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A Rapid Review of Potential Drug Treatments for Children with COVID-19

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Abstract— The paediatric population constitutes a much smaller proportion of COVID-19 patients and seems to be less severely affected. However, the massive numbers of COVID-19 infections mean that many children require treatment in hospital. In the concerted and wide-ranging effort to discover a safe and effective treatment for COVID-19, paediatric involvement is necessary. This review aims to identify leading potential drug treatments and vaccines for COVID-19 that are being investigated with children involved. Clinicaltrials.gov, WHO Trial Registry Platform (ICTRP) and RAPS COVID-19 vaccine tracker webportals were searched for clinical trials in phase 3 that involved children below 15 years of age. Any preliminary results released were searched online. The review found 25 phase 3 drug trials with paediatric participants and 2 vaccine trials. No preliminary findings were found. Remdesivir appears to be a leading candidate drug treatment and 2 vaccines candidates, inactivated nCoV-19 (Sinopharm) and ChAdOx1 (Oxford University), are recruiting children in large phase 3 trials. No treatments are currently licensed for COVID-19 but results from numerous trials are eagerly awaited.

Keywords— COVID-19, child, paediatric, clinical trials, drugs, vaccines.

I. INTRODUCTION

The current Coronavirus disease pandemic caused by the SARs-CoV-2 virus or COVID-19 has now afflicted over 20 million people and has caused over 750,000 deaths globally [1]. UNICEF data states that “children are not the face of this pandemic” [2]. Epidemiological studies on COVID-19 have shown that children constitute a much smaller proportion of the total number of COVID-19 positive patients, compared to their proportion in the general population; with 2.4% of cases in China and 1.7% of cases in the US reported in children <18 years of age [3][4]. Nevertheless, UNICEF warns that children are at risk of being severely affected by the extreme socio-economic impacts of COVID-19 as well as disruptions to the supply of food and vaccines to children living in vulnerable and deprived situations [2]. Considering the massive number of COVID-19 cases, the seemingly small percentage of paediatric patients still comprise a staggering absolute number of patients requiring medical care.

COVID-19 in children shares some similar features to that of adults but also has many unique characteristics. Like in adults, children typically present with cough, fever and fatigue while many positive cases are also asymptomatic [5].

Children seem to present with more gastrointestinal symptoms such as vomiting and diarrhoea compared to adults [6]. Importantly, children seem to be less likely to progress to become severely ill with needing respiratory support or intensive care compared to adults [5]. Between 2% [4] and 6% [7] of children admitted to hospital are seen to have severe COVID-19 infection compared to at least 19% of hospitalised adults [8]. However within the paediatric age ranges, infants are reported to be more vulnerable to severe disease and death [5][7].

The significantly lesser severity of COVID-19 in children is interesting and mirrors that seen in the first SARs epidemic. A major factor is the much higher numbers of adults with underlying chronic health conditions such as cardiovascular disease and diabetes mellitus. However a pathophysiological mechanism has been suggested relating to variable expression of angiotensin-2 converting enzyme (ACE2) receptors [9]. The ACE2 receptor is the cellular receptor for SARs-CoV-2 virus. It decreases with age and lowest expression is seen in elderly people with hypertension and diabetes. SARs-CoV-2 virions compete with angiotensin-2 at the ACE2 receptor binding sites. Angiotensin-2 is a strong pro-inflammatory mediator and is thought to contribute to the hyper-inflammatory state in the

lungs leading to acute respiratory distress which is the hallmark of severe COVID-19. Higher levels of ACE2 in children is suggested to be beneficial as even when angiotensin-2 is elevated in the presence of SARS-CoV-2, the remaining ACE2 that are still viable catalyses angiotensin-2 into angiotensin-1-7 that counteract the inflammatory actions of angiotensin-2 [10].

An emerging complication of COVID-19 in the paediatric population is multisystem inflammatory syndrome in children or MIS-C. This is a syndrome similar to Kawasaki disease or toxic shock syndrome. Several case series have documented children that presented with persistent fevers, rashes and abdominal complaints [11][12][13]. Clinical features included cardiac involvement, effusions, severe inflammation and shock. A number of children became critically ill and between 2-4% died. Many of the children had negative polymerase chain reaction (PCR) swabs but had positive antibody tests suggesting previous COVID-19 infection or had close contacts who were COVID-19 positive. Since MIS-C appears to develop after COVID-19 infection, it is thought that disordered cellular or humoral immune responses are involved [14].

The unique clinical features of COVID-19 in children re-emphasises that children are not small adults [15], thus the clinical management of paediatric COVID-19 patients need to be tailor-made to them by the specialist teams (where available). This includes drug treatment given to paediatric patients; where any new drug for COVID-19 that has indications for use in children, need to have also been proven to be safe and effective through trials that involve paediatric patients[16]. Currently, guidelines for supportive care for children with COVID-19 are similar to adults. Routine measures include respiratory support when necessary, fluid and electrolyte support and empirical antibiotics when bacterial co-infection is suspected.

Therapeutic options for COVID-19 are actively being investigated currently. At present only 1 agent, the broad spectrum antiviral Remdesivir, has been granted an Emergency Use Authorization (EUA) by the U.S. Food and Drug Administration (FDA)[17]. The EUA does not include authorisation for paediatric use. Although no other drugs have been licensed to be used as treatment for COVID-19, a host of drugs are currently undergoing clinical trials as treatment for COVID-19. This rapid review explores potential drug treatments for COVID-19 specifically for children. The main aim is to identify and describe the drug treatments currently being investigated that has the most potential to be effective in treating children.

II. METHOD

An online literature review of clinical trials of drug treatments for COVID-19 involving children was conducted. The method is based on a previous systematic review of paediatric randomised clinical trials of drugs [18], adjusted and simplified to allow for the rapidly developing situation. Briefly, an advanced search was performed on the webportal clinicaltrials.gov [19]. This portal is a database of publicly and privately funded clinical trials conducted globally. It also includes the COVID-19 studies listed on the World Health Organization's International Clinical Trials Registry Platform (WHO ICTRP).

The search was limited to interventional studies that included children using existing age limits under the Eligibility Criteria filter provided by the portal. A further limit to phase 3 studies onwards were applied to identify treatments closest to potential authorisation for paediatric use. Studies examining drug, biological, dietary, traditional or complementary treatments were included. Studies that have not started recruitment were excluded. The search was conducted up until 15 August 2020.

Eligible studies were compiled and tabulated. Information were collected on age ranges of the study participants, severity of COVID-19 infection, study design, the drug being investigated, comparisons made, outcome measures, and particularly any preliminary results reported. Studies that did not recruit below the age of 15 were excluded. When a study has been identified as being at an advanced stage such as having completed recruitment, further information regarding the study is searched online primarily via Google but with focus on pre-print servers such as medRxiv [20]. This is done to collect any results that may have been provided by the study investigators prior to the full study report being published. Vaccine trials are collected from a website tracking COVID-19 vaccine development provided by Regulatory Affairs Professionals Society (RAPS) [21].

III. RESULTS

Clinicaltrials.gov has a dedicated section for clinical studies related to COVID-19 that lists 3009 studies at the time of writing. Meanwhile, the WHO Trial Registry Network (WHO ICTRP) has 2115 clinical studies on COVID-19. When the search limits were applied to both registries, the results yielded 36 and 315 potential clinical trials. The studies were then examined further, leaving 28 trials from clinicaltrials.gov and 9 from ICTRP that were included in this review.

A. *Drugs for children with COVID-19 in phase 3 trials*

A total of 25 drugs are currently being investigated as treatment of COVID-19 in trials that involve children. As expected, the majority are antiviral drugs comprising 11 drugs including a novel antiviral agent, DAS181 or Fludase. Remdesivir is the drug with the most ongoing trials with 5. The combination of Lopinavir and Ritonavir (tradename Kaletra) had the second most trials with 3.

Drugs belonging to the P (antiparasitic) category of the WHO ATC-DDD [22] index were the next most commonly studied treatments for COVID-19 in children. In particular the antimalarial chloroquine/hydroxychloroquine are currently being trialled in 5 clinical trials involving children with COVID-19. Another antimalarial being investigated is primaquine. There are 3 antibiotics currently in clinical trials for COVID-19 that recruit paediatric patients, namely azithromycin, doxycycline and clindamycin. The remaining drugs include 3 corticosteroids and 2 monoclonal antibodies as well as several other drugs. These drugs are shown in Table 1.

B. *Biologics and Vaccines for children with COVID-19*

There are 4 trials involving children investigating convalescent plasma for use in treating COVID-19. Convalescent plasma is an antibody-rich blood product

obtained from patients who have recovered from COVID-19 infection.

The RAPS COVID-19 vaccine tracker currently lists 42 active vaccine clinical studies. Of these, 7 are in phase 3 clinical trials and 2 of the candidate vaccine trials are recruiting paediatric patients. These are the inactivated novel coronavirus vaccine developed in China by the China National Pharmaceutical Group (Sinopharm) and ChAdOx1 vaccine developed by the University of Oxford.

C. Traditional/Complementary Medicine (TCM) and others

Seven (7) clinical trials involving children are investigating TCM products to treat COVID-19. Among these, products from the honeysuckle plant is being tested in 3 trials in China while another trial in Egypt is testing honey to treat COVID-19 patients including children. Other agents being investigated in phase 3 clinical trials involving children include cholecalciferol and the polio vaccine.

D. Preliminary trial findings

There appears to be no preliminary results relating to COVID-19 treatments in paediatric subjects that has been released by any investigators.

TABLE I
COVID-19 DRUGS BEING INVESTIGATED IN CLINICAL TRIALS INVOLVING CHILDREN

Drug	Category	No. of trials
Remdesivir	broad spectrum antiviral	5
Lopinavir/Ritonavir	protease inhibitor antiviral	3
Sofosbuvir	antiviral	3
Ribavirin	antiviral	2
Daclatasvir	antiviral	2
Darunavir	antiviral	1
Cobicistat	antiviral	1
DAS181	novel antiviral	1
Faviripavir	antiviral	1
Ledipasvir	antiviral	1
Chloro/hydroxychloroquine	antimalarial	5
Nitazoxanide	broad spectrum antiviral/antiparasitic	3
Ivermectin	antiparasitic	3
Niclosamide	antiparasitic	1
Ruxolitinib	JAK inhibitor – anti-inflammatory	2
Primaquine	antimalarial	1
Methylprednisolone	corticosteroid	2
Dexamethasone	corticosteroid	2
Ciclesonide	glucocorticoid steroid	1
Interferon	immunomodulator/antiviral	1
Canakinumab	human monoclonal antibody – interleukin blocker	1
Tocilizumab	monoclonal antibody – interleukin blocker	2
Doxycycline	antibiotic	1
Azithromycin	antibiotic	2
Clindamycin	antibiotic	1
Losartan	angiotensin receptor blocker	1

IV. DISCUSSION

The sheer scale and the staggering speed of the COVID-19 pandemic is reflected in the desperate search for an effective treatment. It is unprecedented that so many different drug categories are being investigated. Yet it remains that no treatment has been approved by regulatory agencies except for the EUA given to Remdesivir [17] and a recently announced approval for the Sputnik V vaccine by the Russian government; this has been viewed with general skepticism [23].

The several thousand ongoing clinical trials of treatments for COVID-19 registered in clinicaltrials.gov and WHO ICTRP overwhelmingly recruit adult subjects to be studied. It is heartening that this review has discovered that paediatric patients are also involved in many of the clinical studies. The range of drug treatments investigated in which children are recruited appear to mirror those studied in adult COVID-19 patients. Of note the large trials, either government sponsored such as the RECOVERY trial [24] or privately sponsored such as the CARAVAN trial [25], are actively recruiting children to increase paediatric data regarding potential treatments.

Remdesivir is an antiviral drug that interferes with viral RNA-dependent RNA polymerase. Preliminary results released in May 2020 showed that it reduced recovery times in hospitalised adults and subjects had a non-statistically significant lower mortality rate compared to those on placebo [26]. It is probably at present the most promising drug treatment for hospitalised patients and this review has also found that it is the drug with the most ongoing clinical trials involving children. In the US, remdesivir is available to paediatricians to be prescribed under compassionate use. Recent data released on a cohort of children with severe COVID-19 infection treated with remdesivir showed promising results, with over 80% recovering with the drug [27].

Several other antivirals are being investigated in trials involving children including the combination of Lopinavir and Ritonavir. Recently the WHO announced that this treatment arm has been discontinued due to lack of efficacy [28]. It is expected that many of these antiviral drugs will be excluded as potential treatments in the future when more trial results come to light.

Another treatment arm discontinued by WHO is the antimalarial hydroxychloroquine [28]. Although the underlying scientific basis was tenuous, both chloroquine and hydroxychloroquine were frontrunners as candidate COVID-19 treatments. After evidence accumulated that they were ineffective to treat COVID-19 in adult patients and also had serious risks of cardiac complications, both drugs are now largely excluded as treatments for COVID-19 [29]. This review has found 5 clinical trials of chloroquine/hydroxychloroquine involving children that are still active. Considering the speed of developments, it would be reasonable to expect that these trials would be updated soon.

Malaysia appears to be facing a second wave of the pandemic. As of 2nd October 2020, a total of 11,484 patients have been tested positive for COVID-19 with an increasing trend seen in the daily positive rate [33]. The Ministry of Health (MOH) previously reported that approximately 4% of

COVID-19 positive patients were children; none of the cases required intensive care or died, thus mirroring the trend in children seen worldwide [34]. Tragically MOH reported the death of a 1-year-old infant due to COVID-19 on October 5th. [35]

However with the escalating situation, MOH has released official clinical guidelines for confirmed COVID-19 patients with specific guidance for paediatric patients [36]. In brief, the screening and diagnosis for children is the same as with adults, the standard being respiratory samples of nasopharynx (NP) or oro-pharynx for RT-PCR. In intubated cases, the preferred sample is from the lower respiratory tract such as tracheal aspirate. For severe cases with acute respiratory distress syndrome (ARDS) or shock, the guidelines recommend monitoring disease progression with virology testing and markers. Additionally paediatric patients should be monitored for cytokine release syndrome (CRS).

The guidelines state that there is no specific therapy that has been established to be effective, however since the disease seems to run a mild course in children, supportive care alone is suggested for all cases including severe ones. Detailed recommendations given for supportive care in children include drugs such as antibiotics and steroids. Further the guidelines mentioned the use of the candidate drugs specifically Remdesivir (although not available locally), Lopinavir/Ritonavir and Tocilizumab as part of clinical trials and when the doctors have justified benefit to be above the risk of toxicity [36].

Ultimately, the resolution of this pandemic would require a widely available and effective vaccine. More than 165 candidate vaccines are being studied and 8 are in phase 3 trials [30]. This review searched an alternative vaccine tracking portal [21] to look for trials that recruited paediatric subjects and found that 2 trials in phase 3 that involved children as participants. Both are possibly at the forefront of vaccine development for COVID-19 [31]. The ChAdOx1 nCoV-19 vaccine [32] being trialled by the University of Oxford is currently enrolling over 10,000 adults and children starting from 5 years of age. This review has also noted that Sinopharm is recruiting subjects including children from 6 years old for their candidate vaccine in the United Arab Emirates since they are unable to get sufficient numbers of subjects in China [21]. Again it is encouraging that the leading clinical vaccine trials are recruiting children to obtain paediatric data for candidate vaccines. The paediatric data is in fact a regulatory requirement and the effort by the investigators to obtain such data in large phase 3 trials is a further promising sign that a viable and effective COVID-19 vaccine can be licensed soon.

This review has not discovered any preliminary results on any COVID-19 trials that involve children. At present some preliminary stage 3 trial results in adults are available only for remdesivir [26]. The situation is rapidly evolving with the numerous drugs and vaccines in various stages of clinical trials. A major weakness of this rapid review is that it is clearly unable to cover fully all the clinical trials that include children as subjects, considering the very large volume and rapid turnover of study information submitted to trial registries. However, by focusing on clinical studies at the most advanced stages, the review is able to identify

emerging potential treatments for COVID-19. As the situation develops further with more information on clinical outcomes of patients, the leading treatments may yet change.

V. CONCLUSION

There are currently no drug treatments or vaccines that have been licensed to treat COVID-19, however there are large clinical trials at advanced phases that involve children as subjects to obtain paediatric data. Remdesivir appears to be a leading therapeutic candidate for COVID-19 while 2 leading vaccines, inactivated nCoV-19 and ChAdOx1, are recruiting children in large phase 3 trials. Results including paediatric efficacy and safety data are eagerly awaited.

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