the highest level of clinical evidence for efficacy in a vulnerable population, but due to the lack of availability of pediatric trials, many children hospitalized for COVID-19 are receiving off-label use of therapeutic

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agents with unproven benefit against COVID-19. Off-label prescribing is common practice among children hospitalized in the United States [5]; however, this approach presents safety risks by lacking the structured safety monitoring provided by clinical trials, does not further advance knowledge to provide benefit to future children with the same condition, and fails to encourage long-term follow-up to detect potential harms.

In addition to offering enhanced safety monitoring, enrollment of children in clinical trials ensures that parents and older children are fully informed of the potential risks and benefits associated with use of the therapeutic agent, a conversation often omitted when medications are prescribed off-label. This preserves the autonomy of the parent(s)/guardian(s) and older children capable of providing assent to make informed decisions on behalf of their child and themselves in a setting in which risks and potential benefits need to be closely weighed because therapeutic efficacy is not yet proven. As COVID-19 was only recognized in the last few months, adequately powered data using the gold standard of biomedical evidence for therapeutic efficacy, randomized, double-blind, placebo control trials, is lacking for all leading COVID-19 treatment candidates. Current evidence suggesting agents have a potential therapeutic benefit against COVID-19 mainly relies on case series, in vitro studies, and in vivo animal studies against SARS-CoV-2 or related coronaviruses. The extent of evidence for potential benefit of each of these agents needs to be taken into account when considering either off-label use or clinical trial use for pediatric patients to ensure the potential direct benefit to the child outweighs the commensurate risks associated with the potential therapeutic agent. Only agents with scientific evidence supporting potential direct benefit to the child's condition with low potential toxicities should be considered for pediatric use until additional efficacy data are available in adults.

As the therapeutic benefit of these agents in humans is unclear, enrollment of children in randomized, double-blind, placebo control trials remains ethical. If a therapeutic agent is proven to be efficacious for COVID-19 therapy in adults, it may no longer be ethical to enroll acutely infected pediatric patients in randomized, double-blind, placebo control trials as it would deprive children in a placebo arm from receiving a known efficacious therapy. Therefore, including children in COVID-19 therapeutic trials immediately during the pandemic period may provide the only ethical window of opportunity for obtaining the gold-standard level of efficacy data for COVID-19 therapeutics in children. Moreover, depriving children worldwide the opportunity to have therapeutic recommendations based on the same high-quality level data as adults would be an injustice to this vulnerable population. Pediatric COVID-19 therapeutics trials will require multicenter collaboration to achieve appropriately powered data, and existing clinical trial networks should be mobilized to facilitate this approach.

This approach of using only therapeutic agents with the maximum likelihood of providing direct benefit to pediatric trial participants, enhanced safety monitoring beyond that used in routine clinical care for off-label medication use, and obtaining both written assent from capable children and informed consent from parent(s)/guardian(s) is consistent with the special protections afforded to children involved in research studies by the US Department of Health and Human Services under 45 CFR part 46. We advocate that COVID-19 therapeutic clinical trials should open enrollment to pediatric patients during these early months of the COVID-19 pandemic according to the bioethical principles of autonomy, beneficence, and justice. Inclusion of children in these clinical trials is feasible under current regulations, provides direct benefit to pediatric trial participants from a safety perspective compared to off-label prescribing, and provides systematic collection of the highest quality of evidence for COVID-19 therapeutics in a vulnerable population where SARS-CoV-2 infection behaves differently from adults. Even if sufficient power cannot be obtained for children, stratified age-based analysis of pediatric cohorts embedded in large-scale clinical trials may at least provide preliminary data on whether a therapeutic response difference exists between children and adults to assist with the design of future therapeutic trials and a first look at whether adult data may be generalizable to the pediatric population. Excluding children from COVID-19 therapeutic trials based on age alone risks causing undue harm and perpetuates medical inequalities among a vulnerable population who deserve equal opportunities to receive investigational therapeutic agents in a safe, structured, systematic manner.

Notes

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