

Long-term sensor-augmented pump therapy for neonatal diabetes mellitus: a case series

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Highlights

- We report three patients with NDM who received SAP therapy from the neonatal period.
- SmartGuard is useful for infants in whom hypoglycemia cannot be identified.
- SAP therapy can provide accurate management and reduce family efforts.

Abstract. Neonatal diabetes mellitus (NDM) is a rare metabolic disorder that is mainly present in the first 6 months of life and necessitates insulin treatment. Sensor-augmented pump (SAP) therapy has been widely used in children with type 1 diabetes mellitus, but its use in patients with NDM is limited. We report three patients with NDM who received SAP therapy using the MiniMed™ 640G system starting in the neonatal period. Two patients were treated for 3 months, and one patient continued treatment up to an age of 22 mo. The MiniMed 640G system can automatically suspend insulin delivery (SmartGuard™ Technology) to avoid hypoglycemia when the sensor glucose level is predicted to approach the predefined threshold. We suggest that SmartGuard Technology is particularly useful for infants in whom hypoglycemia cannot be identified. The MiniMed 640G system automatically records the trends of sensor glucose levels and the total daily dose of insulin, which can make the management more accurate and reduce the family's effort. SAP therapy for patients with NDM automatically prevents severe hypoglycemia and is useful for long-term management; however, attention should be paid to its application.

Key words: continuous glucose monitoring, continuous subcutaneous insulin infusion, hypoglycemia, neonatal diabetes mellitus, sensor augmented pump therapy

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Introduction

Neonatal diabetes mellitus (NDM) is present mainly in the first 6 mo of life because of an underlying monogenic defect, with an incidence of 1 per 89,000 newborns in Japan (1, 2). NDM is classified as transient NDM (TNDM), which spontaneously remits by approximately 18 mo of age and sometimes recurs after adolescence, and persistent NDM (PNDM), which requires lifelong insulin administration.

Sensor-augmented pump (SAP) therapy is a treatment method that combines continuous glucose monitoring (CGM) with continuous subcutaneous insulin infusion (CSII) (3). SAP therapy has been widely used in children with type 1 diabetes mellitus (DM), but its use in patients with NDM is limited (4–6). To the best of our knowledge, there are very few reports of patients with NDM who received SAP therapy in the neonatal period for more than several months. In this study, we report three patients with NDM who received SAP therapy using the MiniMed™ 640G system (Medtronic, Tokyo, Japan) starting in the neonatal period. Two patients were treated for 3 months, and one patient continued treatment up to an age of 22 mo. We used SmartGuard™ Technology on the MiniMed 640G system, which can automatically suspend insulin delivery to avoid hypoglycemia when the sensor glucose level is predicted to approach a predefined threshold.

Methods

Settings of the MiniMed 640G system

The MiniMed 640G system (Medtronic) was used for SAP therapy, using a rapid-acting insulin analog (insulin glulisine). We initially set one basal rate all day and gradually added the different basal rates at different times of the day after observing the daily pattern of changes in blood glucose levels for each patient. We used insulin bolus delivery only when there was marked hyperglycemia.

We used a predictive low-glucose suspension system (SmartGuard Technology) for all patients. We predefined a low sensor glucose threshold of 80 mg/dL and high limit of 250 mg/dL. We gradually adjusted these values for each patient during treatment. We enabled all alert types with the alarm sound ON. The number of daily SmartGuard activations and alerts in the first 30 days for each patient is shown in **Table 1**.

Infusion sets and glucose sensor

We used the Silhouette™ infusion set (13-mm cannula) to administer insulin and inserted the infusion set by pinching the skin (7). It was difficult to insert the infusion set by pinching the skin using the Sil-serter™ infusion device; therefore, we inserted the infusion set diagonally by hand into the outer thigh (**Fig. 1**). We avoided inserting the infusion set into the buttocks

because pressure was applied to the tube when changing diapers, which could lead to insulin overload. To measure glucose levels in the interstitial fluid, we used Enlite™ sensors (8). We inserted the Enlite sensor into the upper buttocks, where the subcutaneous tissues had sufficient thickness (**Fig. 1**). It was difficult to insert the Enlite sensor, which should be inserted perpendicularly to the skin, by hand; thus, we used a Sil-Serter infusion device. The left and right insertion sites of the infusion set and sensor were switched during each replacement.

Genetic testing

Genomic DNA was extracted from the peripheral blood samples of the patients and their parents. To examine chromosome 6q24 abnormalities, we performed microsatellite marker analyses on chromosome 6, including 6q24 critical regions and methylation-specific multiplex ligation-dependent probe (MLPA) methods for 6q24 copy number and methylation changes with the SALSA MS-MLPA Probemix ME033-A1 (MRC Holland, Amsterdam, the Netherlands). In addition, *KCNJ11*, *ABCC8*, and *INS* gene analyses were performed through PCR-direct sequencing. Prior to genetic testing, written informed consent was obtained from the patients' parents.

Case Presentation

Patient 1

A male infant was born at another hospital at 36 weeks' gestation with a birth weight of 1992 g (2.3 percentile), length of 39.0 cm (0.2 percentile), and Apgar scores of 8 and 8 at 1 and 5 min, respectively. The patient was delivered via emergency caesarean section because of a non-reassuring fetal status. On day 14 of life, the patient was diagnosed with hyperglycemia, with blood glucose levels exceeding 400 mg/dL according to routine blood testing. The patient was started on an intravenous insulin infusion 0.05 U/kg/h and transferred to our hospital on day 17 of life.

We switched treatment from intravenous insulin infusion (0.01 U/kg/h) to CSII (total daily dose of insulin [TDD], 0.27 U/kg/d) on the day of transfer. His blood glucose levels fluctuated over a wide range. On day 29 of life, we added real-time CGM (RT-CGM), which resulted in gradual stabilization of blood glucose levels. The patient was discharged on day 35 of life with TDD 0.14 U/kg/d.

Insulin was discontinued on day 67 of life (**Fig. 2A**). At 3 yr of age, there was no recurrence of hyperglycemia during routine examinations and no developmental delay. No skin complications were observed after the SAP therapy. There was no family history of DM, excluding type 2 DM, in the paternal grandmother. Microsatellite marker analysis revealed only paternal inherited markers in the 6q24 region; thus, we diagnosed the patient with paternal uniparental disomy (pUPD)

Table 1. Characteristics and clinical information of three patients

	Patient 1	Patient 2	Patient 3
Characteristics			
Sex	Male	Male	Male
Gestational age	36 wk, 4 d	38 wk, 5 d	39 wk, 3 d
Birth weight	1992 g (2.3%tile)	1936 g (0.1%tile)	2754 g (21.6%tile)
Birth height	39.0 cm (0.2%tile)	44.0 cm (1.3%tile)	50.7 cm (82.2%tile)
Family history	Paternal grand-mother: type 2 DM	None	None
Genetic aberrations	pUPD6	Partial pUPD6	N/A *
Clinical information			
Day of presentation of NDM	Day 14	Day 1	Day 0
Day of SAP therapy initiation	Day 29	Day 14	Day 3
Day of discharge	Day 35	Day 46	Day 59
Day discontinued insulin therapy	Day 67	Day 61	Continuing as of 22 mo old
MiniMed 640G system			
Maximum TDD	0.28 U/kg/d (day 18)	0.38 U/kg/d (day 23)	1.34 U/kg/d (day 73)
Number of daily SmartGuard activation in the first 30 days	3.1 ± 2.0	3.5 ± 1.5	3.5 ± 1.6
Number of daily alerts in the first 30 days	8.9 ± 6.0	13.2 ± 5.5	16.1 ± 6.7
Final settings of the low-glucose threshold in the acute phase	80 mg/dL	80 mg/dL	90 mg/dL
Final settings of the high-glucose limit in the acute phase	250 mg/dL	250 mg/dL	300 mg/dL

DM, diabetes mellitus; N/A, not applicable; SAP, sensor-augmented pump; TDD, total daily dose of insulin; UPD, paternal uniparental disomy. * Microsatellite marker analysis of chromosome 6 shows normal biparental inheritance. There were no disease-associated variants in the *KCNJ11*, *ABCC8*, and *INS* genes.



Fig. 1. Silhouettex™ infusion set inserted in the thigh and the Enlite™ sensor inserted in the upper buttock.

of chromosome 6q24, suggesting TNDM (9, 10). There was no disease-associated variant in the *KCNJ11* gene (Table 1).

Patient 2

A male infant was born at another hospital at 38 wk of gestation with a birth weight of 1936 g (0.1 percentile), length of 44.0 cm (1.3 percentile), and Apgar scores of 8 and 9 at 1 and 5 min, respectively. At 4 h of age, the patient was diagnosed with hypoglycemia with a blood glucose level of 36 mg/dL, and glucose infusion was started. Conversely, his blood glucose level reached 372 mg/dL at 20 h of age, and glucose infusion was discontinued. An intravenous insulin infusion (0.05 U/kg/h) was started at 29 h of age. The insulin infusion rate was gradually decreased, and insulin was discontinued on day 11. The patient was transferred to our hospital on Day 12.

We initiated RT-CGM on the day of transfer. His blood glucose levels gradually increased to more than 250 mg/dL, and we started CSII (TDD, 0.06 U/kg/d) on day 14 of life. The insulin dose was gradually increased, and the maximum TDD reached 0.38 U/kg/d on day 23 of life. The patient was discharged on day 35 of life with TDD 0.16 U/kg/d.

Insulin was discontinued on day 61 (Fig. 2B). Temporary eczema was sometimes observed in the thigh, where the tape was attached during SAP therapy. At 3 yr of age, there was no recurrence of hyperglycemia during routine examinations and no developmental delay. The patient had no family history of DM. Microsatellite marker analysis of chromosome 6 revealed biparental

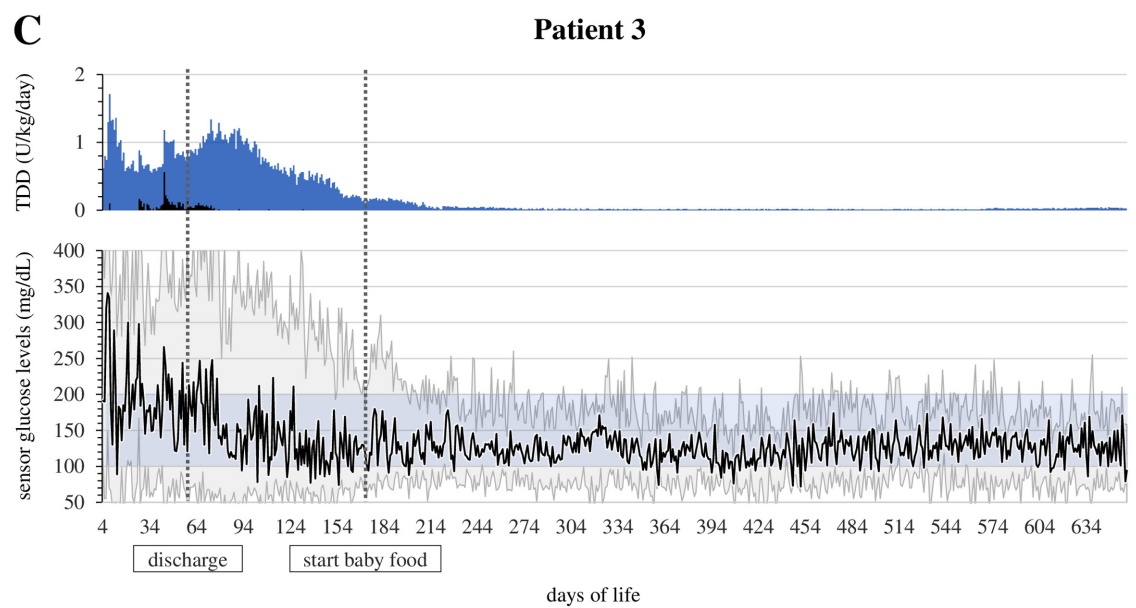
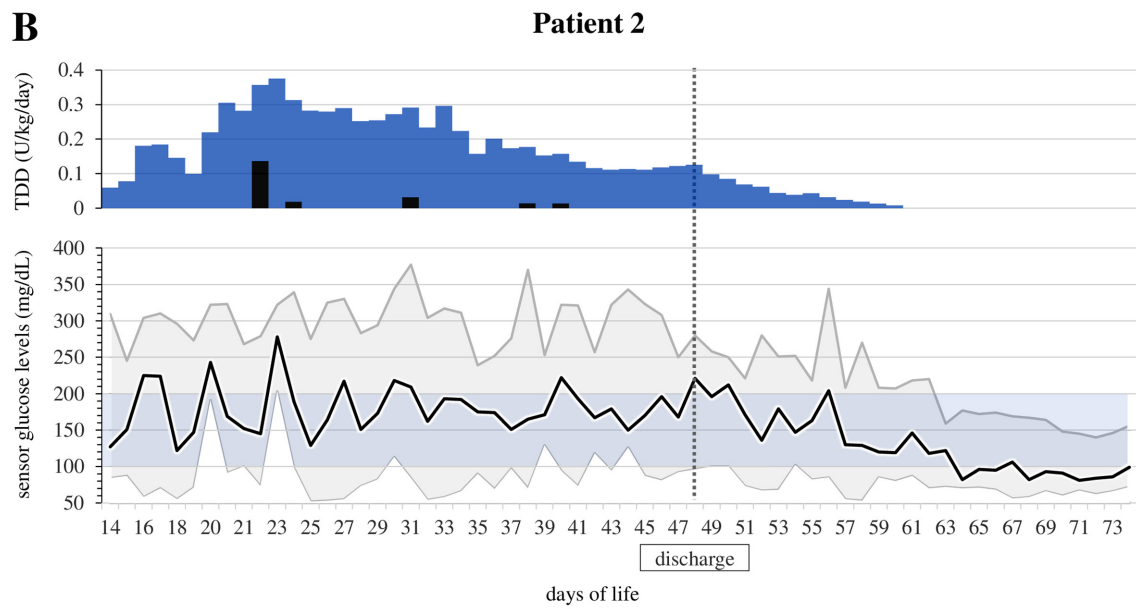
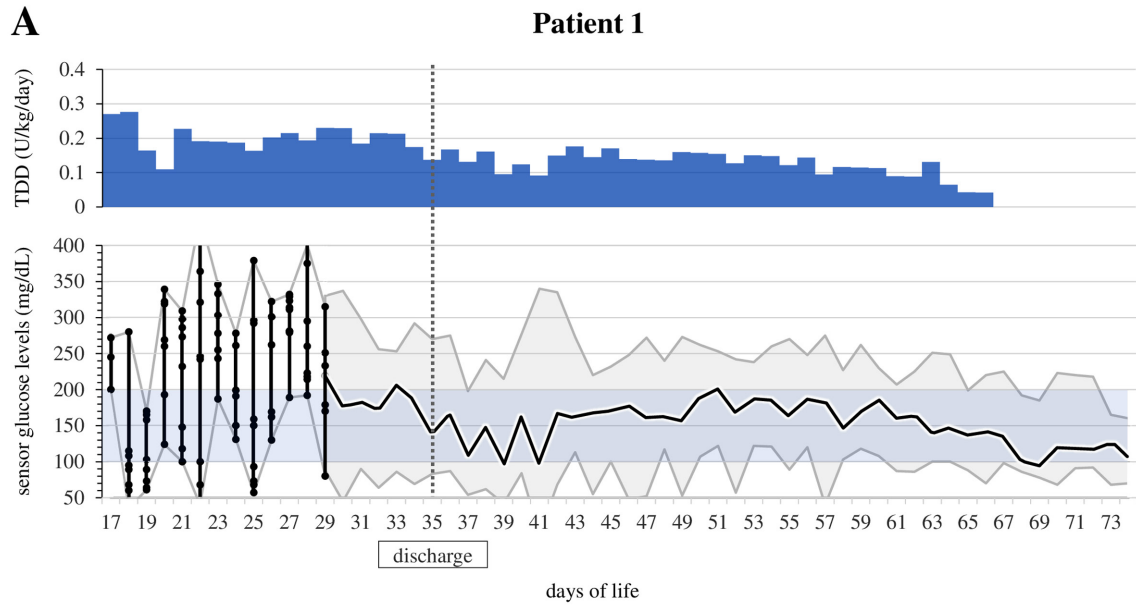


Fig. 2. Trends of the total daily dose of insulin (TDD) and sensor glucose levels. (A) Patient 1. (B) Patient 2. (C) Patient 3. The upper row of each patient image presents TDD (U/kg/d), and the blue and black areas show basal doses and bolus doses of insulin, respectively. The lower row presents sensor glucose levels (mg/dL). The horizontal axis indicates patient age in days. The gray-shaded area in the sensor glucose levels is the range between the minimum and maximum levels of the day, and the blue-shaded area is the range of 100–200 mg/dL. The black line denotes the average sensor glucose levels of the day. At an age of 17–29 d in patient 1, filled circles indicate the measured blood glucose levels.

inherited markers in the short arm and only paternal inherited markers in the long arm in all informative alleles from which the origin of the parents could be identified. The 6p21.2 region was also considered to be inherited biparentally. There were only paternally inherited markers in the 6q25 region. Telomeres after the 6q26 region were undecidable because both parents had the same polymorphism. Therefore, we diagnosed partial pUPD of chromosome 6, including the 6q24 region, which suggests TNDM (**Table 1**) (9, 10). There were no disease-associated variants in the *KCNJ11*, *ABCC8*, and *INS* genes.

Patient 3

A male infant was born at another hospital at 39 wk of gestation with a birth weight of 2754 g (21.6 percentile), length of 50.7 cm (82.2 percentile), and Apgar scores of 8 and 10 at 1 and 5 min, respectively. Umbilical arterial blood gas analysis revealed a blood glucose level of 151 mg/dL. His blood glucose level at 2 h of age was 167 mg/dL, which increased to 212 mg/dL at 4 h of age. The patient was transferred to our hospital 6 h after birth.

On physical examination, the patient was lethargic with cold hands and feet. Venous blood gas analysis revealed the following: glucose, 192 mg/dL; pH, 7.336; and HCO_3^- , 17.7 mEq/L. We started intravenous infusion of normal saline and continued formula feeding. At 14 h of age, the results of blood testing were as follows: glucose, 315 mg/dL; pH, 7.429; HCO_3^- , 11.9 mEq/L; pCO_2 , 18.6 mmHg; and beta-hydroxybutyrate, 5.2 mmol/L. The patient was diagnosed with diabetic ketoacidosis and initiated an intravenous insulin infusion (0.05 U/kg/h). The patient's lethargy gradually improved and ketoacidosis resolved after 12 h of insulin infusion. We started RT-CGM on day 2 of life and switched from the intravenous insulin infusion to CSII (TDD, 0.62 U/kg/d) on day 4 of life. It was difficult to control the sensor glucose levels, which fluctuated drastically from < 40 to > 400 mg/dL. Insulin dose tended to increase from approximately day 40 of life, concomitant with increased feeding. After the family understood the procedure for SAP therapy and the strategy for managing hyperglycemia and hypoglycemia, the patient was discharged on day 59 of life with TDD 0.79 U/kg/d.

During follow up, the insulin dose was gradually increased, and the maximum TDD reached 1.34 U/kg/d on day 73 of life (**Fig. 2C**). Subsequently, the insulin dose decreased, and we attempted to discontinue insulin at 7 mo of age. However, this was unsuccessful, and

the insulin dose started to increase from 20 mo of age. The patient required an insulin dose of approximately 0.04 U/kg/d as of 22 mo of age, suggesting a diagnosis of PNDM. The patient showed normal development at 22 mo of age. Temporary eczema and erythema were sometimes observed in the thigh and buttocks, where the tapes were attached.

The patient had no family history of DM. Microsatellite marker analysis of chromosome 6 revealed normal biparental inheritance. There were no disease-associated variants in the *KCNJ11*, *ABCC8*, and *INS* genes (**Table 1**).

Ethics of experimentation

All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committees and the Helsinki Declaration, as revised in 2013.

Informed consent

Informed consent to publish the patient's data, photographs, and genetic testing results was obtained from the patient's parents.

Discussion

The patients were numbered in the order of admission to our facility. We will discuss the benefits and drawback of SAP therapy for NDM.

One of the difficulties in managing patients with NDM is that their blood glucose levels fluctuate drastically because of frequent intake and variability in the quantity of intake, particularly in the acute phase. Long-term hyperglycemia should be avoided, but attention should be paid to hypoglycemia caused by the excessive effects of insulin. RT-CGM plays a beneficial role in the early detection of hypoglycemia and in reducing the duration of hypoglycemia episodes in low-birth-weight infants (11, 12). The MiniMed 640G system can be programmed to automatically suspend insulin delivery (SmartGuard Technology) to avoid hypoglycemia when the sensor glucose level is predicted to approach or reach the predefined threshold (3). We predefined the low threshold as 80 mg/dL and started management aimed at achieving blood glucose levels of 100–200 mg/dL. During the first 30 days of SAP therapy, SmartGuard Technology was activated approximately three times per day in all patients (**Table 1**). In contrast

to adults who are capable of determining the symptoms of hypoglycemia and attempt to manage the condition themselves, infants cannot identify the symptoms of hypoglycemia. If adults caring for patients with NDM do not recognize hypoglycemia, treatment may be delayed. Although previous reports mentioned that SmartGuard Technology can prevent hypoglycemia in patients with type 1 DM, including children, we suggest that this system is particularly useful for patients with NDM who have difficulty detecting hypoglycemia (13–15).

We used only basal insulin with several basal rates, whereas a previous report treated patients with basal-bolus insulin therapy using carbohydrate counting (16). In our experience, it was not easy to predict the trend of the blood glucose levels after each feeding. Blood glucose levels sometimes did not increase significantly, even after feeding, but sometimes rose slowly and dramatically. We determined that bolus insulin administration at each feeding may not always be effective, but rather would increase the risk of hypoglycemia and destabilize glycemic control. Therefore, we decided to only use basal insulin and administer bolus insulin only when extreme hyperglycemia occurred. When we use basal-bolus insulin therapy for patients with NDM who need frequent feeding in the neonatal period, we should keep in mind the risk of hypoglycemia after insulin bolus administration.

The MiniMed 640G system is designed to alert users when glucose concentrations are higher or lower than the specified thresholds or when time series data meet specified criteria (3). These alerts quickly made us aware of the presence of hyperglycemia and hypoglycemia. However, we experienced a barrage of alerts (approximately 10–15 per day; **Table 1**). These frequent alerts were psychologically burdensome, especially in the acute phase when blood glucose levels were not stable. Mastrototaro *et al.* suggested that we should consider forgoing alerts or only using the low alert for the initial 1–2 wk of sensor use (17). As mentioned previously, infants cannot notify their caregivers of hypoglycemic symptoms. Thus, it is not recommended to deactivate all alarms, but setting only low-glucose alerts may permit treatment to continue with a lower mental burden on alarms.

Although the published experience of SAP therapy for patients with NDM is limited, SAP therapy has been demonstrated to be safe and more effective in obtaining adequate metabolic control in patients with NDM (16, 18, 19). For the long-term management of patients with NDM, it is extremely important to confirm their daily blood glucose levels and insulin doses. The MiniMed

640G system automatically records sensor glucose levels and TDD; therefore, we can easily visualize the trend, as presented in **Fig. 2**. The number of insulin bolus doses and the amount administered, measured blood glucose levels, number of insulin doses (and the times of administration), and other variables are also recorded in detail. It is more accurate and less burdensome to automatically record these data than to obtain this information from the families of patients, making the system suitable for the long-term management of NDM.

SAP therapy is often associated with skin complications (20–22). We started SAP therapy in the neonatal period in all patients and continued treatment for several months. None of our patients discontinued SAP therapy because of skin complications, although temporary eczema or erythema caused by the sticking tape was sometimes observed. We suggest that SAP therapy be performed safely with careful skin observation, even in patients with genetic abnormality on chromosome 6q24, who usually have low birth weight, such as patients 1 and 2 (9, 10, 23). According to prior research, no skin or tissue problems occurred after continuous glucose monitoring was started within the first 24 h of life and continued up to 6 days for preterm and extremely-low-birth-weight infants (24). Further reports are needed to determine whether the skin of extremely preterm infants or extremely-low-birth-weight infants can tolerate SAP therapy for more than a few months.

Conclusion

SAP therapy using the MiniMed 640G system with SmartGuard Technology for patients with NDM prevents hypoglycemia from developing, which is particularly useful in infants who cannot identify hypoglycemia themselves. Responding to frequent alerts was mentally burdensome; however, adjusting the settings may reduce the burden on alarms. The trends of sensor glucose levels and TDD are automatically recorded, which can make management more accurate and reduce the family's effort. During prolonged SAP therapy, it is necessary to monitor skin complications.

Conflict of interests: The authors declare no potential conflicts of interest.

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