Treatment of children with COVID-19

Çocuklarda COVID-19 Tedavisi

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ABSTRACT

Currently, there is not any specific effective treatment for COVID-19. There are many studies published and ongoing especially on adult patients. Treatment options in pediatric patients are determined according to the agents used in adult patients. Although coronavirus disease 2019 (COVID-19) is mild in nearly all children, a small proportion of pediatric patients develop severe or critical illness. Supportive therapy forms the basis of the treatment as the symptoms and disease course in children are mild. There are currently no randomized controlled trials of drugs that can be used to treat COVID-19 in children. However, in severe clinical cases, the drugs used in adults are evaluated and used on a case-by-case basis. There is a growing need for well-designed controlled clinical trials to better define the safety and efficacy of potential treatments for COVID-19 in children.

Key Words: Children, COVID-19, Treatment

ÖZ

COVID-19 için halen spesifik etkili bir tedavi yoktur. Özellikle yetişkin hastalarda yayınlanmış ve devam etmekte olan birçok çalışma bulunmaktadır. Pediatrik hastalarda tedavi seçenekleri yetişkin hastalarda kullanılan ajanlara göre belirlenmektedir. Coronavirüs hastalığı 2019 (COVID-19) neredeyse çoğu çocukta hafif olarak geçirilmesine rağmen, hastaların küçük bir kısmında ciddi veya kritik hastalık gelişebilmektedir. Çocuklarda semptomlar ve hastalık seyri hafif olduğundan destekleyici tedavi tedavinin temelini oluşturur. Çocuklarda COVID-19'u tedavi etmek için kullanılabilecek, randomize kontrollü çalışması olan herhangi bir ilaç bulunmamaktadır. Bununla birlikte, kliniği ağır olan vakalarda, yetişkinlerde kullanılan ilaçlar vaka bazında değerlendirilirmekte ve kullanılabilmektedir. Çocuklarda COVID-19 için potansiyel tedavilerin güvenliğini ve etkinliğini daha iyi tanımlamak için iyi tasarlanmış kontrollü klinik çalışmalara artan bir ihtiyaç vardır.

Anahtar Kelimeler: COVID-19, Çocuk, Tedavi

INTRODUCTION

Currently, there is not any specific effective treatment for COVID-19. There are many studies published and ongoing especially on adult patients. Treatment options in pediatric patients are determined according to the agents used in adult patients. The majority of children with COVID-19 have a relatively mild and self-limited disease, and critical illness and mortality are rare. Therefore, isolation and supportive treatment of the patient have an important place. Other drugs in use for children with COVID-19 are also described in the following sections for severe cases.

1. Isolation of patients

Isolation of confirmed or suspected cases with asymptomatic and mild disease (these children have no respiratory difficulty, are feeding well, have SpO2 > 92%) at home or outpatient settings

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is recommended. Danger signs should be explained. House should be frequently ventilated. The patient should be asked to wear a simple surgical mask and asked to pay attention to cough hygiene. Hand hygiene should be provided in contact with the patient or their immediate environment. For patients isolated in the home, isolation is terminated after negativity is observed in 2 PCR samples taken at 24-hour intervals. Where testing is not possible, isolation is recommended for additional 14 days after symptoms resolved. For additional information for home care in COVID-19, please look at the website at reference (1).

2. Symptomatic and supportive care

There are minimal data about concerning using non-steroidal anti-inflammatory drugs (NSAIDs) in COVID-19 patients (2). Acetaminophen is preferred for antipyretic agent. Respiratory support, including supplemental oxygen and ventilatory support (noninvasive or invasive) should provide. Fluid and electrolyte balance should be regulated. Empiric antibiotics can use as indicated for community-acquired or health care-associated pneumonia; continuation of empiric antibiotics should be determined by cultures and other microbial tests and clinical condition. Bacterial coinfections appear to be infrequent in COVID-19 patients (3). Inhaled medications should be administered by metered dose inhaler, whenever possible, rather than through a nebulizer, to avoid the risk of aerosolization of SARS-CoV-2 through nebulization (4).

3. Antiviral agents

a. Hydroxychloroquine/chloroquine

Chloroquine (CQ) and Hydroxychloroquine (HCQ) are aminoquinoline drugs used in the treatment and protection of malaria for more than 50 years and used in the treatment of inflammatory diseases including SLE and rheumatoid arthritis. Both drugs have a weak diprotic base feature and increase the pH in the endosomes, thereby suppressing the entry of the virus into the cell (5, 6). Hydroxychloroquine is an analogue of chloroquine and has fewer side effects than chlorocine (7). Many clinical trials investigating the safety and efficacy of chloroquine and hydroxychloroquine in COVID-19 pneumonia have been launched simultaneously in more than 10 hospitals in different states of China, including Wuhan. Considering the data that more than one hundred patients were examined, it was seen that the chloroquine phosphate group was better in relieving pneumonia exacerbation from the control group, improving radiological findings, cleaning the virus and shortening the disease duration. No chloroquine phosphate-related side effects have been reported in these patients. Following this, Chinese State officials agreed on the potent effect of chloroquine phosphate on COVID 19 pneumonia at the conference held on February 15, 2020, where decision-makers and regulators and executives of clinical studies took place, and entered the guideline recommendations of the Chinese Public Health Agency (8).

Both chloroquine and hydroxychloroquine have been reported to inhibit SARS-CoV-2 in vitro, although hydroxychloroquine appears to have more potent antiviral activity (9) . Randomized trials for their clinical use are going on now. The trial reportedly found no difference in 28-day mortality among 1542 patients who were randomly assigned to receive hydroxychloroquine compared with 3132 patients who received standard care (25.7 versus 23.5 percent, HR 1.11, 95% CI 0.98-1.26); there were also no differences in length of hospital stay (10). Most observational studies have also not suggested a benefit with hydroxychloroquine or chloroquine In an observational study from United States (US) concluded that hydroxychloroquine had no effect on clinical course of adult patients with COVID-19 (11). In an another observational comparative study from France, 84 patients who were given hydroxychloroquine were compared with 89 patients who were not and no differences were detected on survival without acute respiratory distress syndrome at day 21, survival on 21 days (12). Finally United States Food and Drug Administration has revoked the emergency use authorization (EUA) to use hydroxychloroquine and chloroquine to treat COVID-19 in certain hospitalized patients when a clinical trial is unavailable or participation is not feasible on June,15 (13).

Hydroxychloroquine may be an alternative to remdesivir for children if remdesivir is unavailable (14). Given the lack of proven benefit, potential risks, and the revocation of the emergency use authorization, it should only be used in the context of a clinical trial. Hydroxychloroquine should be avoided in children with underlying QTc abnormalities and those who require other medications with potential for serious drug interactions with hydroxychloroquine (15).

In Turkey, hydroxychloroquine has recommended both adults and children in the treatment of COVID-19. In adult patients hydroxychloroquine has recommended for outpatient and inpatient with or without pneumonia. In children, it is recommended for COVID-19 with pneumoniae with or without azithromycin. For details, look at website of Turkish Ministry of Health for COVID-19 (16).

b. Lopinavir-ritonavir

Lopinavir (LPV) is an effective drug that inhibits the protease activity of the coronavirus. Proteinase is a key enzyme for the polyprotein synthesis of CoV. Lopinavir (LPV) is an anti-retrovirus proteinase inhibitor used since 2000 in the second-generation treatment of HIV-1 infection. In SARS-CoV and MERS-CoV diseases, LPV has been studied in vivo and in vitro and has been shown to inhibit replication. It has been shown to be effective against viral 3-chymotrypsin-like protease (3CLpro) in SARS-CoV-1. Ritonavir (RTV) increases the serum concentration of LPV by inhibiting the metabolism of LPV via the CYP3A pathway. The antiviral effect of the LPV / r combination is similar to the effect of LPV alone. LPV / R, by competing with HIV protease, causes dysregulation in the structural and functional

proteins of the virus, causing formation of immature and non-infectious virus particles and inhibition in HIV replication (17-19).

Qiu H et al. (20) evaluated 36 children (mean 8.3 years, SS 3.5 years), they gave inhaled interferons to all cases 2 times a day. In 14 cases (39%), 12 (medium-weight pneumonia, 2 were mild clinical) gave the drug LPV/R. While 19 (53%) of the patients in the study had pulmonary CT findings, others were reported to have mild clinical signs of the disease. In this study, no comparison was made between patients who were given LPV/R and those who were not. Because LPV/R treatment group mostly consists of patients with pneumonia. It was emphasized that the pediatric patients were mild or moderate, and the number of cases was low. All of the patients were recovered and discharged (20). Ye XT et al. (21) gave LPV/R treatment in 42 patients in which 47 COVID positive patients were taken. They gave inhaled interferon and arbidol tablets to remaining 5 patients. The age distribution of the patients was 5-68 years old, 9 patients were under the age of 30 and 38 patients were over the age of 30. In the patient groups they compared, the duration of the body temperature to return to normal values, WBC, lymphocyte and CRP values were found to be significantly shorter than the control group. It was observed that nCoV-RNA became negative earlier in the group treated with LPV/R. In addition, ALT and AST values were higher in the group treated with LPV/R. As the restrictive aspects of the study, the number of patients in the control group was reported to be low (21). The efficacy and safety assessment of the use of oral LPV/R (400 mg/100 mg, twice a day) of Cao et al. (22) (LOTUS China trial) in SARS-CoV-2 infection. They randomly gave LPV / r to 199 adult COVID-19 patients with severe clinics. They applied LPV/R to 99 patients and standard care to 100 patients, and LPV/R treatment did not cause a statistically significant clinical improvement compared to the control group (HR 1.24, 95% CI, 0.90-1.72), did not decrease mortality on day 28 (19.2 % 25.0%, 95% CI, -17.3-5.7) and no reduction in viral RNA detection in the throat. Viral RNA was still detected in 40.7% of the treated group at the end of treatment. Nausea, vomiting and diarrhea were more common in the group receiving LPV/R, and similar disorders were observed in the laboratory parameters between the two groups. However, the absence of a blind study, it was stated in the limitation section of the article that it was possible to be affected by the clinical condition of the patient when deciding the treatment group and whether it was observed whether steroid use was observed in patients (22). Although there are no efficacy and safety studies for the use of LPV/R in the treatment of COVID-19, it is still in the research phase. LPV/R is recommended in China 2020 COVID guide. It is recommended as an alternative drug in case of clinical worsening in children and pregnant patients (16).

It is available in the name of Kaletra © and is sold as a 200 mg / 50 mg film-coated tablet. Each tablet contains 200 mg liponavir and 50 mg ritonavir. In adult COVID-19 pregnant women, 1 tablet 2 times a day is recommended for 10-14 days, whereas 16 mg/kg/dose lopinavir dose is calculated twice a day in children between 14 days and 6 months. Between 6 months and 18 years: 15-25 kg: 200 mg 2 times a day (2x1 tablets), 26-35 kg: 300 mg 2 times a day (2x1.5 tablets),> 35 kg: 400 mg 2 times a day (2x2 tablet) oral administration has been recommended (16).

Although the drug is generally well tolerated, there may be interaction with chloroquine and hydroxychloroquine used in the treatment of COVID (http://www.covid19-druginteractions.org/) (23).

c. Favipiravir

Favipiravir is a pro-drug of ribofuranosil-5p-triphosphate (24). Its active form inhibits RNA polymerase, stopping viral replication. Most of the pre-clinical data of favipiravir was obtained from its antiviral effect against influenza and Ebola; However, the agent also shows wide activity against other RNA viruses (25).

Limited clinical experience supporting FPV use has been reported for COVID-19. In a study in which treatment was compared with lopinavir / ritonavir (LPV/R) and FPV, FPV was independently associated with faster viral clearance and a higher recovery rate in lung imaging (26). However, in another prospective, randomized, multicenter study comparing FPV and umifenovir (arbidol), clinical recovery was higher in the FPV group on the 7th day in patients with moderate COVID-19 infection (27). It has been stated in the current guideline of the Ministry of Health of the Republic of Turkey that favipiravir can be used in adult patients with severe pneumonia and / or potential / definitive COVID-19 worsening under treatment (16).

Favipiravir has a weight-dependent complex, nonlinear, time- and dose-dependent pharmacokinetics (28, 29). Since favipiravir is both metabolized and inhibited by aldehyde oxidase, initial oral loading is required to achieve adequate blood levels (24). In the current treatment guidelines, a 5-day treatment regimen is recommended in the form of 2x600 mg maintenance following the loading dose of 2x1600 mg in adult patients (16).

The plasma half-life is 4 hours. People with liver dysfunction should be monitored for blood concentration and dose adjusted. Favipiravir or its metabolites have been detected in semen and breast milk. Antibacterial agents such as piperacillin, penicillin, tazobactam, and pyrazinamide have been reported to interact with various medications, particularly antidiabetic and antihypertensives (30).

The most common side effects are diarrhea, increased serum uric acid levels, increased serum transaminases (ALT, AST, ALP) and total bilirubin levels and decreased neutrophil levels. Digestive system side effects (nausea, increased gas) and psychiatric symptoms can also be seen. It is not recommended for use in pregnancy due to its teratogenic nature. Transition

to breast milk has been reported. It is mainly excreted through the kidneys, but no dosage adjustment is recommended by the manufacturer. If a dose reduction is to be made, the loading dose is administered in the same way, but the maintenance dose can be reduced (31).

Data on the use of FVP in children is very limited in the literature and is mainly based on Ebola virus infection treatment (32). The complete maturation profiles of enzymes (mainly aldehyde oxidase) included in the metabolic pathway of favipiravir at 12 months make the drug a good candidate for treatment in children over 1 year old (33). In a study examining the use of high doses of FVP in children with Ebola virus infection, it was shown that FVP was generally tolerated and that it was not necessary to discontinue the drug due to side effects (34). It is true that extensive clinical trials are needed to routinely recommend the use of FVP in children in COVID-19 infection.

d. Remdesivir

Remdesivir is intracellularly metabolized from a prodrug of a nucleotide analogue to an analogue of adenosine triphosphate which inhibits viral RNA polymerases. Remdesivir has shown prophylactic and therapeutic efficacy in nonclinical models of these coronaviruses which has broad-spectrum activity against members of several virus families, including filoviruses (e.g., Ebola) and coronaviruses (e.g., SARS-CoV and Middle East respiratory syndrome coronavirus [MERS-CoV] (35-39). Remdesivir has activity against SARS-CoV-2 shown with in vitro testing . It was stated that remdesivir has a favorable clinical safety profile, with reports on the basis of experience in approximately 500 persons, including healthy volunteers and patients treated for acute Ebola virus infection (39-41). There is a recent study evaluating patients hospitalized for severe COVID-19 who were treated with compassionate-use remdesivir, in which clinical improvement was observed in 36 of 53 patients (68%) (41). A multinational, randomized, placebo-controlled trial of remdesivir (given for up to 10 days or until death or discharge) included 1059 patients with confirmed COVID-19 and evidence of lung involvement; 89 percent had severe disease and 26 percent were receiving invasive mechanical ventilation or ECMO at baseline (42). According to a preliminary report, remdesivir resulted in a faster time to recovery, defined as discharge from the hospital or continued hospitalization without need for supplemental oxygen or ongoing medical care (median 11 versus 15 days with placebo; rate ratio for recovery 1.32, 95% CI 1.12-1.55). In contrast, in a double-blind randomized trial in China of 237 patients with severe COVID-19 (hypoxia and radiographically confirmed pneumonia), time to clinical improvement was not statistically different with remdesivir compared with placebo for 10 days (median 21 versus 23 days; HR for improvement 1.23 [95% CI 0.87-1.75]) (43).

Also there is a planned phase II/III clinical trial of remdesivir to treat paediatric patients hospitalised with Covid-19 to assess the safety, tolerability, pharmacokinetics and efficacy of remdesivir in around 50 paediatric patients suffering from moderate-to-severe Covid-19, including newborns and adolescents, at more than 30 sites across the US and Europe.

But still measurement of efficacy requires further randomized, placebo-controlled trials of remdesivir therapy.

4. Convalescent Plasma

Convalescent plasma and hyperimmune immunoglobulin may reduce mortality in patients with respiratory virus diseases, and are currently being investigated in trials as a potential therapy for COVID-19.

In an open-label trial from China, 103 patients with life-threatening or severe (on invasive COVID-19 were randomly assigned to receive standard treatment with or without convalescent plasma (44). Although convalescent plasma improved the rate of nasopharyngeal viral RNA clearance at 72 hours compared with standard treatment alone (87 versus 38 percent), there were no statistically significant differences in the overall rates of clinical improvement or mortality by 28 days. Among the subset of patients who had severe but not life-threatening disease, the rate of clinical improvement was greater with convalescent plasma (91 versus 68 percent)

In Cochrane study, eight studies was included(seven case-series, one prospectively planned, single-arm intervention study) with 32 participants, and identified a further 48 ongoing studies evaluating convalescent plasma (47 studies) or hyperimmune immunoglobulin (one study), of which 22 are randomised. It was stated that there is uncertainity whether convalescent plasma is effective for people admitted to hospital with COVID-19 as studies reported results inconsistently, making it difficult to compare results and to draw conclusions (45).

5. Tocilizumab

Tocilizumab is an IL-6 receptor inhibitor used for rheumatic diseases and cytokine release syndrome and is being evaluated in randomized trials for treatment of COVID-19. Elevated interleukin 6, C–reactive protein (CRP), and ferritin, have been shown to be higher in patients with severe COVID–19 and predictors of mortality (46,47). In one study, in critically ill COVID–19 patients who required mechanical ventilation or vasopressor support compared to those with milder disease, the level of interleukin 6 was noted to be 10 times higher and interleukin 6 level correlated with the detection of COVID-19 RNAaemia (48). These findings suggest that anti–cytokine targeted therapies might be of benefit for patients with severe COVID–19. In a study, tocilizumab cohort had a higher rate of improvement in oxygen–support category for both subsets of patients who required invasive and non–invasive oxygen support. Among intubated patients, tocilizumab cohort had 5 days shorter median time to clinical improvement and

the median duration of vasopressor support and invasive mechanical ventilation were both 3 days shorter in tocilizumab cohort compared to no tocilizumab cohort. Overall, median length of stay in hospital was 4 days longer in tocilizumab cohort but it was stated that importantly higher proportion of these patients required admission to intensive care unit (49).

It was also noted that previous studies suggested that SARS–CoV–2 can cause over–activation of immune system and clinicians need to be vigilant against cytokine release syndromes (50). Measurement of inflammatory biomarkers may guide clinicians to select appropriate patients for immunosuppressive therapy .

In a preliminary report evaluating tocilizumab for treatment of severe COVID-19 patients, tocilizumab administration did not reduce ICU admission or mortality rate in a cohort of 21 patients (51). These studies show that additional data are needed to understand the effect(s) of tocilizumab in treating patients diagnosed with COVID-19.

Sarilumab and siltuximab are other agents that target the IL-6 pathway and are also being evaluated in clinical trials.

CONCLUSION

There is a growing need for well-designed controlled clinical trials to better define the safety and efficacy of potential treatments for COVID-19 in children.

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