Rapid Evidence Review

Clinical evidence for the use of intravenous immunoglobulin in the treatment of COVID-19

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National Centre for Pharmacoeconomics
NCPE Ireland

Medicines Management Programme

Prepared by the COVID-19 Evidence Review Group with clinical contribution from Dr. Niall Conlon, Consultant Immunologist, St. James Hospital, Dr. Mary Keogan, Clinical Lead National Clinical Programme for Pathology & Consultant Immunologist, Beaumont Hospital.

Key changes between version 2 and version 3 (19th February 2021)

This updated version of the report focuses on published randomised controlled trials (n=3) and observational cohort studies (n=6).

The COVID-19 Evidence Review Group for Medicines was established to support the HSE in managing the significant amount of information on treatments for COVID-19. This COVID-19 Evidence Review Group is comprised of evidence synthesis practitioners from across the National Centre for Pharmacoeconomics (NCPE), Medicines Management Programme (MMP) and the National Medicines Information Centre (NMIC). The group respond to queries raised via the Office of the CCO, National Clinical Programmes and the Department of Health and respond in a timely way with the evidence review supporting the query.

Summary

Intravenous immunoglobulin is a pooled preparation of normal human immunoglobulin G used for the treatment of primary and secondary immunodeficiencies, and infection-related sequelae. It is used at standard doses in replacement therapy for humoral immune disorders and at high doses for autoimmune/inflammatory conditions and neuroimmunologic disorders. Clinical opinion highlighted that pooled IVIG products will not contain specific antibodies to SARS-CoV2; any potential effect will be non-specific.

A small number of randomised controlled trials of generally poor quality have reported their findings. A number of descriptive, observational studies were retrieved following a literature search. However, given the observational, single-armed, open-label design there is considerable bias in the estimates of benefit derived from IVIG. In several studies, IVIG was a component of a multiple treatment strategy and it is therefore highly uncertain which treatment was beneficial.

In published clinical guidelines, recommendations range from explicit advice against its routine use due to lack of evidence on its benefit, or for its use to be confined to clinical trials alone.

Other than its broad use as an anti-inflammatory agent at high doses, there is limited rationale for the use of IVIG in COVID-19. The prothrombotic effect of IVIG may be a cause for concern in patients with severe COVID-19 who may have elevated D-dimer levels. There is a risk that use of IVIG as a rescue therapy would compromise the supply of IVIG to patients established on it for conditions where benefit has been demonstrated.

Conclusion

Like many treatments proposed to treat this condition, non-SARS-CoV-2 intravenous immunoglobulin is unlicensed for the treatment of COVID-19. This Rapid Evidence Review finds that there is currently insufficient evidence to support the use of IVIG in the management of patients with COVID-19. In addition, recommendations from expert groups advise against the use of IVIG in the treatment of COVID-19, or to confine its use to the clinical trial setting.

Rapid Evidence Review

Introduction

Intravenous immunoglobulin is a pooled preparation of normal human immunoglobulin G, used for the treatment of primary and secondary immunodeficiencies, and infection-related sequelae. It is used at standard doses in replacement therapy for humoral immune disorders and at high doses for autoimmune/inflammatory conditions and neuroimmunologic disorders. Licensed indications for IVIG include immune thrombocytopaenia purpura, chronic inflammatory demyelinating polyneuropathy, Kawasaki disease, myasthenia gravis exacerbations, allogeneic bone marrow transplantation and Guillain Barré Syndrome.

Mechanisms involved in modulation of the immune response include complement scavenging, neutralisation of autoantibodies by idiotypic network; enhancement of degradation of autoantibodies by neonatal Fc receptor saturation; inhibition of activation of various innate immune cells including dendritic cells, monocytes, macrophages and neutrophils, and secretion of inflammatory mediators; suppression of effector T helper cells Th1 and Th17, and reciprocal enhancement of immunoprotective regulatory T cells (Tregs); and blockade of B-cell activation(1–4).

The focus of this rapid evidence review is the use of pooled immunoglobulin therapy i.e. non-SARS-CoV-2 specific for the treatment of COVID-19. This product is not licensed for the treatment of COVID-19.

Intravenous immunoglobulin as a therapeutic option in COVID-19

It is not common practice to use IVIG in the setting of infectious disease(5). There is some evidence to support its use in CMV pneumonitis in the transplant setting, while rotavirus can also be treated in this manner. Evidence also exists to support the use of IVIG in toxic shock syndrome due to Group A streptococcus(2). There is currently no evidence of efficacy for IVIG in MERs and studies in SARs-CoV are inconclusive. IVIG and a related product, IgM enriched immunoglobulin, have long been considered potential therapeutic options in sepsis(6,7). Whilst systematic reviews have suggested benefits, variable trial quality precludes widespread application of IVIG. Similarly, IgM enriched immunoglobulin seems to be associated with improved mortality, but the data is inconsistent(8). A recent in-depth review of cytokine release syndromes associated with multiple factors, did not include IVIG as a therapeutic option(9).

Evidence on the use of IVIG in patients with COVID-19

Randomised controlled trials

Three randomised controlled trials, of generally poor quality, have reported on the use of IVIG in patients with COVID-19.

Gharebaghi *et al* (Iran) conducted a randomised, placebo-controlled, double-blind trial in 59 patients with severe COVID-19 infection who did not respond to prescribed first-line therapies that included at least one antiviral agents and one chloroquine class drug(10). Patients included had O_2 saturation ($satO_2$) of < 90% and a PCR confirmed diagnosis. Inadequate response to other treatments was defined as lack of improvement of fever, $satO_2$ < 90%, need for O_2 to maintain $satO_2$ > 90%, after 48 hours of treatment.

One group received IVIg 5g daily for 3 days (in addition to initial treatment) (n=30), while the control group received a placebo (saline) (n=29), in addition to initial treatments. The study was retrospectively registered with the Iranian Registry of Clinical Trials so it unclear whether this was a protocol driven clinical trial. The primary outcome is not stated but data were collected on in-hospital mortality in addition to other clinical outcomes. The in-hospital mortality rate in the IVIg group was 20% (n=6) compared to 48.3% (n=14) in the control group, p = 0.025. A multivariate regression analysis demonstrated that administration of IVIg was associated with an adjusted mortality rate of 0.003 [95% CI: 0.001–0.815]; P = 0.042)(10). However, as patients who died before 72h after the administration of IVIg and placebos were excluded from the study due to an incomplete course of treatment, the analysis is subject to survivorship bias. In addition, at baseline there were statistically significant differences between the randomised groups. Patients in the control group had poorer renal function at enrolment and had a higher white cell count indicating that these patients may have had poorer prognostic indicators that may have increased their risk of mortality, thus potentially overestimating the benefit of IVIG in the treatment arm. The intervention group also had longer periods of in-hospital stays which may be solely related to their better baseline profile rather than any difference conferred by the administration of IVIG.

Sakoulas *et al* reported the findings of a small prospective randomised open-label study from the US(11). COVID-19 infection may be mediated by neutrophil and platelet interactions which is thought to play a role in the development of immunothrombosis. The rationale for the study was to assess the use of IVIG specifically to modify neutrophil activation through FCRIII binding. Patients were eligible for inclusion if they were aged 18 years or older, had an SPO_2 <90% on ≥4l O_2, but were not on mechanical ventilation. Patients were considered for enrolment when treating physicians notified the study team for consideration. Subjects were randomised to receive IVIG 0.5g/kg/day for 3 days in addition to standard of care which included glucocorticoids, convalescent plasma and remdesivir (n=16), while the control group received standard of care

(SOC) alone (n=17). At baseline, a total of 10/17 patients in the SOC arm were on steroids, compared to 7/16 patients in the IVIG arm. The average dose in both arms was 20 and 125 mg of dexamethasone or methylprednisolone respectively and the median duration in the SOC arm was 11 days compared to 9 days in the IVIG arm. Due to the prophylactic protocol for prevention of IVIG-associated headache, all patients in the IVIG arm not on baseline steroids received methylprednisolone 40mg IV 30 minutes prior to the administration of IVIG (n=9). The alveolar-arterial (A-a) gradient was calculated for each subject at time of enrolment. The co-primary endpoints were progression to respiratory failure requiring receipt of mechanical ventilation or death from non-respiratory causes prior to receipt of mechanical ventilation. Seven SOC versus two IVIG subjects required mechanical ventilation (p = 0.12, Fisher exact test). Among subjects with an A-a gradient of greater than 200mm Hg at enrolment, the IVIG group showed a lower rate of progression to requiring mechanical ventilation (2/14 vs 7/12, p = 0.038 Fisher exact test); shorter median hospital length of stay (11 vs 19 days, p = 0.01 Mann Whitney U test); shorter median ICU stay (2.5 vs 12.5 d, p = 0.006 Mann Whitey U test); and greater improvement in PaO_2/FiO_2 at 7 days (median [range] change from time of enrolment +131 [+35 to +330] vs +44·5 [–115 to +157], p = 0.01, Mann Whitney U test), than standard of care. PaO_2/FiO_2 changes between enrolment and day 7 of the 10 SOC patients who received glucocorticoid therapy were median +53 (range, –115 to +216), a difference that remained significantly lower than the IVIG group (p = 0.0057, Mann Whiney U test(11). The findings from this small study must be considered with caution. Firstly, the study was not blinded and therefore selection and performance bias may have been introduced. There is also potential confounding due to the administration of the prophylactic dose of methylprednisolone to all patients in the IVIG arm, the incorporation of remdesivir into treatment protocols during the study enrolment period, and practice changes away from early intubation/mechanical ventilation in favour of self-proning protocols.

Tabarsi *et al* (Iran) reported the findings of a randomised open-label controlled trial which recruited 84 patients who were severely ill with COVID-19, based on bilateral infiltration on CT and satisfied the WHO case definition for COVID-19 severe pneumonia i.e. respiratory rates: ≥ 30 breaths/min, SpO2 ≤ 93%, and PaO_2/FiO_2 ≤ 300 mmHg(12). Patients in the treatment arm (n=52) received 400mg/kg IVIG for three doses and were premedicated with paracetamol, hydrocortisone (100mg) and an antihistamine. Patients in both arms received lopinavir/ritonavir and hydroxychloroquine. The primary outcomes included the need for ventilation and oxygenation, need for admission to ICU and mortality rate. There was no difference in mortality rate between the 2 groups (p=0.8) nor in the need for mechanical ventilation (p=0.39)(12). The findings of the study did not demonstrate any added benefit with the addition of IVIG to the baseline medications.

Observational studies (Table 1)

Six observational studies were retrieved in the literature search reporting on the use of IVIG in patients with COVID-19; summary information is available in Table 1(13–18).

Cao *et al* described the treatment of IVIG (0.3-0.5g/kg) in 3 patients with severe COVID-19, when added in to existing prescribed medications including antiviral agents, antibiotic therapy, and supportive care(13). In their descriptive presentation of the three cases, it was postulated that the progression of the disease was blocked by IVIG due to a temporal association with administration of IVIG and patient improvement in terms of normalisation of temperature, improvement in respiratory function and laboratory parameters. These findings may however be confounded by co-prescribed medications.

Xie *et al*, in a retrospective analysis reported in a letter, investigated the effect of IVIG on the primary outcome of 28-day mortality, in a cohort of 58 patients with severe COVID-19, and the secondary outcomes of 14-day mortality, hospital length of stay (LoS), ICU LoS and use of mechanical ventilation(17). The cohort was stratified according to administration of IVIG within 48 hours of admission to ICU, and those initiated more than 48 hours after admission to ICU. A total of 23 of the 58 patients died within 28 days of admission, 7 in the ≤48 h group and 16 in the >48h group. There was a statistically significant difference in 28-day mortality between the two groups (p=0.009). The hospital LoS for the ≤48 h group was significantly shorter than in the >48h group (11.50 ±1.030 vs 16.96 ±1.620 days, p=0.0055), and ICU LoS for the ≤48 h group was also shorter than that of the > 48 h group (9.533±1.089 vs 13.50 ±1.632 days, p=0.0453). The proportion of patients requiring mechanical ventilation in the ≤48 h group was also statistically significantly lower than in the > 48 h group (6.67% vs 32.14%, p=0.016)(17). The results of this study should be interpreted with caution. The cohort was initially stratified according to the use of IVIG within 24 hours of admission, not 48 hours, and this analysis demonstrated no significant statistical difference. The subsequent stratification by initiation of IVIG within 48 hours or >48 hours of admission resulted in the statistically significant findings presented. The *post hoc* analysis nature of these findings is associated with uncertainty as a pre-planned analysis was not incorporated into the study methods. In addition, there appears to be no adjustment made for differences between patients, and these differences between the two groups may reflect differences between patients rather than between treatment effects, and therefore the comparison between the groups will be biased.

In a report submitted as a letter in December 2020 to Signal Transduction & Targeted Therapy, Zhou et al described the effect of combined low-dose corticosteroid use and IVIG in their cohort of 40 patients treated in the early months of the pandemic in First Hospital of Changsa, China(18).

In all 40 patients, they reported that the $PaCO_2/FiO_2$ ratio improved ($p<0.05$), as did the APACHE II score ($p<0.05$) and patients' temperature ($p<0.05$). There were also statistically significant improvements in a range of laboratory markers and inflammation-related biomarkers. . The added benefit of co-administration of IVIG with corticosteroids cannot be fully separated from the overall results presented.

Shao *et al* conducted a multicentre retrospective cohort study to determine the primary outcome of 28-day mortality and 60 day-mortality in a cohort of 325 patients with either severe or critical COVID-19 infection, of whom 174 patients received IVIG(16). There was no difference in the 28-day ($p=0.872$) or 60-day mortality ($p=0.222$), or survival time ($p=0.225$) between those received IVIG and those who did not. The authors claim that following an adjusted COX regression sub-group analysis, that there was some evidence that early use of IVIG following admission and treatment with higher daily doses were associated with a greater curative effect(16). However, the analysis adjusted for baseline patient factors on admission alone, but not for differences that occurred after admission. Therefore, changes in patient clinical status following admission were not adjusted for, which may have contributed to factors influencing decision-making around initiation of IVIG or not. The analysis may also be biased due to the absence of adjustments for differences in other prescribed interventions or additional supportive measures between the two groups.

Herth *et al* described the clinical course of a case series of 12 patients whose patient records were reviewed in one centre in Germany and two hospitals in the US(15). Data was retrieved on patient demographics, laboratory/inflammatory indices, and clinical course during their hospital stay following IVIG administration at doses of 0.5-2g/kg over 1-4 days(15). Eight patients were on concomitant and various antiviral treatments while 6 were co-administered corticosteroids. In patients who received IVIG early in the course of their admission (i.e. $\leq$4 days) (n=5), demonstrated a shorter length of stay than those receiving it more than 7 days after admission ($p=0.03$). This study again bases its outcomes on an arbitrary stratification of timing of administration of IVIG in a similar way to Xie *et al*. There is considerable uncertainty associated with the interpretation of the findings as any treatment benefit may be confounded by the observational nature of the study, the retrospective analysis and the potential confounding due to co-administration of other agents, particularly corticosteroids, which at the time of accrual of the data was not known to have a significant benefit in severely ill patients.

Esen *et al* evaluated the effect of adjuvant treatment with IVIG on clinical outcomes and biomarkers in critically ill patients with COVID-19(14). This is a retrospective analysis of patients in ICU in one hospital, who were treated according to a locally developed algorithm. The study was retrospective in design, open-label, non-randomised and involved two cohorts of patients

who were on a standard treatment bundle of hydroxychloroquine, favipravir, azithromycin and oseltamivir, and where inflammatory markers were raised, tocilizumab or anakinra, methylprednisolone, high dose vasopressors and vitamin C. Into this treatment regimen, IVIG was added at a dose of 30g/day for five consecutive days which was initiated on an individual case basis. Outcome markers assessed on treatment included CRP, ferritin, procalcitonin, IL-6, D-dimers and WBC. Clinical outcome measures included duration of specific treatment modalities, time to start mechanical ventilation, change in ventilation mode, ICU and hospital discharge and overall survival. Of 93 patients, 51 received IVIG therapy. Overall survival was 61% in the IVIG arm compared to 38% in the control arm (OR 2.3. (95%CI 0.9-5.4, p=0.091), but this difference was not statistically significant when corrected for imbalances in the APACHE score at baseline (OR: 2.2, 95%CI 0.9-5.5, p=0.091).

Table 1 – Summary of observational studies focussing on the role of IVIG in the treatment of COVID-19

Study Title (location)	Methodology	Population	Outcome assessed	Efficacy data
Cao et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with Coronavirus Disease 2019 (China)(13)	Case series	Patients (n=3) were classified with severe COVID-19 following admission.	Impact of treatment interventions on a) haematological indices particularly % lymphocytes, b) inflammatory markers: ESR, HsCRP; c) liver transaminases; d) coagulation markers (incomplete data) & a number of others	Descriptive presentation of the effect of IVIG at a dose of 25g (0.3-0.5g/kg) daily for 5 days added to existing prescribed medications including antiviral agents, antibiotic therapy and supportive care. Postulated that the addition of IVIG successfully blocked the progression of the disease cascade of COVID-19 as evidenced by clinical improvement shortly after administration resulting in normalising temperature (within 1-2 days), and respiratory function improvement (within 3-5 days). Improvements in % lymphocytes, ESR and CRP and O_2 saturation. Limitations: Small number of patients, confounding with other agents Comment from authors: Timing of IVIG may be best prior to development of overall systemic damage
Xie et al. Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-1 (China)(17)	Case series	58 patients with severe COVID-19 admitted to ICU	Primary: 28-day mortality Secondary: 14-day mortality, hospital length of stay, ICU LoS; use of mechanical ventilation	58 patients retrospectively analysed and stratified according to administration of IVIG 20g within 48 hours of admission to ICU vs those initiated on IVIG therapy after >48 hours. Results: 11 patients (18.96%) required mechanical ventilation, 5 (8.62%) non-invasive mechanical ventilation, 6 (10.3%) invasive mechanical ventilation, and 2 (3.45%) high-flow oxygen aspiration. A total of 23 of the 58 patients died within 28 days of admission, 7 in the ≤48 h group and 16 in the > 48 h group. There was a statistically significant difference in 28-day mortality between the 2 groups (p=0.009). The hospital LoS for the ≤48 h group was significantly shorter than in the > 48 h group (11.50 ±1.030 vs 16.96 ±1.620 days, p=0.0055), and ICU LoS for the ≤48 h group was also shorter than that of the > 48 h group (9.533±1.089 vs 13.50 ±1.632 days, p=0.0453); proportion of patients requiring mechanical ventilation in the ≤48 h group was also significantly lower than in the > 48 h group (6.67% vs 32.14%, p=0.016). Limitations: Beneficial outcomes in this retrospective case series may be confounded by the co-administration of additional interventions including LMWH; the absence of adjustment for differences in patients between the 2 groups; the arbitrary assignment of initiation of IVIG at a selected time point following admission without accounting for changes in clinical status of patients leading to the potential decision to initiate IVIG
Shao et al. Clinical Efficacy of Intravenous Immunoglobulin Therapy in Critical Patients with COVID-19: A Multicenter	Multicentre retrospective cohort study	325 patients with severe (68%) or critical (32%) COVID-19 of whom 174 received IVIG	Primary: 28-day mortality and 60-day mortality Secondary: Hospital LoS; ICU LoS; duration of mechanical ventilation	The IVIG group were older, had higher APACHE II scores & SOFA scores, higher levels of total bilirubin, direct bilirubin, creatine, CRP, IL-6, & lactate, but lower platelets and lymphocyte count (all $P<0.05$), & decreased PaO2/FiO2 ($P=0.011$). There was no significant difference in 28-day and 60-day mortality between the IVIG group and non-IVIG group ($P=0.872$ and $P=0.222$, respectively), and no significant difference in survival time ($P= 0.225$). The in-hospital day & total duration of disease was longer in the IVIG group (both $P < 0.001$), consistent with the more serious initial condition of IVIG group. Subgroup analysis showed that only in the critical type patients IVIG could significantly

Retrospective Cohort Study (China)(16)				decrease the inflammatory response, improve some organ functions, reduce the 28-day mortality rate, and prolong the survival time. The study showed that early use of IVIG (admission≤ 7 days) with high dose (>15 g/d) exhibited a more significantly curative effect. Limitations: Non-randomised assignment to an IVIG arm, retrospective analysis, subgroup analysis not protocol driven, COX model not adjusted for changes in clinical status of patients following admission
Zhou et al. Low-dose corticosteroid combined with immunoglobulin reverses deterioration in severe cases with COVID-19(18)	Case series – retrospective descriptive analysis	40 patients with severe COVID-19	$PaCO_2/FiO_2$ ratio, APACHE score, laboratory biomarkers, inflammatory biomarkers	$PaCO_2/FiO_2$ ratio improved ($p<0.05$); APACHE II score improved ($p<0.05$); body temperature improved ($p<0.05$); lymphocyte count improved ($p<0.05$); CRP, neutrophils, leukocytes, platelets, liver and kidney function, myocardial enzymes, CK, LDH all statistically significant improvements ($p<0.05$); SPO2, PaCO2 & lactic acid improved. Limitations: open-label, no blinding, effect of IVIG confounded by co-administration of corticosteroids,
Esen et al. Effects of adjunct treatment with intravenous immunoglobulins on the course of severe COVID-19: results from a retrospective cohort study (14)	Retrospective, open-label, non-randomised cohort study	2 cohorts (n=93) of patients with severe COVID-19 of whom 42 received standard intensive care (SIC) and 51 SIC with IVIG	Plasma biomarkers of inflammation & clinical outcomes including duration of specific treatment modalities, time to start of mechanical ventilation, change in ventilation mode, ICU & hospital discharge & overall survival.	Overall ICU survival was 61% in the IVIG and 38% in the SIC group. The difference in survival probability between the 2 groups was not statistically significant after correction for imbalances in the APACHE II score at baseline (odds ratio: 2.2, 95% CI: 0.9–5.4, p=091). There were no significant differences between groups in time-to-clinical event parameters such as time to ICU or hospital discharge (medians 15 vs. 12 and 38 vs. 20 days, p>0.1 respectively). With regard to biomarkers, IVIG treatment was associated with a reduced CRP levels within 6 days whereas those remained fairly constant in the SIC-only group. Generally, changes in remaining biomarkers of inflammation were rather small, with non-statistically significant differences between groups. Limitations: Retrospective analysis; non-randomised (addition of IVIG based on clinical decision-making/local treatment algorithm)
Herth et al. Use of Intravenous Immunoglobulin (Prevagen or Octagam) for the Treatment of COVID-19: Retrospective Case Series (15)	Retrospective case series	12 patients reviewed on the basis that they had received IVIG during the course of their illness	Laboratory & inflammatory biomarkers, clinical outcomes including days on mechanical ventilation, days in hospital, IVIG dose & total dose	Total IVIG dose ranged from 0.5g/kg yo 2.0g/kg over 1-4 daily doses. Median time of IVIG administration was 9 (range 0-48) days post admission. The 5 patients who received IVIG <4 days after admission had a shorter LoS (median 7 days range 3-14 days) compared to the 7 patients that received it > 7 days post admission (median 33, range 8-48 days)., p=0.03, (Mann-Whitney U test) Limitations: Retrospective, case series, lack of protocol, descriptive analysis, arbitrary cut-off to time of administration of IVIG used to estimate benefit, confounded by administration of other potentially disease-modifying therapies.

Paediatric use of IVIG

The association between infection with SARs-CoV-2 and a syndrome resembling Kawasaki Disease (KD) in children began to emerge in early May 2020(19). The standard treatment for Kawasaki Disease involves administration of IVIG and aspirin(20). The current terminology used to describe this disorder is multi-system-inflammatory syndrome in children (MIS-C), and it shares some similarities with KD. A number of evidence syntheses have described the clinical features, management and outcomes in children affected by it and first-line interventions include IVIG and antithrombotic therapy(21–23). The recently published American College of Rheumatology guidelines on the management of MIS-C associated with SARS-CoV-2 and hyperinflammation in children include immunomodulatory therapy with IVIG and/or glucocorticoids as first line therapy(24). Therefore, the use of IVIG in this setting is anticipated.

On-going clinical trials

There are three pivotal adaptive, randomised controlled clinical trials on-going globally to assess the efficacy of a number of interventions for COVID-19, namely the SOLIDARITY trial, the RECOVERY trial and REMAP-CAP(25–27). None of these trials considered non-SARs-CoV2-19 IVIG as a therapeutic option in their protocols. RECOVERY and REMAP-CAP did include convalescent plasma as a potential agent for managing patients with the infection but in January 2021, the findings from the RECOVERY trial showed that there was no benefit, and subsequently it was decided to close recruitment to this arm in REMAP-CAP(28).

Guidelines

A number of published guidelines refer to the use of non-SARs-CoV-2 IVIG in patients with COVID-19. The general consensus is that there is insufficient evidence to support its use:

1. **Surviving Sepsis Campaign Guidelines on the Management of Adults with Coronavirus Disease 2019 (COVID-19) in the ICU**(29) **(29th Jan 2021)**

Recommendation 45. In critically ill adults with COVID-19, suggest against the routine use of standard intravenous immunoglobulins (IVIG). (*Weak recommendation, very low-quality evidence.)*

2. **Infectious Disease Society of America (IDSA)**(30) **(Feb 22nd 2021)** *(recommendation unchanged since April 9th 2020)*

Intravenous immunoglobulin (IVIg) has been used as an adjuvant to treat a variety of pathogens either as a pooled product or in a concentrated more pathogen focused (hyperimmune) form.

As the community from which a given batch of IVIg is derived from includes increasing numbers of individuals who have recovered from SARS-CoV-2, the possibility of protective antibodies being present in the pooled product is increased. However, the potential utility of IVIg for the treatment of SARS-CoV-2 is unknown at this time. Its use has been reported in a few patients with COVID-19 but studies are needed to determine if there may be a role for IVIg in the treatment of SARS-CoV-2.

3. **National Institute of Health (NIH)**(31) **(Feb 23rd 2021)** (*recommendation from July 17th 2020)*

Non-SARS-CoV-2-Specific Intravenous Immune Globulin Recommendation:
The Panel recommends against the use of non-SARS-CoV-2 specific IVIG for the treatment of COVID-19, except in a clinical trial (AIII). This recommendation should not preclude the use of IVIG when otherwise indicated for the treatment of complications that arise during the course of COVID-19.

4. **NHS Speciality Guide**

On 27th March 2020, an NHS speciality guideline was published relating to the management of patients requiring immunoglobulin treatment during the coronavirus pandemic and management of supply(32). This document, developed by the Immunology and Allergy Clinical Reference Group, did not recommend the use of IVIG for the treatment of patients with COVID-19 infection at that time.

The BMJ COVID-19 living review states specifically that evidence for IVIG is limited(33).

Safety of IVIG

Administration of IVIG is associated with known adverse reactions that are generally mild, transient and reversible. The risk of adverse events increases with high doses and rapid rates of infusion particularly on first dose infusion. Prevention strategies include adequate patient hydration, slow rates of infusion followed by gradual increases, and premedication with paracetamol and/or antihistamines. Additional risks at high doses include renal failure, thrombosis and aseptic meningitis.

COVID-19 is associated with a hypercoagulable state and there is evidence of an increased risk of thromboembolic events in hospitalised patients(34–36). Appropriate prophylactic anticoagulation is therefore recommended in the hospital setting(37,38). The administration of IVIG could pose an added risk of thromboembolic events in hospitalised patients.

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Appendix 2

IVIG search strategy February 29th 2021

Source	Search
PubMed	Search (((("coronavirus pneumonia" OR “COVID-19” OR “2019 novel coronavirus infection” OR “2019-nCoV” OR "SARSCoV2" OR "SARS-CoV2" OR SARSCov19 OR "SARS-Cov19" OR "SARSCov-19" OR "SARS-Cov-19"))) AND (("Immunoglobulins, Intravenous"[Mesh] OR "intravenous immunoglobulin" OR "intravenous immunoglobulins" OR IVIG OR "intravenous IG")
Google Scholar	allintitle: "coronavirus pneumonia" OR “COVID-19” OR “2019 novel coronavirus infection” OR “2019-nCoV” OR "SARSCoV2" OR "SARS-CoV2" OR SARSCov19 OR "SARS-Cov19" OR "SARSCov-19" OR "SARS-Cov-19" AND "intravenous immunoglobulin’’ OR ‘’IVIG’’ (since 2019)
LitCovid	"intravenous immunoglobulin’’ OR ‘’IVIG’’
ClinicalTrials.gov	COVID-19 (synonyms 2019-nCoV, SARS-CoV-2, 2019 novel coronavirus, severe acute respiratory syndrome coronavirus 2) and intravenous immunoglobulin OR IVIG
EudraCT	COVID-19 (synonyms 2019-nCoV, SARS-CoV-2, 2019 novel coronavirus, severe acute respiratory syndrome coronavirus 2) and intravenous immunoglobulin OR IVIG