Peripheral infiltration of remdesivir in 3 patients with COVID-19: Case series and discussion

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Purpose. The coronavirus disease 2019 (COVID-19) pandemic resulted in accelerated market access to remdesivir worldwide. Therefore, data about complications experienced during use of the drug are limited. This is the first published case series (1 case report exists) to describe remdesivir infiltration in 3 patients with COVID-19.

Summary. In the first case, a 91-year-old woman experienced remdesivir infiltration resulting in edema, hematoma at the area of infiltration; on palpation, the affected area felt cooler than the surrounding areas. Swelling was still present after 6 weeks. In the second case, remdesivir infiltration occurred in a 72-year-old male, resulting in edema, hematoma, and pain at the area of infiltration. The hematoma lasted for 7 days. The third case concerned a 67-year-old woman, in whom remdesivir infiltration led to edema and a small hematoma. The hematoma regressed to a negligible size within 3 days. However, a week after infiltration, redness had reappeared. In 2 cases, the patient was immediately treated with hyaluronidase injections, but no specific treatments were provided in the other case.

Conclusion. Based on the product information provided by remdesivir's manufacturer, we believe symptoms and signs observed in the 3 cases may have resulted from the low pH (~4) of the nonbuffered remdesivir solution, although the patients were not formally assessed for caustic injury. Previous experience with other noncytotoxic medications suggests that infusion-specific factors (eg, volume of leaked fluid) and patient-specific factors (eg, advanced age) may have a role in the outcome of remdesivir infiltration. The possibility of symptoms caused by cyclodextrins in the formulation or by intrinsic toxicity of remdesivir warrants exploration.

Keywords: case series, COVID-19, infiltration, remdesivir

Am J Health-Syst Pharm. 2021;78(x):xxx-xxx

In hospitalized patients, unintentional leakage of an intravenously administrated agent into the surrounding subcutaneous tissue occurs with an incidence ranging from 0.1% to 6%.[1] This leakage is defined as extravasation if the administered agent has the potential to initiate severe tissue damage. Mostly, this potential to harm the surrounding tissue is based on the distinguishing between vesicant and nonvesicant agents.[1,2] According to this definition, leakage of a nonvesicant solution into the surrounding tissue is defined as infiltration. Leaked agents can cause tissue injury depending on the characteristics of the agent, the physiochemical properties of the solution, the infiltrated volume, and patient characteristics.[1] The mechanisms of tissue damage caused by subcutaneous leaked noncytotoxic agents are explained in Table 1.[1,3,4]

Treatment of infiltration is based on the underlying mechanism of tissue damage and is drug specific. However, nonpharmacological general supportive care must be applied first in the event of subcutaneous leakage of any infused agent (Box 1).[4]

Based on the possible mechanisms of damage that can be caused by an infiltrated medication, additional interventions may be required (Table 1). Pharmacological and nonpharmacological postinfiltration interventions can roughly be divided into 2 groups: "disperse and dilute" and "concentrate and condensate."[5] The disperse-and-dilute method is mainly preferred when the potential for tissue damage is related to the concentration of the solution. When the infiltrated solution will be diffused into a larger area, it is diluted and the harmfulness decreases. For instance, this applies to solutions at extremities of pH. The pH will restore to a more neutral acidity after dilution and therefore be less harmful. The use of warm compresses in the disperse-and-dilute method will lead to vasodilation and

subsequently to enhanced absorption. Besides warm compresses to induce vasodilatation, hyaluronidase injections can be used to break down tissue to increase the available area for absorption. Furthermore, flushing with 0.9% sodium chloride injection can also be used to disperse and dilute. Flushing can be applied when the catheter is not removed. The concentrate-and-condensate method is preferred if subcutaneously leaked agents have the potential to cause highly severe tissue injury. Dispersing these agents may lead to a larger area of tissue injury. This method is applicable to all vesicant and irritating drugs except for vinca alkaloids and vasopressors. In order to keep the drug in the area of infiltration, cold compresses can be used to achieve vasoconstriction and to lower the absorption. Therefore, inflammation or necrosis induced by the agent may be reduced. Furthermore, specific antidotes to counteract local pharmacological effects can be used depending on the infiltrated drug (eg, phentolamine for vasoconstrictors).[5]

Remdesivir (Veklury, Gilead Sciences) is an antiviral drug that is currently used on a major scale worldwide for the treatment of hospitalized patients with coronavirus disease 2019 (COVID-19). Remdesivir is a prodrug that is intracellularly metabolized into the active metabolite GS-443902 and inhibits the replication of viral RNA.[6,7] In the United States, remdesivir was approved by the Food and Drug Administration (FDA) on May 1, 2020, through an emergency use authorization (EUA); in the European Union, the drug received a conditional marketing authorization by the European Medicines Agency (EMA) on June 3, 2020.[8,9] Therefore, data about the effects and adverse events of remdesivir are still relatively limited. Remdesivir's product label reports infiltration as an adverse event during EUA-authorized use without specifying corresponding symptoms, whereas infiltration or extravasation was not reported as a common or serious adverse event in phase 3 clinical trials.[10,11] Therefore, the manufacturer does not provide instructions regarding follow-up or

treatment.[7,12] Based on the product information provided by the manufacturer, remdesivir is a nonvesicant agent. To our knowledge, there is 1 prior published case report describing painful blisters, hemorrhage, and localized edema following remdesivir extravasation.[13] In this case series, we describe the clinical manifestations of remdesivir infiltration in 3 hospitalized patients with COVID-19.

Case descriptions

All 3 patients were admitted to our teaching hospital, Amsterdam University Medical Center. Basic facts of the 3 cases are summarized in Table 2.

Case 1. Firstly, we report the case of a 91-year-old woman who presented to the emergency unit of our hospital with dyspnea, coughing, tiredness, diarrhea, and decreased general clinical condition. The patient had a medical history of dementia, hypertension, hypothyroidism, chronic obstructive pulmonary disease, and arthrosis. On admission, her weight was 78.4 kg, her temperature was 38.5°C, oxygen saturation (SpO_2) was 79% (without supplemental oxygen), and the C-reactive protein (CRP) concentration was 160 mg/L. A chest x-ray showed no signs of viral pneumonia. However, COVID-19 was suspected, and the patient was admitted to the hospital for oxygen supplementation. The day after admission, a reverse transcription polymerase chain reaction (RT-PCR) assay of a nasopharyngeal swab was positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, confirming COVID-19. In line with our hospital's protocol at the time, treatment with remdesivir and dexamethasone was promptly initiated.

Remdesivir was started with a loading dose of 200 mg (40 mL of 100 mg/20 mL remdesivir solution for injection) diluted with 60 mL of 0.9% sodium chloride injection. Thereafter, a daily maintenance dose of 100 mg (20 mL of remdesivir solution for injection)

diluted with 80 mL of 0.9% sodium chloride injection was administered for the remaining 4 days of treatment. The infusion was administered intravenously via peripheral access in her left wrist. On day 4 of treatment, a swollen area of approximately 3 × 3 cm around the injection site was noticed by the nursing staff. Redness of the area of infiltration was observed, and upon palpation the area felt cooler than the surrounding tissue. No additional histological examinations were performed. Considering that these effects occurred after the end of the infusion, it was determined that the administered dose, containing 100 mg of remdesivir, had possibly fully leaked into the surrounding tissue. However, the exact amount of leakage remained unclear. Additionally, infiltration of 0.9% sodium chloride injection could not be ruled out. The patient had not noticed the infiltration, nor did she have any complaints, such as pain.

The hospital pharmacist was consulted, and general care was carried out according to the recommendations in Table 2. An attempt to aspirate the ostensibly leaked remdesivir solution through the catheter with an empty syringe did not succeed. Based on information provided by the manufacturer about the acidic pH of the solution (pH of 4), it was advised to use warm compresses and administrate hyaluronidase injections in accordance with the disperse-and-dilute method. After consultation with a plastic surgeon, hyaluronidase was diluted with 0.9% sodium chloride injection to a concentration of 150 units/mL, and 255 units were injected by the attending physician in separate injections of 0.2 mL subcutaneously or intradermally along the edge of the infiltration area. Approximately 18 hours after the infiltration, the area was still swollen, the area continued to feel cooler than the surrounding tissue, and a hematoma appeared (Figure 1). The affected area of infiltration was not expanding, nor did the patient report any pain. By the seventh day, the hematoma and swelling were decreasing in size. The temperature of the area, assessed by

palpation, now felt normal compared to the surrounding tissue, and the patient had not experienced any pain (Figure 1). At a follow-up visit after 4 weeks, the hematoma was no longer visible. The swelling at the area of infiltration had further decreased but was still visible (Figure 2). The patient had not reported any pain. After 6 weeks the area of infiltration was still slightly swollen and had not decreased in size. No other signs could be observed, nor did the patient report discomfort or pain.

Case 2. The second case involved a 72-year-old male who presented to the emergency unit of our hospital with increasing dyspnea, coughing, and ongoing fever. He had been diagnosed by the Public Health Service of Amsterdam as having SARS-CoV-2 infection via RT-PCR assay of a nasopharyngeal swab 2 days earlier. He had a history of hypertension and diabetes. On admission, his weight was 79.9 kg, his temperature was 39.6°C, SpO_2 was 95% (with 2 L of supplemental oxygen), and the CRP concentration was 17 mg/L. Chest computed tomography (CT) showed bilateral interstitial pneumonia, consolidations, and ground-glass opacities suggestive of COVID-19. He was admitted to the hospital for oxygen supplementation, and remdesivir and dexamethasone treatment were initiated.

Remdesivir was administrated intravenously via peripheral access in the right hand in the same dosages as described for case 1. On the second day of remdesivir treatment, the patient noticed swelling and a painful sensation around the site of administration. No histology was performed. Remdesivir infusion was discontinued, but the infiltrated volume was not documented by the nursing staff and therefore was not precisely known. The area of infiltration was marked. However, no other general care measures (eg, aspiration of the leaked fluid and elevation of the affected body part; see Box 1) were performed by the clinical staff due to unfamiliarity with recommended interventions. The hospital pharmacist

was consulted, and it was decided to administer local hyaluronidase injections. A few hours after the infiltration, swelling and a small hematoma were visible. By the seventh day, the swelling had diminished and the hematoma had decreased substantially (Figure 3). At a follow-up visit after 4 weeks, there were no more visible signs, nor did the patient report any symptoms.

Case 3. The third case involved a 67-year-old woman who presented to the emergency unit of our hospital with increasing dyspnea, coughing, fatigue, and diarrhea. She had been diagnosed with SARS-CoV-2-infection through RT-PCR assay of a nasopharyngeal swab by the Public Health Service of Amsterdam 8 days before hospital admission. She had a medical history of asthma and migraines. On admission, her weight was 72.3 kg, her temperature was 37.6°C, SpO_2 was 88% (without supplemental oxygen), and the CRP concentration was 67 mg/L. Chest CT showed emphysema and ground-glass opacities suggestive of COVID-19. The patient was admitted to the hospital for oxygen supplementation, and subsequently remdesivir and dexamethasone treatment were initiated.

A remdesivir infusion was administrated intravenously via peripheral access in the right wrist in the same dosages as described for case 1. On the second day, the patient noticed an area of severe tenderness on her dorsoradial right wrist around the infusion site. The nursing staff reported a tender and erythematous swelling at the area of infiltration of approximately 3 cm in diameter after administration of the infusion. No histology was performed on the affected area. The area of infiltration was marked, and the nursing staff attempted to aspirate the leaked remdesivir solution. Considering that the observed effects occurred after the end of the infusion, it was possible that the administered dose, containing 100 mg of remdesivir, fully leaked into the surrounding tissue, but the exact

amount was unclear. Furthermore, infiltration of 0.9% sodium chloride injection could not be ruled out. The hospital pharmacist was consulted and advised local administration of hyaluronidase. However, hyaluronidase was not available at the department, and observation was initiated in consultation with a plastic surgeon. In addition, general care interventions (Table 2) were performed. The following day, the marked infiltration area was still swollen and red (Figure 4). These signs decreased by the second day after the infiltration, with only minimal discomfort reported by the patient, and completely resolved by the third day. However, a week after the infiltration, a rust-colored redness had reappeared and, on palpation, the affected area felt cooler than the surrounding tissue, without signs of edema or symptoms of pain (Figure 5). At a follow-up visit after 4 weeks, there were no visible signs of redness or a skin temperature difference. The patient did not report experiencing any symptoms.

All patients provided written informed consent for us to publish the data and photos included in this report.

Discussion

Only 1 prior report of remdesivir infiltration has been published.[13] Infiltration of remdesivir at the infusion site has been reported previously as an adverse event.[7,12] However, the clinical impact of the infiltration in clinical studies was not described. Therefore, treatment advice in our hospital was based on the known pharmacological properties of remdesivir, patient characteristics, and mechanism of tissue damage of noncytotoxic agents (Table 1). The excipients present in the remdesivir formulation are sulfobutylether-β-cyclodextrin (SBECD), hydrochloric acid, sodium hydroxide, and water for injection.[6] SBECD is added to the formulation to increase solubility and stability by accommodating remdesivir molecules within the cavity of SBECD.[14] However, the effect of

SBECD on the subcutaneous tissue is unknown. Furthermore, the pH of the nonbuffered diluted infusion solution is 4 (information obtained from the manufacturer). Infiltration of solutions with a low pH (<5) can lead to vasoconstriction and precipitation of proteins and, finally, severe tissue injury (Table 1).[15] Remdesivir was administrated in our hospital through a 100-mL infusion at a rate of 200 mL/h. Depending on the infiltrated volume, mechanistic damage could also result in tissue injury. In 2 of the described cases the infiltration was noticed after the end of the infusion. Therefore, a high amount of infiltrated volume may have been possible, and mechanistic damage was considered. Furthermore, damage related to the formulation's osmolality was not expected due to the osmolality being 320 mOsm/kg, according to information obtained from the manufacturer. That osmolality does not exceed the threshold for harmful hyperosmolality (Table 1). Damage caused by cations was not expected due to the absence of cations in the formulation.

Data on the pharmacological effect of remdesivir on subcutaneous tissue are limited. However, infiltrations of other antiviral nucleotide and nucleoside analogues have been reported previously.[16,17] The injuries described in those reports (tissue necrosis and bullae formation) were believed to be caused by the alkalinity of the acyclovir and ganciclovir solution (pH of 11).[16,17] Therefore, the observed injuries are unlikely to represent a class effect, but rather are likely a consequence of the pH of the formulation. Acidic pH is considered to be a risk factor for tissue injury.[18,19] For instance, infiltration of amiodarone, with an acidic pH (3.5-4.5), was reported to result in severe pain, erythema, and warmth.[20] Furthermore, reported cases of infiltration of vancomycin (pH of 2.5-4.0) involved an ischemic lesion or vesicle redness and swelling.[21,22] Therefore, signs and symptoms observed in our cases may have been a result of the acidic pH of the solution, although causality could not be established.

The effect of SBECD on the severity of infiltration could not be defined, as it was unknown whether remdesivir would be released from SBECD in the subcutaneous tissue similarly to the drug's dilution in plasma.[23] Furthermore, there is no published information on the pharmacokinetics of SBECD in subcutaneous tissue or infiltration of other agents formulated with SBECD.[24] Other factors that may have affected the occurrence of the infiltration were infusion-specific factors and patient-specific factors.[1] With regard to the infusion-specific factors, the high infiltration volume (possibly up to 100 mL) and the high infusion rate (200 mL/h) were risk factors. In addition, catheter location in the dorsum of a hand (case 2) and the need for catheter readjustments (case 1) could have increased the risk of infiltration.[1] Patient-specific factors that might have influenced the clinical manifestations were patient age and condition (in case 1)[1]; however, the relationship of these risk factors to the case remains unproven.

Hyaluronidase injections were the recommended intervention for the remdesivir infiltration cases in our hospital. Hyaluronidase has been proven to be effective in treatment of extravasation of hyperosmolar drugs.[4] Its mechanism of action is due to hydrolysis of the enzyme hyaluronic acid in connective tissue; this results in degradation of the interstitial barrier, facilitating an increase in distribution and absorption of the infiltrated drug.[1,25] Therefore, the duration of symptoms and signs (eg, swelling) is limited.[1] Moreover, some case reports describe that symptoms after infiltration of acidic or alkaline drugs resolve quickly after hyaluronidase administration.[1,20] Therefore, hyaluronidase could in theory be an option after infiltration of acidic drugs when the goal is to disperse and dilute the infiltrated drug.[25]

The acidic pH of the remdesivir solution and the possibility of high infiltrated volumes in our cases were considered the most important factors on which to base the

treatment strategy. Therefore, administration of hyaluronidase injections was recommended for quick distribution and absorption. Some observed signs in our cases appeared to resolve after these injections, although causality remains unclear. In the previously published case of remdesivir infiltration involved blisters, hemorrhage, and localized edema.[13] Treatment consisted of oral prednisolone to suppress inflammation. However, local or systemic administration of corticosteroids has not been proven to be effective for treatment of infiltration or extravasation.[25] In future, other treatment strategies for remdesivir infiltration—for instance, flushing with 0.9% sodium chloride injection to distribute and dilute the infiltrated drug or use of warm compresses and other supportive care, as recommended for acidic drugs (Table 1)[1]—could also be considered

Conclusion

We have presented 3 cases of a remdesivir infiltration and possible mechanisms of tissue injury after infiltration. Clinical effects observed in our cases were swelling (for up to 6 weeks), hematoma or redness, severe pain, and cooler temperature in the affected area compared to the surrounding tissue. We identified the low pH of the solution as a possible cause of the observed signs, and therefore administration of hyaluronidase injections was recommended in addition to general care interventions (eg, elevation of the affected body part). The presence of any intrinsic toxicity of remdesivir on tissue and the role of cyclodextrins in the formulation remain to be studied. Some effects, such as swelling, pain, and hematoma, appeared to decrease after hyaluronidase administration, although a relationship cannot be established.

Disclosures

The authors have declared no potential conflicts of interest.

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Key Points

- Observed symptoms and signs following remdesivir infiltration (edema, hematoma, decreased temperature by palpation, and pain) decreased in a few days.
- The acidic pH of the remdesivir solution may have influenced the signs and symptoms observed in the 3 cases of remdesivir infiltration reported here.
- Reappearance of signs a week after remdesivir infiltration occurred in 1 case not involving treatment with hyaluronidase injections.

Figure 1. Affected area of wrist in case 1 seven days after remdesivir infiltration.

Figure 2. Affected area of wrist in case 1 twenty-eight days after remdesivir infiltration

Figure 3. Affected area of hand in case 2 seven days after remdesivir infiltration.

Figure 4. Affected area of wrist in case 3 two days after remdesivir infiltration.

Figure 5. Affected area of wrist in case 3 seven days after remdesivir infiltration.

Table 1. Mechanisms of Tissue Damage Caused by Subcutaneously Leaked Noncytotoxic Agents, With Treatment Options[1,3,4]

Type of Toxicity	Effect or Agents Involved and Mechanism(s) of Tissue Damage	Treatment	Example(s)
Mechanical	Fluid volume: • Large volumes in subcutaneous tissue increase pressure on surrounding tissue; compression of vascular structures may lead to ischemia and eventually tissue necrosis	Surgical intervention (eg, fasciotomy)	Any drug
Physiochemical	Hyperosmolar agents (≥500 mOsmol/L) and hypo-osmolar agents (≤200 mOsmol/L): • Due to differences in osmotic values at the cellular membrane, the cell volume dysregulates, which may lead to DNA damage, inflammation, and eventual cell apoptosis	Disperse and dilute: hyaluronidase injections in combination with use of warm compresses	Dextrose injection (10%-50%), mannitol injection (20%), TPN, contrast fluids
Physiochemical	Cationic solutions, primarily calcium- or potassium-containing formulations: • Tissue damage or cell death may be induced by calcium- or potassium-induced vasoconstriction and protein precipitation	Disperse and dilute: hyaluronidase injections in combination with use of warm compresses	TPN, calcium solutions, potassium solutions
Physiochemical	Extremities of pH: • Alkaline (pH ≥9.5): Hydroxide ions may cause liquefactive necrosis leading to deep tissue damage • Acidic (pH ≤5.5): Coagulative necrosis may be caused by hydrogen ions and the reducing efficacy of acid anion salts; may be caustic to endothelial tissue	Disperse and dilute: hyaluronidase injections in combination with use of warm compresses	Alkaline: phenytoin, sodium bicarbonate Acidic: vancomycin, amiodarone
Pharmacological properties	Vasopression: • Local ischemia caused by vasoconstriction	Antidote phentolamine added to warm compresses	Dopamine

Abbreviations: TPN, total parenteral nutrition.

Table 2. Treatment-Specific Details, Clinical Effects and Observations, and Interventions and Monitoring in 3 Cases

Variable	Case 1	Case 2	Case 3
Remdesivir dosage	100 mg IV daily	100 mg IV daily	100 mg IV daily
Duration and rate of infusion	30 min, 200 mL/h	30 min, 200 mL/h	30 min, 200 mL/h
Infusion characteristics			
Pump	Infusomat Space (B Braun)	Infusomat Space (B Braun)	Infusomat Space (B Braun)
Catheter site, age	Peripheral catheter (20 gauge) in basilica vein; 4 d	Peripheral catheter (20 gauge) in dorsal metacarpal vein; 2 d	Peripheral catheter (20 gauge) in cephalic vein; 2 d
Other IV drugs or fluids	0.9% sodium chloride injection	None	0.9% sodium chloride injection
Site checks	Every 4-6 h for first 24 h, then at least every 12 h	Every 4-6 h for first 24 h, then at least every 12 h	Every 4-6 h for first 24 h, then at least every 12 h
Observations during last check	Near dislodgement of needle; addressed by flushing and new covering	No abnormalities	No abnormalities
Day of event in the remdesivir regimen	Day 4	Day 2	Day 2
Time until observation of infiltration	1.5 h after administration of full dosage	During administration; infusion discontinued	5 h after administration of full dosage
Pain	No	Yes	Yes
Swelling	Yes	Yes	Yes
Color	Hematoma	Hematoma	Red
Temperature (by palpation)	Felt cooler	No difference	Felt cooler
Was general care (Table 2) carried out?	Yes	Only marking of area and discontinuation of infusion	Yes
Were hyaluronidase injections administrated?	Yes	Yes	No; observation only
Continuation of remdesivir regimen?	Yes	Yes	Yes, but last (day 5) dose not infused
Time until no more visible signs nor symptoms	Unknown	4 wk	4 wk
Total follow-up duration	6 wk	4 wk	4 wk

Abbreviation: IV, intravenously.

Box 1. Standard General Care in Cases of Extravasation or Infiltration[4]

- Immediately stop the infusion or injection, and do not remove the intravenous catheter.
- Attempt to aspirate the leaked solution with an empty syringe through the catheter.
- Remove the needle.
- Mark the area of infiltration and take a picture.
- Note the hour.
- Elevate the affected body part (for 48 hours) and immobilize it.
- Perform additional care based on the characteristics of the infiltrated agent (Table 1).
- Monitor the patient until the symptoms disappear.