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REVIEW ARTICLE

Pharmacotherapy in SARS CoV 2 Infection in Children – A Review

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ABSTRACT

The pharmacotherapy in SARS CoV has been a challenge with respect to pediatric SARS CoV 2 infection. The guidelines evolve each day, however there are limited number of studies and trials in children regarding the drugs available, their dosage and their safety profiles. This review article details the drugs that have been tried against SARS CoV 2 infection from a pediatric perspective. The drugs have been classified into 3 main groups: (i) Drugs with antiviral activity like remedesvir, ivermectin and ribavirin that directly act on the virus affecting viral entry, assembly and replication.(ii) Drugs that are immunomodulators like anakinra and interferons which act upon the immune system to modulate the immune response to the virus (iii) Drugs that mitigate the complications like immunoglobulins, glucocorticoids and anticoagulants like aspirin which act at the cytokine release and in treatment of complications like Pediatric Multisystem Inflammatory Syndrome. Pediatric weight loused dosage and safety profiles have been established in other conditions and are being explored in SARS CoV2 infection in these drugs and many drugs are still to establish pediatric doses. (iv) Drugs that have been tried earlier were hydroxychloroquine, lopinavir/ritonavir and azithromycin but have not shown any therapeutic benefit over the course of the pandemic. With the SARS CoV 2 global pandemic causing varied clinical pictures and outcomes in children, that differ from adults, knowledge of the drugs that can be used in children, their safety profile and their dosage is imperative and will guide the way in the future management of pediatric SARS CoV 2 infection.

Key Words: *Drug therapy, Pediatric COVID infection, Remedesvir, Tocilizumab, IVIG, PIMS and MISC*

INTRODUCTION

The SARS-CoV-2 disease has become a global pandemic in 2020 and the disease is still in its evolution with newer disease spectrums emerging. This disease has shown to affect the adult population with a milder disease spectrum in children according to majority of the literature available so far. However, recent studies from around the world have shown the emergence of a rare Kawasaki like syndrome that affects children 1-6 weeks after the infection. The mortality and morbidity of the disease is more among the vulnerable population i.e. elderly. Hence more and more research has been focussed in finding treatment options that cater to anyone of the three situations; (i) treatment of SARS-CoV-2 by acting upon the virus, (ii) treatment to reduce/mitigate

the complications of SARS-CoV-2 and (iii) prophylactic treatment options. A lot of literature is available online with evidence from adult studies, very few studies are however available on children. Among the available literature in pediatrics, most of the literature is only the clinical presentations and prevalence and hardly any literature is available about the treatment options in children. This article is an attempts to consolidate available literature regarding drug therapy in pediatric SARS-CoV-2 infection.

BACKGROUND

The structure of the SARS-CoV-2 virus and the mechanisms utilized by the virus during its replication is central to the options of drug treatment by identifying potential areas where various drug classes can act.

The SARS-CoV-2 virus is a spherical shaped RNA virus with a diameter of approximately 125 nm[1], having club-shaped spike like projections emanating from its surface. This appearance is like the radiation of the sun or solar corona, hence giving the virus its name. It contains four main structural proteins

I. Spike (S) protein– This makes up the spike-like projections on the surface of the virus and facilitates viral attachment to the host receptor. Mutational changes have been noted in the spike protein. The N501Y mutation alters the most important part of spike making it easier for the virus to enter. Another mutation, H69/V70 deletion, has been reported in which a small part of the spike is removed.

II. Membrane (M) protein – This protein is most abundant on the surface of the virus, gives the virus its spherical shape and facilitates binding to the nucleocapsid. Along with the E [envelope] protein, it helps in forming the viral envelope.

III. Envelope (E) protein– This protein is found inside the virion in smaller amounts. The main function is in viral reproduction and in the pathogenic potential of the virus.

IV. Nucleocapsid (N) protein– This protein is on the nucleocapsid and helps in viral replication.

Pathogenesis[2,3]: (Flowchart 1)

Multisystem Inflammatory Syndrome in Children (MIS-C)/ Pediatric Multisystem Inflammatory Syndrome (PMIS)

MIS-C is a rare complication of COVID-19 that can range from a mild illness to a severe disease which rapidly progresses to hemodynamic compromise, even leading to death. A multi-disciplinary approach including various pediatric specialities is necessary for an individual patient guided treatment. Pharmacotherapy in MIS-C includes multiple drugs including steroids, immunoglobulins, biologicals and anti-coagulants. The American College of Rheumatology has given guidelines for the treatment of MIS-C.[4]

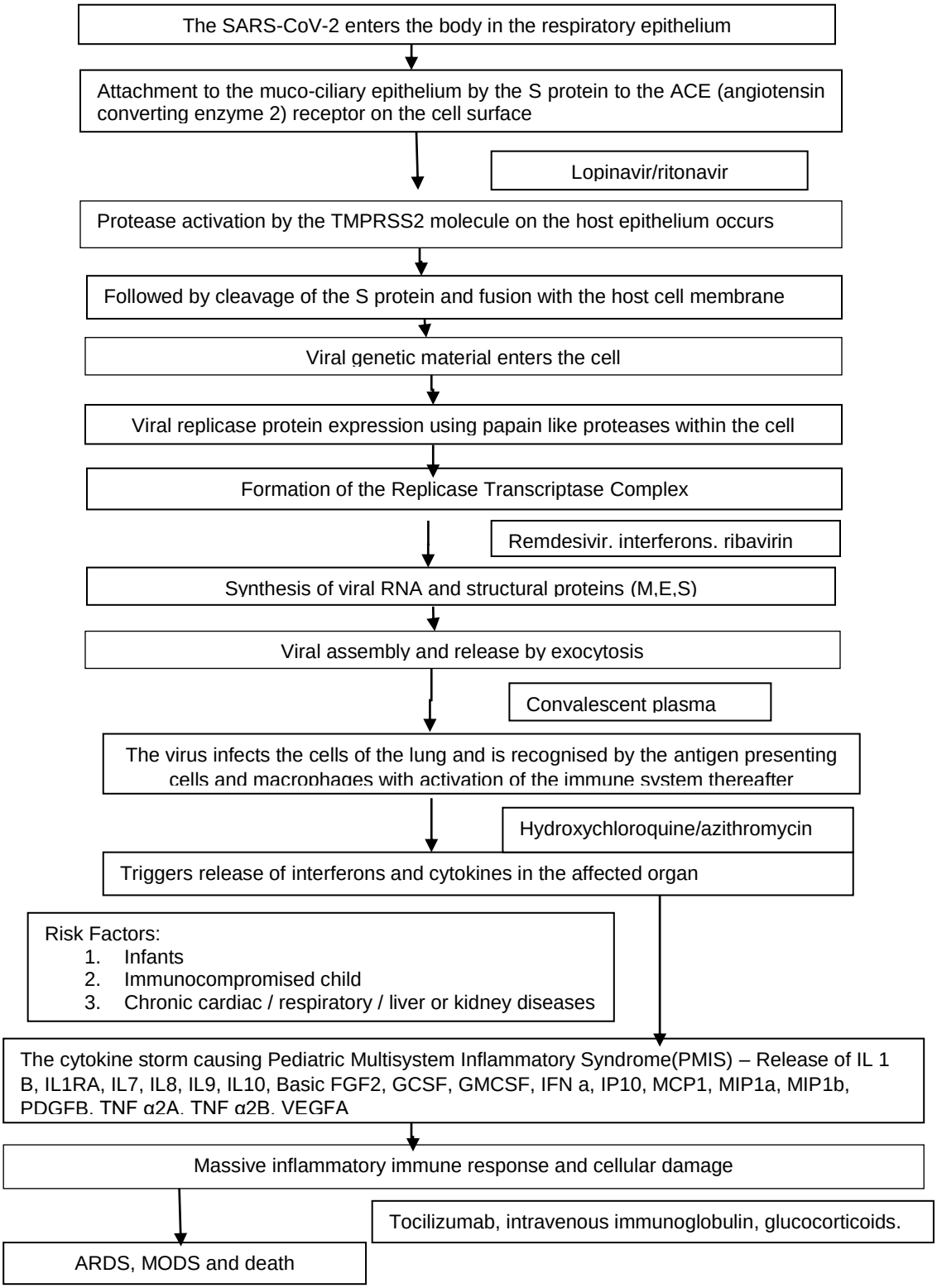
Pharmacotherapy

The list of drugs (table 1) that have been found to have any role in the treatment of corona virus or mitigating its complications have been discussed giving the pediatric perspective. Previously, many drugs were used for the treatment of COVID-19 infection, which are not recommended now. The drugs that are currently being used and recommended by pediatric regulatory bodies around the world have been elaborated in detail.

TABLE 1: Drug used in SARS CoV2 infection

Sr. No	Drug Name
1.	Remdesivir
2.	Toclizumab
3.	Intravenous Immunoglobulin (IVIG)
4.	Glucocorticoids
5.	Anticoagulants
6.	Interferons
7.	Anakinra
8.	Ribavirin
9.	Ivermectin
10.	Azithromycin
11.	Hydroxychloroquine&Chloroquine
12.	Lopinavir& Ritonavir
13.	Favipiravir
14.	Levamisole + inhaled Formoterol/Budesonide

Flowchart 1: Pathogenesis of SARS CoV 2 infection



REMDESIVIR

Remdesivir is a nucleotide prodrug belonging to antiviral group of drugs acting on the RNA dependent RNA polymerase. It is currently the only approved antiviral drug against SARS-CoV2 which is found to be strongly efficacious against hospitalized children with moderate-severe/critical disease. Antiviral therapy is not indicated for routine administration in pediatric COVID 19.

Mechanism of action*:* Remdesivir is an adenosine nucleotide prodrug. Here the adenosine triphosphate analogue of remdesivir (remdesivir triphosphate) competes with SARS-CoV-2 for incorporation into RNA chains by RNA dependent RNA polymerase. SARS-CoV-2 is delayed during RNA replication as a result of this competitive inhibition. [16]

Route of administration: IV infusion (25-100ml 0.9% NaCl) over 30-120 minutes and not to be co-administered with any other drugs/fluids except normal saline. [17]

Dosage: Efficacy and dosage has not been fully established, yet it is an FDA approved drug for children >12 years and with FDA emergency use authorisation (EUA) for <12 years with moderate to severe/critical COVID 19 disease who are critically ill and hospitalized; it is recommended to be given for 5 days but can be extended up to 10 days in pediatric patients requiring mechanical ventilation or extracorporeal membrane oxygenation (table 2).[17]

TABLE 2: Pediatric dose of remdesivir

Weight	Formulation	Loading dose	Followed by
≥ 3.5kg to <40kg	Lyophilized powder; IV	5mg/kg/dose on day 1	2.5mg/kg/dose daily once
≥ 40kg	Lyophilized powder; IV	200mg on day 1 (Max 200mg)	100mg daily once (Max 100mg)

Safety profile: Increased hepatic transaminases and infusion related reactions. Therefore it requires daily assessment of renal function and liver function.

Evidence so far: Remdesivir has so far been used in MERS infection. Sheahan et al reported in vivo evidence of superiority of a combination of remdesivir and interferon beta over lopinavir/ritonavir. Prophylactic remdesivir curtails the replication of MERS-CoV along with curbing acute lung injury features while the therapeutic remdesivir improves the functions of lung in combination with lopinavir/ritonavir and interferon beta.[18]

In SARS-CoV-2 infection: Martinez in his review article considered remdesivir in treatment of SARS-CoV-2 due to its inhibition properties on SARS-CoV replication in in-vitro cultures.[18] Various trials are ongoing regarding the usage of remdesivir in treatment of pediatric SARS-CoV-2[19,20] including Fleming method trial[15] whose results are awaited. Chiotos et al in their multicentric guidance study in 2020 for use of antivirals in children recommend antiviral and preferred remdesivir and recommended that it should to be used only in severe cases.

Used in: Emergency authorisation of usage of remdesivir in SARS-CoV-2 by FDA in children < 12 years or 3.5kg to 40kg and FDA approved for use in children > 12 years under special circumstances in the adult dose.[21]

TOCILIZUMAB (TCZ)

Tocilizumab is a biologic drug for targeted therapies that is an IL 6 receptor antagonist.

Mechanism of action: Tocilizumab is a humanised, monoclonal antibody directed against Interleukin-6 receptor (IL-6R). IL 6 is an important inflammatory cytokine implicated in the pathogenesis of cytokine storm in PMIS, its level and correlation with the disease severity and prognosis is well documented. Tocilizumab binds to the IL-6R and inhibits the IL-6–mediated signalling as well as blocks gp130 signal transduction, accentuating clinical recovery. It is widely believed that binding of TCZ with the receptors inhibits the receptor-mediated uptake and clearance of IL 6 from circulation causing the

transient increase in IL 6 levels after treatment.

Route of administration: Intravenously or subcutaneously and currently is used in pediatric Systemic onset Juvenile Idiopathic Arthritis (SoJIA) aged 1 year and above; administered every 2 weeks[32] and in Polyarticular Juvenile Idiopathic Arthritis (PJIA) aged 2 years and above; every 4 weeks[33,34]

Dosage: Infants, Children, and Adolescents: IV: In MIS-C, weight based dosage should be employed (body weight <30 kg, 12 mg/kg IV; body weight ≥30 kg, 8 mg/kg IV, maximum 800 mg). If no effect after 1st dose, can repeat one more dose after 8 to 12 hours. Tocilizumab is given as an intravenous infusion in normal saline over 1 hour.[35]

Adverse reactions are anemia, gastrointestinal perforation, hepatitis and infusion reaction.

Evidence so Far: Luo et al retrospectively analysed data involving 15 adult SARS-CoV-2 positive patients receiving tocilizumab in Wuhan, China. Among the 15 subjects included in the study, eight (53.3%) were given TCZ with concomitant steroids (methylprednisolone) and five (33.3%) subjects required repeat doses of TCZ. This study also noted the transient rise in serum IL 6 levels among 10/15(66.7%) after starting TCZ. 4 patients did not respond to TCZ and showed persistent, elevated levels of IL 6, thereby implicating the role of IL 6 in pathogenesis and deterioration in SARS-CoV-2.[36]

Xu et al retrospectively analysed 20 critically ill SARS-CoV-2 cases and noted that TCZ therapy brought symptomatic improvement in 15/20 (75%) with radiological resolution in 19/20 (90.5%). All 20 patients showed remarkable recovery and were discharged within 16 days of TCZ administration. Therefore tocilizumab was found to improve the clinical outcome and reduce mortality in severely affected SARS-CoV-2 patients.[37]

Shekerdemian et al studied 48 SARS-CoV-2 positive children and found that 25% were male, 68% were severe and critically ill children, 38% required invasive ventilation and one required ECMO. 11 children had more than two organ failures. TCZ was used in 5 children; as monotherapy in one child and in combination with other drugs in the other 4 children. But the dose used and outcome of the children who received TCZ has not been clearly mentioned in this study.[38]

An 8-year-old boy from South India presenting with hyper-inflammatory syndrome and Kawasaki like disease following SARS-CoV-2 infection was successfully treated with IVIG and tocilizumab, discharged 2 weeks post illness with no adverse reactions.[24]

SUMMARY

Tocilizumab binds to the IL 6 receptor and mitigates the cytokine storm of SARS-CoV-2 infection in critically ill population. Pediatric doage is available as it has been used in pediatric rheumatological conditions. Compared to standard care, tocilizumab may be effective in reducing mortality and ICU admission in patients with severe COVID19 pneumonia and signs of hyperinflammation; however, patients treated with tocilizumab may be at higher risk for bacterial and fungal infections.

INTRAVENOUS IMMUNOGLOBULIN (IVIG)

Intravenous immunoglobulin (IVIG) is a blood product that contains pooled polyclonal Immunoglobulin G from healthy donors.

Mechanism of action: IVIG is a complex product with several bioactive molecules and its pleiotropic mechanism of action is not entirely understood. It has been proposed that the IgG-Fc fragment interacts with Fc fragment located on various inflammatory cells and blocks them bringing about various functional changes such as expansion of regulatory T helper cell, modulation of antigen presentation, immune cell maturation and differentiation as well as neutralisation of the inflammatory cytokines.[22] The multiorgan dysfunction in SARS-CoV-2 described as PMIS in the earlier flowchart is temporally associated with SARS-CoV-2.Treatment with IVIG in PMIS reduces the effects of this cytokine storm thus reducing the multiorgan damage and hastening recovery.

Dosage: High dose IVIG (2 gram/kg/day) (Maximum dose 100grams) based on body weight for severe, hospitalized patients with MIS-C is recommended as the first line treatment. Single

dose (2 g/kg) is given for patients with good cardiac function and adequate fluid status. In patients with cardiac dysfunction, 2 divided doses as 1 g/kg over 2 days is recommended along with diuretics and close monitoring. A second dose of IVIG is not recommended in patients with refractory disease due to risk of volume overload and hemolysis.[4]

The evidence so far: IVIG has an immunomodulatory function and used in autoimmune diseases, inflammatory conditions and for treatment and prophylaxis of severe infections.

In SARS-CoV-2 infection: A case series published by Cao et al reported the successful treatment and recovery in 3 adult patients with high dose IVIG in early stages of clinical deterioration.[23] Balasubramaniam et al described an 8 year old child in early stages of hyperinflammatory syndrome due to SARS-CoV-2 who showed good clinical response with IVIG and other immunomodulators.[24] Another case series published described 6 children from London presenting with hyperinflammatory syndrome requiring IVIG during the SARS-CoV-2 pandemic. There also emerging reports of Kawasaki-like illness among children and is usually seen after a month after the peak of the pandemic. All these children showed drastic improvement after IVIG and other immunomodulators. All these suggest that in pediatric SARS-CoV-2 infection which is milder and may be followed by a delayed hyperinflammatory syndrome or Kawasaki-like illness IVIG along with other immunomodulators show good response.

SUMMARY

IVIG is now the recommended first line therapy with/without glucocorticoids in patients diagnosed with MIS-C.[4]

GLUCOCORTICOIDS

Dexamethasone is the first line corticosteroid in COVID-19 disease presently reducing morbidity and oxygen requirement by one-third and mortality by one-fifth and is recommended by WHO as the standard corticosteroid of choice in MIS-C and COVID 19 disease based on UK RECOVERY trial. Methylprednisolone, prednisone, prednisolone, hydrocortisone and triamcinolone are some of the more potent synthetic steroids that are also commonly used.

Mechanism of action: Cortisol is the naturally produced glucocorticoid that has anti-inflammatory and immunomodulatory function. The rationale supporting the use of corticosteroids in SARS-CoV-2 infection is to reduce the lung injury associated inflammation as well as to prevent the cytokine storm and the hyper-inflammatory state that usually results in clinical deterioration. There is paucity of published data to support the same, especially among children.

Dosage: Dexamethasone administered intravenously at a dose of 0.15 mg/kg once daily (Max: 6 mg) is the preferred corticosteroid. Duration - 10 days. Low-moderate dose glucocorticoids - Methylprednisolone (1-2 mg/kg/day) is recommended as adjunctive therapy along with IVIG for MIS-C patients with shock or organ-threatening disease. Low-moderate dose therapy can also be given to patients with mild disease, persistent fever and symptoms despite IVIG therapy. High-dose pulse therapy (10-30 mg/kg/day), as part of intensification therapy, is to be considered for patients with poor response to IVIG and low-moderate dose glucocorticoid therapy, especially in severely ill patients requiring high dose multiple inotrope/vasopressor support.[4]

The evidence so far: Glucocorticoids have been extensively used for inflammatory and autoimmune disorders like allergy, asthma, septic shock, etc.[25]

In SARS-CoV-2 infection: Veronese et al have analysed 4 studies and concluded there is insufficient evidence to encourage the routine use of glucocorticoids in moderate and severe SARS-CoV-2 cases and said that mortality in severe disease can be reduced by methylprednisolone but definitive conclusive evidence is lacking.[26] Similarly Ling et al has reported statistically significant increased viral loads as well as delayed clearance due to the immunosuppressive effect of steroids along with high rates of complications such as hyperglycemia, diabetes etc and discourage its widespread use.[27,28] Evidence from WHO states that, lymphocytopenia and increased proinflammatory responses can be caused by the hypothalamic pituitary axis (HPA)

stimulation following glucocorticoid therapy and can worsen the clinical condition.[29]

On the contrary, Belhadjer et al reported 35 pediatric cases with MIS-C/PMIS and ventricular failure who were treated with IVIG. 1/3rd of these children required concurrent steroids but all showed good clinical recovery.[30] Wu et al had reported that the use of methylprednisolone in 1/3rd of patients with ARDS showed reduced risk of mortality, hence justifying the rational use of steroids in a clinical scenario where the benefits outweigh the risks.[31]

SUMMARY

Thus, as recommended by the American College of Rheumatology, glucocorticoids are to be used along with IVIG as adjunctive therapy in patients with severe MIS-C or as intensification therapy in refractory disease.[4]

ANTICOAGULANTS

Anticoagulation and antiplatelets by using oral or parenteral drug therapy has been evaluated in critically ill SARS-CoV-2 infection.

Mechanism of action: SARS-CoV-2 causes an inflammatory cytokine storm and a variant of secondary hemophagocytic lymphohistiocytosis (HLH) in predisposed individuals. This triggered inflammatory cytokine storm and secondary HLH is characterised by microvascular injury, elevated D-dimers and a prothrombotic state thereby predisposing them to various complications such as deep vein thrombosis, ischemia, pulmonary thromboembolism and stroke. Tang et al have reported that 75.1% of the nonsurvivors and 0.6% of survivors had evidence of disseminated intravascular coagulation (DIC). Reports of Kawasaki-like illness occurring among pediatric cohorts requiring the use of high dose aspirin also support the need of anticoagulants.[39] As per the recommendations of The Children's Hospital of The King's Daughters, prophylactic doses of low molecular weight heparin such as enoxaparin need to be strongly considered in all pediatric patients unless contraindicated. In such cases, at least mechanical prophylaxis and early ambulation should be tried if feasible.[40].

Recommendation

Current recommendations in children with COVID 19 is to assess the risk of thromboembolism and based on that (2 or more risk factors) to start pharmacological prophylaxis using low-molecular-weight heparin/unfractionated hepatic (LMWH/UFH) over other agents owing to extensive studies are available on heparin agents in pediatric population and therapeutic anticoagulation is recommended for suspected/proven venous thromboembolism (VTE). Exclusive randomised control trial on use of thromboprophylaxis in children with COVID 19 (COVAC-TP trial) is underway.

American College of Rheumatology Recommendation: Anticoagulation with preferably enoxaparin along with low-dose aspirin should be routinely started in children with MIS-C presenting with features of Kawasaki like illness or with coronary artery changes, it is not recommended with other presentations.

Low-dose aspirin should be started in patients with MIS-C and Kawasaki disease like illness with coronary artery changes, especially those with thrombocytosis (platelet count >4,50,000) until platelet count normalizes and normal coronary arteries are documented by echocardiography 4 weeks after diagnosis. Other anti-coagulants like enoxaparin or warfarin are warranted if there is evidence of coronary artery size abnormalities on echocardiography (z-score >10).

Patients with poor ejection fraction (EF<35%) and thrombosis are to be treated with enoxaparin until 2 weeks after discharge. In patients with moderate to severe left ventricular dysfunction, prolonged therapy with enoxaparin is recommended.[4]

Dosage: LMWH include enoxaparin, reviparin, nadroparin, adreparin and dalteparin.

Enoxaparin is the widely used LMWH in children it is given via subcutaneous route twice daily Therapeutic dose: 1 mg/kg/dose SC BID (max 40 mg/dose)

Prophylactic dose: 0.5 mg/kg/dose SC BID (max: 40 mg/dose) (each 1 mg is 100 IU) (Anti Xa goal 0.5-1 U/ml drawn 4 hours after 3rd or 4th dose)

High-dose aspirin 80-100 mg/kg/day q6h (max1000mg q6h or 4 g/day) and change to low-dose once afebrile for 48 hours has also been recommended in few studies. Low-dose Aspirin (3-5 mg/kg/day, maximum 81 mg/day)

INTERFERONS (IFN)

Interferons (IFNs) are soluble glycoproteins that play a role in innate and adaptive immunity and classified based on the signalling process of the receptors as Type I IFN, Type II IFN and Type III IFN.[12]

Mechanism of action: After viral infection, there is activation of Interferon gene resulting in the stimulation and synthesis of interferons. This results in the blocking of the viral RNA synthesis and replication by sending signals to uninfected cells. The signals of apoptosis induction are sent to the infected cells along with immune system activation which promote clearance of the virus and accentuate recovery.[3]

Route of administration: Interferon-Beta-2b by nebulization

Dosage: Interferon beta-2b is widely available and used as subcutaneous injection. For use as nebulisation, it is reconstituted with 2ml Water for injection (WFI) according to Chinese CDC guidelines and is stable at room temperature for 1 hour and administered using jet nebuliser.

Nebulisation doses[13]

Mild cases = 100,000–200,000 IU/kg BID for 5–7 days

Severe cases = 200,000–400,000 IU/kg BID

Safety profile: Flu like symptoms

Evidence so far: Interferons have been used in adults for treating chronic hepatitis C infection, leukemias, large hemangiomas, multiple sclerosis, etc. Interferon alfa-2 has been used in the treatment of chronic hepatitis B (In children ≥1 year with compensated liver disease)

In SARS-CoV-2 infection: Nile et al discussed the role of recombinant interferons in SARS-CoV-2 due to its inhibitory activity on protein synthesis and viral replication.[3] Similarly, Sallard et al proposed early treatment with interferon and stated that SARS-CoV-2 may show increased sensitivity to interferon as compared to other coronaviruses.[14] Of all the interferons, the interferon β subtype appears to be the most suited for SARS-CoV-2 treatment and detailed studies are warranted. Usage of IFN α-2b is under clinical trial by Fleming [15]with a recommended dose of 5million units/nebulization BID.

SUMMARY

Interferons have been in use in the treatment of chronic viral infections and malignancies. Dosage in pediatrics has been advocated for chronic hepatitis B infection. In SARS-CoV-2 infection the recommendation is for nebulized interferon alpha 2b, however no such nebulisation formulations are available. They have to be reconstituted with solvent to be used for nebulisation. Adult studies (Chinese and European) are available iterating the safety and efficacy of nebulised Interferon. However studies are needed to identify the efficacy in children with SARS-CoV-2 infection.

ANAKINRA

Anakinra is a non-glycosylated, recombinant, interleukin-1 receptor antagonist belonging to disease-modifying anti-rheumatic drugs.

Mechanism of action: Anakinra acts as an interleukin 1 receptor antagonist, mitigating the effects of the cytokine storm.[41]

Route of administration: Sub cutaneous injection

Dosage: Dose in SARS-CoV-2 infection in pediatric population is not yet validated. Cavalli et al in their retrospective study advocated high dose anakinra 5 mg/Kg IV BID and showed clinical recovery in 72% of adult patients.[42]

Safety profile: Injection site reactions, headache, thrombocytopenia.

Evidence so far: Anakinra has been used so far in pediatric rheumatological conditions like secondary paediatric hemophagocytosis lymphohistiocytosis, systemic onset juvenile rheumatoid arthritis and in neonatal onset multisystem inflammatory disease.

In SARS-CoV-2: The immune response to SARS-CoV-2 infection via the cytokine storm indicates the role of immune modulators in patients with severe infection in reducing the mortality and mitigating the pulmonary inflammation. Anakinra being an immunomodulator serves a role in the cytokine storm. Balasubramanian et al in their special article report the role of anakinra in adult patients suffering from hyper-inflammation and have reported lesser adverse reactions with its

use.[43]

SUMMARY

Anakinra has been used in pediatric rheumatological conditions and has an established pediatric dosage. Its role in SARS-CoV-2 needs exploring and specific pediatric guidelines are to be formulated through detailed clinical trials.

RIBAVIRIN

Ribavirin, a guanosine analogue acts by interfering with the replication process of RNA and DNA viruses.

Mechanism of Action: Ribavarin interferes with RNA capping and helps in destabilization of viral RNA by inhibiting inosine monophosphate dehydrogenase which inhibits natural guanosine production.[5] The viral replication process is slowed down and random mutations are introduced reducing the viral viability in presence of ribavarin.[6] It boosts the anti-viral Th1 arm of the immune system. Ribavirin's multimodal mechanism of action helps in reducing viral load, tissue damage and transmission rate.

Dosage[7]

Age - >3 years (USA) and >6 years(China)

Dose-10mg/kg/dose BID-TID (Max 500mg)

Precautions – When creatinine clearance is <50 mL/min, it is not recommended and is discontinued when serum creatinine is > 2 mg/dL.

Safety profile: Hemolytic anemia is the most concerning side effect. Leukopenia, rash, gout, fatigue and pruritis are the other side effects.

Route of administration: Intravenously, orally and by aerosolization.

The evidence so far: Ribavarin is used for severe respiratory syncytial virus (RSV) bronchiolitis in infants and in chronic hepatitis C infection. The role of ribavirin in SARSCoV epidemics and MERSCoV outbreaks has been researched.[8] The use of high-dose ribavirin versus low dose along with corticosteroids has been studied at various centres against SARS-CoV-2003 with good outcomes but had very high rate of adverse effects and as it was used in combination with steroids, hence the precise therapeutic effects of ribavirin is not proven.[9,10]

Ribavarin, in combination with interferon-β was used in the treatment of MERS. The good safety profile of the combination of lopinavir/ritonavir, ribavirin and IFNα2a along with its efficacy against SARS-CoV 2003 and MERS has been the most encouraging evidence that this may be effective against the SARS-CoV-2.

In SARS-CoV-2 infection: Hung et al worked on this triple combination therapy in adults with SARS-CoV-2 and reported that the group treated with triple combination of Interferon 1b, lopinavir/ritonavir and ribavirin showed significant reduction in viral shedding and hospital stay in mild to moderate disease.[11]

SUMMARY

Ribavirin is an antiviral guanosine analogue and is used in the pediatric RSV infection. With respect to SARS-CoV-2 infection, so far no specific treatment guidelines have been identified and pediatric trials are pending. However, in adults it has been used as a combination with lopinavir/ritonavir and interferon α2a.

IVERMECTIN

Ivermectin is a FDA approved broad spectrum anti-parasitic activity drug with extended antiviral spectrum making it an exciting therapeutic option in SARS-CoV2. Being a repurposed drug, the dosage, adverse effects are better known in comparison to the newer antivirals, making it a therapeutic option that is available in children.

Mechanism of action: Ivermectin mediated inhibition of importin α/β1 mediated transport of viral proteins to and from the nucleus is speculated as a possible mechanism of action. Importins, are a type of karyopherins, exemplify a major class of soluble transport receptors which play a crucial role in nucleo-cytoplasmic transit of various substrates This proposed mechanism is yet to be validated.[44]

Route of administration: Oral

Dosage*:* Multiple clinical trials have been using Ivermectin at a dose of 0.2mg to 1.2mg/kg body weight, for a duration of 3–7 days. However, there is insufficient evidence of the safety of ivermectin at higher doses and in children less than 15 kg.[44]

Safety profile: Fever, pruritus, arthralgia.

Evidence so far: Ivermectin has shown its potent in vitro antiviral effects against several RNA viruses, such as Zika virus, Influenza A virus, Newcastle disease virus, Chikungunya virus, Yellow fever virus, Dengue virus, Japanese encephalitis virus and DNA virus such as BK polyomavirus and Equine herpesvirus type 1.[45]

In SARS-CoV-2: Taiub et al conducted a randomized control trial of 116 patients with mild to moderate disease comparing ivermectin-doxycycline treatment with hydroxychloroquine-azithromycin treatment. They found that ivermectin-doxycline treatment showed better symptomatic relief, lesser duration to recovery, better patient compliance and low adverse reactions. They concluded that ivermectin-doxycycline was the better choice of treatment.[46] In another retrospective study done by Raiter et al on 280 patients with SARS-CoV-2, lower mortality was seen in those treated with ivermectin, even in patients with severe respiratory disease, although no significant difference was seen in rates of extubation.[47]

- Hydroxychloroquine & Chloroquine
- Azithromycin
- Lopinavir and Ritonavir
- Favipiravir
- Levamisole + Inhaled Formoterol/Budesonide

These drugs were initially used in the treatment of SARS-COV-2 patients. However, they are currently not recommended and hence were not elaborated in this article.

SUMMARY

Multiple ongoing trials exist currently in the European Union, India and US whose results are awaited. Current trials show promising results with good viral load reduction and symptom relief at the above-mentioned dose.[44]

CONCLUSIONS

The SARS-CoV-2 pandemic has thrown open a huge challenge when managing the pediatric population. The risks and the poor availability of safety profiles in children become a roadblock in the pharmacotherapy that can be used in children. In this review we have attempted to study most of the available literature in the drug therapy in SARS-CoV-2 infection and during the literature search we found significant paucity of studies in pediatric SARS-CoV-2 infection.

Drugs like hydroxycholoquine, lopinavir/ritonavir, favipiravir, levamisole and azithromycin have not found to be useful in pediatric SARS CoV2 and are not recommended anymore in the pharmacotherapy of SARS-CoV-2 infection.

To summarise:

1. *In the antiviral group of drugs:* Remdesivir is the preferred antiviral in neonatal and paediatric population hospitalized with moderate/critical illness. Nebulized interferon-alpha, anakinra, ribavirin have found limited use in case management but need pediatric guidelines in SARS-CoV-2 infection
2. *In the drugs that reduce disease severity:* Adequate literature is available with proven efficacy and pediatric dosage in the management of critically ill pediatric SARS-CoV-2 infection with glucocorticoids and intravenous immunoglobulins. Both these drugs have been used in the management of the MIS-C and Kawasaki like presentation of the SARS-CoV-2 infection and have shown benefit. IL 6 blockers like tocilizumab has been efficacious in managing the complications like cytokine storm and this has been reported to be beneficial even in children. Anticoagulation with aspirin has been useful in the management of complications like PIMS/MISC and Kawasaki like illness.

Evidence based practice in SARS-CoV-2 infection is evolving each day and attempts to understand the disease, its complications and to titrate management accordingly, remain a challenge in children.

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