Intravenous Immunoglobulin

Last Updated: July 21, 2023

Recommendations

• The COVID-19 Treatment Guidelines Panel (the Panel) recommends against the use of intravenous immunoglobulin (IVIG) for the treatment of acute COVID-19 in adults and children, except in a clinical trial (AIII). This recommendation should not preclude the use of IVIG when it is otherwise indicated for the treatment of underlying conditions or complications that arise during the course of COVID-19.

• For the Panel’s recommendations on the use of IVIG in children with multisystem inflammatory syndrome in children (MIS-C), see Therapeutic Management of Hospitalized Children With MIS-C, Plus a Discussion on MIS-A.

Rationale

It is unknown whether IVIG products derived from pooled donor plasma contain high titers of SARS-CoV-2-neutralizing antibodies. Information on SARS-CoV-2 antibody titer was not reported in the clinical trials that evaluated the use of IVIG for the treatment of COVID-19. The levels of SARS-CoV-2 antibodies in IVIG products likely vary depending on which SARS-CoV-2 variant was dominant when the plasma products were collected, and different lots of IVIG may have different titers of antibodies. Although IVIG preparations may have general immunomodulatory effects, these theoretical effects do not appear to benefit patients with COVID-19.¹

Clinical Data for COVID-19

In a meta-analysis of 6 randomized controlled trials that enrolled hospitalized patients with COVID-19, the use of non-SARS-CoV-2-specific IVIG was not associated with a survival benefit.¹ All of the included trials were conducted in 2020, when the presence of SARS-CoV-2 antibodies in blood donors was likely uncommon. None of the studies measured the titers of anti-SARS-CoV-2 antibodies. Blood supplies collected since that time likely have a higher level of these antibodies, and the IVIG derived from those supplies could be expected to have a higher level of SARS-specific antibodies. A British study performed in 2022 evaluated serum anti-SARS-CoV-2-spike antibody titers before and after IVIG infusion in 35 patients with primary immunodeficiencies who were receiving regular immunoglobulin replacement therapy.² The study found that anti-spike antibody titers and the neutralization capacity of serum increased after IVIG infusion in most patients. Different brands of commercially available IVIG products exhibit different levels of neutralizing activity against SARS-CoV-2 variants (e.g., BA.1, BA.4, BA.5, BQ.1.1, XBB).

These data do not provide clear evidence for a clinical benefit of IVIG administration in people with COVID-19. Randomized controlled trials are needed to further define the role of IVIG in the treatment of COVID-19. The use of non-SARS-CoV-2-specific IVIG for the treatment of COVID-19 should be limited to clinical trials.

Concentrated antibody preparations derived from pooled plasma collected from individuals who have recovered from COVID-19 can be manufactured as SARS-CoV-2 hyperimmunoglobulin (hIVIG). Treatment with SARS-CoV-2 hIVIG did not alter patient outcomes in a large randomized controlled trial of hospitalized patients, and hIVIG is not currently available for clinical use in the United States.³
Considerations in Pregnancy

IVIG is commonly used during pregnancy for other indications, such as alloimmune thrombocytopenia. However, because there is no clear evidence that IVIG is an effective treatment for acute COVID-19 in nonpregnant adults, the Panel recommends against the use of IVIG for the treatment of acute COVID-19 in pregnant individuals, except in a clinical trial (AIII). This recommendation should not preclude the use of IVIG when it is otherwise indicated for the treatment of underlying conditions or complications that arise during the course of COVID-19.

Considerations in Children

No comparative studies have evaluated the use of IVIG in pediatric patients with acute COVID-19. IVIG is used in combination with glucocorticoids to treat MIS-C in pediatric patients. However, because there is no clear evidence that IVIG is an effective treatment for acute COVID-19 in adults, the Panel recommends against the use of IVIG for the treatment of acute COVID-19 in children, except in a clinical trial (AIII). This recommendation should not preclude the use of IVIG when it is otherwise indicated.

For the Panel’s recommendations for children with MIS-C, see Therapeutic Management of Hospitalized Children With MIS-C, Plus a Discussion on MIS-A.

References

Ivermectin

Last Updated: March 6, 2023

Ivermectin is a Food and Drug Administration (FDA)-approved antiparasitic drug used to treat several neglected tropical diseases, including onchocerciasis, helminthiases, and scabies.¹ For these indications, ivermectin has been widely used and is generally well tolerated.¹² Ivermectin is not approved by the FDA for the treatment of any viral infection.

Proposed Mechanism of Action and Rationale for Use in Patients With COVID-19

Ivermectin has been shown to inhibit replication of SARS-CoV-2 in cell cultures.³ However, pharmacokinetic and pharmacodynamic studies suggest that achieving the plasma concentrations necessary for the antiviral efficacy detected in vitro would require administration of doses up to 100-fold higher than those approved for use in humans.⁴⁵

The safety and efficacy of ivermectin for the prevention and treatment of COVID-19 have been evaluated in clinical trials and observational cohorts. Summaries of the studies that informed the COVID-19 Treatment Guidelines Panel’s (the Panel) recommendation can be found in Table 7b. The Panel reviewed additional studies, but these studies are not summarized in Table 7b because they have study design limitations or results that make them less definitive and informative.

Recommendation

- The Panel recommends against the use of ivermectin for the treatment of COVID-19 (AIIa).

Rationale

The Panel’s recommendation is primarily informed by adequately powered, randomized trials of ivermectin that reported clinical outcomes. Studies that randomized participants to ivermectin or a matched placebo had the greatest impact on the Panel’s recommendation.⁶⁻¹³

Trials have failed to find a clinical benefit from the use of ivermectin for the treatment of COVID-19 in outpatients. In TOGETHER, an adaptive platform trial conducted in Brazil, there was no apparent difference between the ivermectin and placebo arms for the primary outcome of risk of emergency department visits or hospitalization (14.7% vs. 16.4%).¹⁴ In addition, there was no statistically significant difference between the ivermectin and placebo arms in mortality (3.1% vs. 3.5%). In COVID-OUT, a randomized factorial trial, the use of ivermectin when compared with a matched control (5.7% vs. 4.1%) did not reduce occurrences of a composite outcome of emergency department visits, hospitalization, or death.⁶

The ACTIV-6 trial was an adaptive platform trial conducted in outpatients with mild to moderate COVID-19 in the United States.¹⁵,¹⁶ Participants were randomized to an ivermectin regimen (either 400 μg/kg for 3 days or 600 μg/kg for 6 days) or a matching placebo. In the 400 μg/kg phase of the study, the median time to sustained recovery was 12 days for the ivermectin arm and 13 days for the placebo arm. In the 600 μg/kg phase of the study, the median time to sustained recovery was 11 days for both arms.

I-TECH, an open-label trial conducted in Malaysia, found no difference between the ivermectin and standard of care arms (21.6% vs. 17.3%) for the primary outcome of risk of progression to severe COVID-19.¹⁷ The ivermectin arm had a lower risk of mortality than the standard of care arm (1.2% vs. 4.0%) (relative risk 0.31; 95% CI, 0.09–1.11; P = 0.09), but this difference was not statistically
The study populations in most of the reviewed trials were patients with mild to moderate COVID-19 who had a relatively low risk for disease progression, and the number of deaths was low (as expected). In these randomized trials, completely excluding an effect of ivermectin on COVID-19 disease progression is difficult because the trials were not powered to detect differences in secondary outcomes, such as death. However, data from these trials do not provide evidence that the use of ivermectin is effective for the treatment of COVID-19. For this reason, and because other medications now have demonstrated clinical benefit for the treatment of COVID-19, the Panel recommends against the use of ivermectin for the treatment of COVID-19 (AIIa).

See Table 7b for summaries of the key studies that informed the Panel’s recommendation.

**Drug Availability**

Ivermectin is not approved or authorized by the FDA for the treatment of COVID-19.

**References**


