Pediatric RESEARCH

COMMENT

Ensuring continued progress for development of COVID-19 therapeutics in children

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Once it became evident that children can also develop severe illness associated with SARS-CoV-2 infection,[1,2] it was clear that the development of drugs to treat children with these infections would be needed. Building upon knowledge accrued from work in related coronaviruses, the identification and testing of potential therapeutics for COVID-19 has progressed rapidly in adults. The nonclinical and preliminary results from the Adaptive COVID-19 Treatment Trial (ACTT) provided sufficient evidence to support initiation of trials to evaluate the safety, pharmacokinetics, and activity of remdesivir in children with SARS-CoV-2 infections.[3] Other direct acting antivirals (DAAs) that could offer similar benefits such as galidesivir, favipirivir, molnupiravir (EIDD-2801) and SARS-CoV-2-neutralizing antibodies are advancing through preclinical and early clinical development.[4] In addition to the potential therapeutic benefits of DAAs, the contribution of immune pathophysiology associated with SARS-CoV-2 infection has raised the possibility that repurposing immune modulators directed at targets such as interleukin-6, janus kinase (JAK), signal transducer and activator of transcription, sphingosine-1-phosphate receptors, and tumor necrosis factor and using dexamethasone to reduce pulmonary inflammation could be used as adjunctive therapies to antivirals.[5] Aligning with this strategy, ACTT has seamlessly been modified to study the combination of remdesivir plus baricitinib (JAK inhibitor) in adults with serious COVID-19.[6] Clearly COVID-19 treatment is rapidly evolving. For pediatric development of investigational COVID-19 therapeutics to keep pace with progress in adults, it is important to focus on optimizing methods for obtaining data to evaluate the safety and efficacy of promising investigational agents.

First, it is important to consider how much adult efficacy data can be extrapolated to children (Fig. 1) based on the similarity of the condition and treatment response. Experience in optimal development of antiretrovirals leading to rapid availability of innovative drugs to treat children with human immunodeficiency virus can serve in guiding this approach.[7] For DAAs with activity against SARS-CoV-2, the mode of action and the response to treatment at a given drug exposure are anticipated to be similar across the age spectrum in most cases. Using this paradigm, the pediatric development program for remdesivir was started within weeks after the interim ACTT results were reported and was supported by safety data from adults and children treated by compassionate use and trials in which remdesivir was used to treat Ebola. Similarly, the Emergency Use Authorization issued for use of remdesivir to treat hospitalized COVID-19 patients included dosing recommendations for pediatric patients weighing greater than 3.5 kg based on estimations using physiologically based pharmacokinetic methods.[8] Although the remdesivir ACTT trial did not include children, adolescents (>12 years of age) are included in the two phase 3 trials conducted by Gilead. Because the disease and response to therapy were assumed to be similar between adults and children, a pediatric trial of approximately 52 pediatric patients (birth to <18 year of age) was designed to assess safety and PK with virologic and clinical outcomes as secondary endpoints.[9] A consideration for the timing of the start of pediatric trials was a risk/benefit assessment which included the consideration of the seriousness of the disease, the preliminary data in adults, and the cumulative safety profile of remdesivir. As new DAAs are developed, these same elements can be used for planning a pediatric development program. This planning will need to consider factors such as the characteristics of the drug, availability of prior efficacy, and safety data that may be available as the result of assessing these drugs in infants and children with non-SARS-CoV-2-related diseases, the timing of intervention in the course of the disease, and practical considerations such as drug formulation which may require substantial efforts to enable administration to infants and young children.

In contrast to DAAs where the activity against the virus is expected to be similar regardless of the host once similar concentrations are achieved, advancing host response modifiers as therapies for COVID-19 in children, either alone or in combination with DAAs, may need to proceed at a pace that depends on how rapidly our understanding of the inflammatory processes associated with infection progresses. Because many of the immune responses suspected to mediate SARS-CoV-2-associated inflammation involve pathways for which small- and large-molecule inhibitors have already been successfully used to treat chronic inflammatory diseases, the potential for using these drugs to treat patients with SARS-CoV-2 has been widely recognized. Many of these agents have been assessed, and in some instances approved for use in children with chronic inflammatory diseases. This experience provides important information regarding their safety and tolerability and could allow for assessing the potential benefit and risk of studying these therapies in SARS-CoV-2 children such that trials involving children could progress more rapidly than if this information was not available. As this experience is considered in making decisions to advance with trials involving children it will also be important to recognize that the role of these host defense modifiers in modifying the course of an acute respiratory infectious disease process in children or an inflammatory process that is likely the basis for multisystem inflammatory syndrome in children (MIS-C) are not well established. In addition, although there may be

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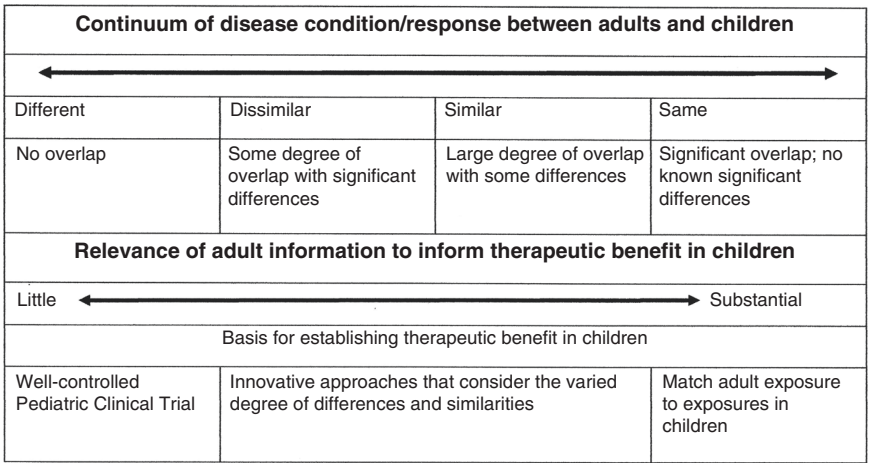

Fig. 1 Pediatric development of new therapies considers the continuum of disease condition/response between adults and children. Extrapolating the experience in adults to children varies depending on the similarity and differences in the condition and response to therapy for that condition. For direct antiviral agents, establishing therapeutic benefit may proceed in alignment with COVID-19 condition/response being similar or the same between adults and children. Establishing therapeutic benefit for other therapies, such as host defense modulators, will require considering the similarity and differences in condition/response between adults and children in planning for the work needed to establish therapeutic benefit for children.

significant experience in using these existing therapies for chronic immune-mediated diseases in children, there may be little or no experience in using them in patients who would be at the greatest risk from COVID-19 such as infants, those who are otherwise immunocompromised, and those with pre-existing complex medical conditions. As potential benefits are being recognized for these drugs in adults with SARS-CoV-2 infections, transition to studying them in children will need to consider the similarity of the early and late inflammatory responses in adults and children. Remarkable progress is being made in establishing the molecular basis for SARS-CoV-2 infection involving in vitro and animal model work.[10] If the characterization of the proinflammatory cytokine and chemokine responses caused by SARS-CoV-2 in adult patients can be extended to work involving children with acute infections and MIS-C, it can be expected that studies involving host response modifiers in children will progress rapidly thereafter.

Under circumstances where extrapolation of adult efficacy data to any pediatric population is appropriate, pediatric programs should be driven by consideration of what additional data are needed and the optimal trial designs to obtain the needed data. Juvenile animal toxicity studies that incorporate appropriate endpoints may also be needed to support enrollment of pediatric patients, typically those less than 12 years of age. Once drugs and biologic products advance into clinical trials, safety data in adults may be used to assess risk and potential benefit in the decision to begin trials in children. A sequential approach (i.e. studying older pediatric subpopulations before younger subpopulations) is not always needed and could slow completion of the pediatric development program. A sequential approach should only be considered if there is a need for specific information from the older subpopulation (e.g. safety information) or other practical issue (e.g. development of a formulation).[11] Absence of such justification, trials should include all relevant pediatric age groups similar to the approach used for the remdesivir pediatric trials which is enrolling children of all ages including full-term and prematurely born newborns. For dose selection, modeling and simulation methods can be adequate in estimating dosing for adolescents, and often for children older than 2 years of age, without the need for a dedicated, separate PK study prior to enrolling children in a trial assessing safety and efficacy. Other approaches to improve the efficiency of trials that involve children exclusively include Bayesian and adaptive designs which may allow for smaller trial sample sizes and use of master protocols, which would allow evaluation of multiple therapies or regimens, share a control arm and thus can substantially reduce the number of children needed to complete trials. Another important principle in advancing pediatric development is to engage pediatricians with experience in product development in the process of designing adult trials to ensure that information from these early trials related to pharmacokinetics and exposure–response relationships is available for use in transitioning rapidly from studies involving adults to those involving children.

Similar to adults, the development of these therapies in pediatric patients should be scientifically sound, should involve collection of data that is interpretable and can be used in making regulatory decisions. In this regard it is important to follow the direction provided in the FDA Guidance on Development of Drugs and Biologics for COVID-19 [https://www.fda.gov/regulatory-information/search-fda-guidance-documents/covid-19-developing-drugs-and-biological-products-treatment-or-prevention] which encourages that discussion of pediatric drug development occurs with regulatory authorities early in the course of clinical development and that "… Decisions on the timing of initiating pediatric studies depend on several factors, including but not limited to the amount of available clinical and/or nonclinical safety data." Although these positions are not unique to COVID-19 product development, the urgency of establishing new therapies in the face of a pandemic and the value of these practices in making pediatric drug development efficient make them especially important to consider. This same Guidance also underscores that "… if dosing recommendations for a drug are the same for adults and adolescent and there is sufficient prospect of benefit to justify the risks, then it may be appropriate to include adolescents in the initial phase 3 clinical trials." As already seen with the development of remdesivir, the inclusion of children as young as 12 years of age in initial phase 3 trials is possible. This approach, especially with additional antivirals and as the role of host response modifiers becomes better defined, could result in early approvals for these drugs in older children which, to date, may represent the largest group of pediatric patients that have developed severe SARS-CoV-2 infections.

In the recent past, it has not been unusual for ten years to pass between the time a drug is established as safe and effective in adults and when this safety and efficacy is established in children. Although challenges exist in rapidly advancing new

therapies to treat children with SARS-CoV-2 infections, these challenges can and must be addressed to meet the urgent need for safe and effective drugs to treat children with COVID-19 illnesses.

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ADDITIONAL INFORMATION

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REFERENCES

1. DeBiasi, R. L. et al. Severe COVID-19 in children and young adults in the Washington, DC metropolitan region. *J. Pediatr.* https://doi.org/10.1016/j.jpeds.2020.05.007 (2020).
2. Zachariah, P. et al. Epidemiology, clinical features, and disease severity in patients with coronavirus disease 2019 (COVID-19) in a Children's Hospital in New York City, New York. *JAMA Pediatr.* e202430. https://doi.org/10.1001/jamapediatrics.2020.2430 (2020).
3. Beigel, J. H. et al. Remdesivir for the treatment of Covid-19—preliminary report. *N. Engl. J. Med.* **383**, 992–994 (2020).
4. Li, G. & De Clercq, E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nat. Rev.* **19**, 149–150 (2020).
5. Zhong, J., Tamg, J., Ye, C. & Dong, L. The immunology of COVID-19: is immune modulation an option for treatment? *Lancet Rheumatol.* https://doi.org/10.1016/S2665-9913(20)30120-X (2020).
6. NIAID Office of Communications. RemNIH clinical trial testing antiviral remdesivir plus anti-inflammatory drug baricitinib for COVID-19 begins. https://www.nih.gov/news-events/news-releases/nih-clinical-trial-testing-antiviral-remdesivir-plus-anti-inflammatory-drug-baricitinib-covid-19-begins (2020).
7. Penazzato, M. et al. Optimizing research to speed up availability of pediatric antiretroviral drugs and formulations. *Clin. Infect. Dis.* **64**, 1597–603 (2017).
8. US Food and Drug Administration. Fact sheet for health care providers emergency use authorization (EUA of remdesivir (GS5734™). https://www.fda.gov/media/137566/download.
9. ClinicalTrials.gov. Study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of Remdesivir (GS-5734™) in participants from birth to <18 years of age with coronavirus disease 2019 (COVID-19). https://www.clinicaltrials.gov/ct2/show/NCT04431453.
10. Blanco-Melo, D. et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. *Cell* **181**, 1036–1045 (2020).
11. Ollivier, C., Mulugeta, Y., Ruggieri, L., Saint-Raymond, A. & Yao, L. Paediatric extrapolation: a necessary paradigm shift. *Br. J. Clin. Pharmacol.* **85**, 675–679 (2019).