Received: 8 February 2024 | Revised: 16 July 2024 | Accepted: 30 July 2024

https://doi.org/10.1016/j.rpth.2024.102542

REVIEW

Comprehensive literature review of protein C concentrate use in patients with severe congenital protein C deficiency

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Handling Editor: Dr Kristen Sanfilippo

Abstract

Severe congenital protein C deficiency (SCPCD) is a rare disorder associated with life-threatening purpura fulminans and disseminated intravascular coagulation that typically present within hours after birth. Treatment options for patients with SCPCD include replacement therapy with a plasma-derived protein C concentrate. In this targeted literature review, we summarize information on the use of protein C concentrate as long-term prophylaxis (>1 week of treatment) for patients with SCPCD. In total, 18 publications were included in the review, of which 15 were case studies. Treatment with protein C concentrate (Ceprotin; Baxalta US Inc, a Takeda company; Takeda Manufacturing Austria AG) was reported in 11 publications, and treatment with protein C concentrate (Protexel; LFB Biomedicaments) was reported in 2 publications. One publication reported on both Ceprotin and Protexel. Details of protein C concentrate treatment regimens, including the dose, administration frequency, and route of administration, were reported in 11 publications. Dosing regimens varied across all 11 publications, possibly due to different protein C trough levels among patients or the administration of concomitant medications. Seven of the 11 publications reported on patients who initially received intravenous protein C concentrate and subsequently switched to subcutaneous administration. Treatment outcomes with protein C concentrate were generally favorable, including the prevention of coagulopathy and thrombosis and the healing of cutaneous lesions. Three adverse events in 1 publication were identified as being possibly related to Ceprotin administration. Although published data are limited, this review provides valuable insights into the treatment of patients with SCPCD in clinical practice, including protein C concentrate dosing regimens, administration routes, and associated clinical outcomes.

KEYWORDS
disseminated intravascular coagulation, protein C deficiency, purpura fulminans, retinal hemorrhage, venous thrombosis

Essentials

- Severe congenital protein C deficiency can be treated with intravenous replacement therapy.
- This review summarizes protein C concentrate replacement therapy reported in 18 publications.
- Regimens varied across the publications; 7 reported switching from intravenous to subcutaneous treatment.
- Treatment outcomes with protein C concentrate were generally favorable.

1 | INTRODUCTION

Protein C is a vitamin K–dependent anticoagulant zymogen and precursor of activated protein C that is involved in the regulation of thrombin formation [1]. A deficiency in protein C results in decreased downregulation of thrombin generation by factor (F)Va and FVIIIa during the augmentation phase of coagulation activation [2].

Severe congenital protein C deficiency (SCPCD) is a rare autosomal recessive disorder caused by either homozygous or compound heterozygous mutations in the *PROC* gene located on chromosome 2(q13-14) [2]. Patients with SCPCD typically present with purpura fulminans and disseminated intravascular coagulation within hours after birth, although symptoms can also develop later in infancy [2,3]. The lesions associated with purpura fulminans initially present as small ecchymoses, which rapidly develop into larger purple-black lesions with bullae. If left untreated, these lesions ultimately become necrotic and life-threatening [4]. SCPCD is also associated with an increased risk of thromboembolic events [2–4]. Cerebral vessel thrombosis can result in cerebral infarction, often with secondary hemorrhage and hydrocephalus, causing long-term neurologic sequelae [3]. Patients with SCPCD are also at risk of blindness as a result of retinal vessel thrombosis [3].

Treatment options for patients with SCPCD include heparin/low-molecular-weight heparin, vitamin K antagonists, fresh frozen plasma, and replacement therapy with plasma-derived protein C concentrate [2,3]. The International Society on Thrombosis and Haemostasis recommendations and guidelines for the diagnosis and management of SCPCD recommend protein C concentrate as the preferred option for long-term prophylaxis (LTP) in the management of patients with SCPCD [3]. Subcutaneous (s.c.) rather than intravenous (i.v.) administration is also recommended as the preferred administration route for protein C concentrate owing to problems associated with central venous line devices [3].

Protein C concentrate (Ceprotin; Baxalta US Inc, a Takeda company; Takeda Manufacturing Austria AG) is prepared from human plasma using a multistep purification process, including monoclonal antibody immune affinity chromatography, to yield a highly purified protein C concentrate, which is indicated for the prophylaxis and treatment of patients with SCPCD [5,6]. For LTP, 45 to 60 IU/kg every 12 hours is recommended, although the dose of Ceprotin should be adjusted according to the pharmacokinetic (PK) profile and plasma protein C levels of each individual patient [5,6]. Although Ceprotin is approved only for i.v. administration [5,6], s.c. administration has been reported in clinical practice [7–9].

Protein C concentrate (Protexel, LFB Biomedicaments) is another replacement therapy available in Europe that is indicated in neonates with SCPCD experiencing venous thrombosis and in adults with SCPCD switching from heparin to vitamin K antagonists [10]. Protexel is also indicated for the prevention of thrombosis in patients with heterozygous SCPCD during surgical operations and cesarean sections when heparin or vitamin K antagonists are either contraindicated or ineffective [10]. As a preventive treatment for severe protein C deficiency, 100 IU/kg/d, 1 to 3 times a week, is recommended [10]. As with Ceprotin, Protexel is only approved for i.v. administration [10].

The main aim of this review was to extract and summarize information on the use of protein C concentrate as LTP for the management of patients with SCPCD.

2 | METHODS

This review was conducted following the Population, Intervention, Comparison, Outcome, and Study design framework [11], with searches run in the MEDLINE, Embase, and BIOSIS Previews electronic databases. The search eligibility criteria are shown in Table 1.

Publications identified from the literature review were selected by 3 reviewers (M.K.O., A.W., and V.T.). Publications were excluded if they did not report any long-term use of protein C concentrate, defined as any treatment lasting for >1 week. Long-term use is typically defined as treatment ≥3 months in duration; however, owing to the limited number of published sources, a shorter treatment duration was used in this review to try to identify as many publications as possible reporting on the treatment of patients with SCPCD using protein C concentrate. No date or language restrictions were applied.

Where available, information on the publication, patient population, administered interventions, and treatment outcomes were extracted from each publication that met the eligibility criteria. Extracted information included whether the publication was a full-text publication or a congress abstract, study objectives, study design, country, inclusion/exclusion criteria, and conclusions. Patient information included the number of patients reported in each publication as well as patient age and sex (male/female). For administered interventions, the dose, administration frequency, and route of administration of protein C concentrate were extracted, along with details of any concomitant medications. Reported treatment outcomes encompassing efficacy, safety, and patient quality of life were also extracted. Efficacy outcomes included the extent to which skin lesions resolved during treatment with

TABLE 1 Eligibility criteria.

PICOS	Criteria
Population	• Children and adults diagnosed with homozygous or compound heterozygous SCPCD
Intervention	• Protein C concentrate
Comparison	• None
Outcomes	• Efficacy outcomes • Safety outcomes • Health-related quality of life • Activities of daily living
Study design	• Observational studies and case reports • All studies with no long-term[a] use of protein C concentrate were excluded

PICOS, Population, Intervention, Comparison, Outcome, and Study design; SCPCD, severe congenital protein C deficiency.
[a]Long-term was defined as any treatment lasting for >1 week.

protein C concentrate. Safety outcomes included any reported adverse events (AEs), serious AEs, and the development of antibodies against protein C. Data were extracted by 1 reviewer (M.K.O.) and validated independently by a second reviewer (A.W.). Any discrepancies were resolved through discussions with a third reviewer (V.T.).

3 | RESULTS

3.1 | Search results

In total, 462 records were identified in the initial database search, of which 21 publications met the eligibility criteria and 18 were included in the review (Figure and Supplementary Table S1). Of the 18 publications included in the review, 7 were conference abstracts [12–18], and 11 were full-text publications [7–9,19–26]. The 3 publications that met the eligibility criteria but were excluded from the review were abstracts [27–29]. The data reported in each of these abstracts were subsequently reported in full-text publications that were included in the review [9,15,25]; therefore, these abstracts were excluded to avoid repetition.

3.2 | Publications

Fifteen of the 18 publications were case studies [7–9,12–14,16–18,20,22–26], 1 was a literature analysis [19], 1 was a multicenter retrospective study [21], and 1 was a noninterventional registry study [15] (Supplementary Table S1). Overall, 11 publications reported on patients with SCPCD who had received treatment with Ceprotin [7–9,12,15,20,22–26], and 2 publications reported on patients who had received treatment with Protexel [14,21]. One publication reported on both Ceprotin and Protexel [19]. In addition, 4 publications reported on the treatment of patients with SCPCD using an unspecified protein C concentrate [13,16–18]. Twelve publications were published after 2005 [7,9,12,13,15–18,20,21,24,25], and 3 were multinational [9,15,22].

3.3 | Patient information

Two publications reported solely on adult patients (≥18 years old) with SCPCD [20,26]. Ten publications reported exclusively on female patients [8,14,16–18,20,23–26], and 2 publications reported solely on male patients with SCPCD [7,12]. Purpura fulminans was commonly reported at clinical presentation, with many patients also experiencing thromboembolic events (Table 2). Incidences of visual impairment or blindness among patients were reported in 9 publications [7–9,13,14,21–23,25].

3.4 | Treatment with protein C concentrate

Details of protein C concentrate treatment regimens, including the dose, administration frequency, and route of administration, were reported in 11 publications (Table 3). Nine publications reported on Ceprotin [7–9,12,20,22–25], and 2 reported on an unspecified protein C concentrate [17,18]. The initiation of treatment with protein C concentrate within the neonatal period (<28 days old) was reported in 8 publications [7–9,17,22–25]. Protein C activity levels prior to treatment initiation were low in all patients for whom these data were reported (Table 3).

Dosing regimens varied across all 11 publications (Table 3). For the i.v. administration of Ceprotin, doses included 100 IU/kg every 12 hours [24], 25 IU/kg twice weekly [12], and 90 U/kg 3 times per week [25]. Dosing regimens for the s.c. administration of Ceprotin included 100 IU/kg every 12 hours [24] and 350 IU/kg every 48 hours [23]. Seven publications reported on patients who initially received Ceprotin via i.v. administration and subsequently switched to s.c. administration [7–9,20,22–24]. In all 7 publications, the decision to switch to s.c. administration was associated with challenges encountered with i.v. administration, such as venous access or line-related infections [7–9,20,22–24]. In another case study, attempts to switch the patient from i.v. to s.c. administration of an unspecified protein C concentrate failed [17]. No explanation was given as to why switching to s.c. administration could not be achieved for this patient [17].

Of the 7 publications not included in Table 3, 4 provided either no or limited information on protein C concentrate treatment regimens [13,15,16,19]. The 3 other publications were excluded as the route of administration, either i.v. or s.c., was not disclosed [14,21,26]. Two of these publications were case studies, one of which described a patient who received 50 IU/kg Protexel twice weekly concomitant with an unspecified oral anticoagulant [14]. The other case study described the experience of a patient who received 50 IU/kg Ceprotin 3 times per week during pregnancy [26]. The third publication was a

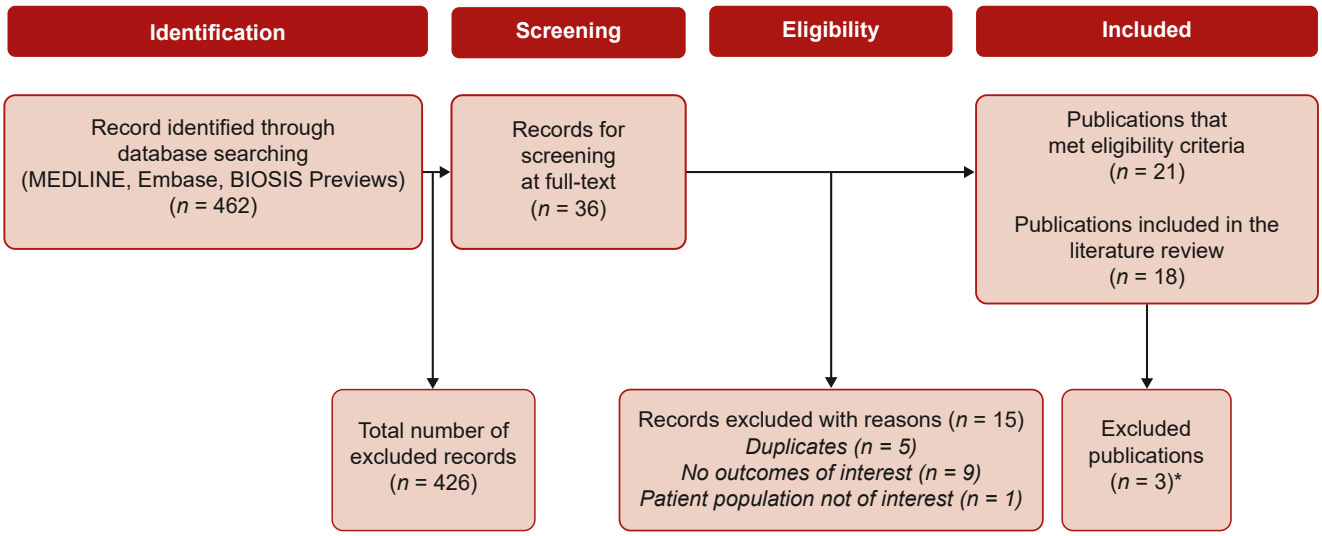

FIGURE Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram showing the identification of publications included in the literature review. *The 3 publications that met the eligibility criteria but were excluded from the review were abstracts. The data reported in each of these abstracts were subsequently reported in full-text publications that were included in the review.

multicenter retrospective study that reported on 9 patients who received treatment with Protexel [21]. In the study, 30 replacement therapy courses were recorded with a mean dose ranging between 24 and 90 IU/kg/d for prophylactic courses and 51 and 209 IU/kg/d for treatment courses [21].

3.5 | Outcomes

Table 4 summarizes the efficacy and safety outcomes reported in each publication following treatment with protein C concentrate. Quality-of-life outcomes were not commonly reported in the literature. Protein C concentrate was generally effective in the treatment of patients with SCPCD, with reported outcomes including the prevention of coagulopathy and thrombosis, and the healing of cutaneous lesions (Table 4).

In terms of safety, 1 abstract reporting on data collected from a noninterventional registry noted that 83 AEs occurred in 17 patients during treatment with Ceprotin, of which 3 events experienced by 1 patient were considered possibly related to treatment administration. The 3 events were abdominal pain, pain in the extremity, and purpura fulminans, of which abdominal pain and pain in the extremity were considered serious AEs [15]. Another publication reporting on the experience of 14 patients who had received treatment with Ceprotin noted that 3 patients experienced adverse effects: 1 patient experienced induration at the injection site; 1 patient, who was also receiving low-molecular-weight heparin, developed a hematoma; and 1 patient developed an infection at the injection site [9]. This publication did not specify whether any of these events were related to Ceprotin [9]. A literature analysis reported that among 79 patients treated with Ceprotin, there were 10 cases of moderate allergic reaction and 12 cases of hemorrhage, although the publication also acknowledged that it was unclear whether the reported bleeding events were treatment-related [19]. This publication also reported on the experience of 1 patient who received treatment with Protexel in combination with a vitamin K antagonist [19]. In the first year of treatment, this patient experienced 3 episodes of lower-limb thrombosis, which were considered possibly related to underdosing of protein C [19].

Another abstract reporting on a patient case study observed that while the patient was receiving warfarin and 80 IU/kg/d of an unspecified protein C concentrate via i.v. administration, any decrease in the dose or increase in the administration interval led to a rapid increase in D-dimer and complications with the catheter [17]. The development of antibodies against protein C was not reported in any of the 18 publications included in this review [7–9,12–26].

4 | DISCUSSION

Overall, this review identified 18 publications reporting on the treatment of patients with SCPCD using protein C concentrate, of which the majority were case studies and 39% were conference abstracts. Most publications reported on Ceprotin. The reported Ceprotin dosing regimens varied greatly, regardless of the administration route. This variation might suggest that treatment was tailored to each individual patient. Different baseline protein C trough levels among patients with SCPCD and the administration of concomitant medications, such as anticoagulants, may also explain the variation in dosing regimens.

Only 3 publications reported on the use of Protexel [14,19,21]. One case study reported on the experience of a 34-month-old patient with SCPCD who, from the age of 18 months, received treatment with 50 IU/kg twice-weekly Protexel prophylaxis in combination with an unspecified oral anticoagulant [14]. Another was a literature analysis that did not provide any detailed information on Protexel dosing

TABLE 2 Patient information.

Author and year of publication	Patients, *n*	Male, *n* (%)	Female, *n* (%)	Patient population[a]	Clinical presentation	Visual impairment
Prescrire Editorial Board [19],[b] 2003	Unclear[c]	NR	NR	Pediatric and adult	PF, cutaneous necrosis, DIC, and thromboembolic events	NR
Aytac et al. [12], 2018	1	1 (100)	0 (0)	Pediatric	Recurrent DVT since the age of 2; history of skin necrosis	NR
Boey et al. [20], 2016	1	0 (0)	1 (100)	Adult	Unprovoked proximal left leg DVT	NR
Boz et al. [13], 2019	6[d]	4 (66.7)	2 (33.3)	NR	PF typically seen in neonatal period for all 6 patients	Blindness reported in 5 patients[e]
Chambost et al. [14], 1997	1	0 (0)	1 (100)	Pediatric	Thrombotic purpura on left leg 24 h after birth; evidence of DIC	Bilateral retinal hemorrhages secondary to retinal arterial occlusion—retinal damage resulted in total blindness
de Kort et al. [7],[f] 2011	1	1 (100)	0 (0)	Pediatric	PF on feet and scalp; evidence of DIC	Bilateral vitreous hemorrhage resulting in bilateral retinal detachment and total blindness
Dreyfus et al. [22], 1995	9	3 (33.3)	6 (66.7)	Pediatric	PF, evidence of DIC, and thromboembolic events	5 patients were completely blind in both eyes; 1 patient was partially blind
Dreyfus et al. [21], 2007	9	5 (55.6)	4 (44.4)	Pediatric and adult	PF and thromboembolic events	Blindness mentioned in 1 patient
Manco-Johnson et al. [15], 2016	25	13 (52)	12 (48)	Pediatric and adult	Primarily thromboembolic events and PF	NR
Mathias et al. [8],[f] 2004	2	0 (0)	2 (100)	Pediatric	Patient 1 Purpuric rash over feet, legs, hands, scalp; evidence of DIC Patient 2 PF within 24 h after birth; periventricular infarction	Patient 1 Behaviorally blind with extensive bilateral vitreous hemorrhages and bilateral retinal detachment Patient 2 Behaviorally blind with total bilateral retinal detachment
Minford et al [9],[f] 2014	14	1 (7.1)[g]	1 (7.1)[g]	Pediatric	Varying combinations of PF (*n* = 10), cerebral ischemia, infarction, or hemorrhage (*n* = 6), eye involvement (*n* = 9), and renal vein thrombosis (*n* = 1)	Blindness/visual impairment reported in 12 patients
Özdemir et al. [16], 2017	1	0 (0)	1 (100)	Pediatric	Progressive skin necrosis on legs; intracranial and retinal hemorrhage	NR
Richards et al. [26], 1997	1	0 (0)	1 (100)	Adult	No significant past medical history Left calf DVT at first pregnancy with subsequent postpartum PE[h]	NR

(Continues)

TABLE 2 (Continued)

Author and year of publication	Patients, *n*	Male, *n* (%)	Female, *n* (%)	Patient population[a]	Clinical presentation	Visual impairment
Sanz-Rodriguez et al. [23],[f] 1999	1	0 (0)	1 (100)	Pediatric	PF; bilateral vitreous hemorrhages; area of brain infarction in right parietotemporal lobe; evidence of DIC	Patient was blind
Shah et al. [24], 2016	1	0 (0)	1 (100)	Pediatric	PF on scalp, thighs, and legs; evidence of DIC	NR
Tcheng et al. [25], 2008	2	0 (0)	2 (100)	Pediatric	Patient 1 PF within 24 h after birth; evidence of DIC; intraventricular hemorrhage and multiple areas of parenchymal hemorrhage	Patient 1 Clinically blind; bilateral vitreous hemorrhages with retinal detachment
					Patient 2 PF within 24 h after birth; evidence of DIC; bilateral periventricular hemorrhages; right renal dysgenesis with hypertension	Patient 2 Bilateral detached retinas
Veron et al. [17], 2019	1	0 (0)	1 (100)	Pediatric	Prenatal diagnosis of CNS hemorrhage; developed PF at 12 h old	NR
Williams et al. [18], 2009	1	0 (0)	1 (100)	Pediatric	Episode of hematuria in the first week of life; developed extensive PF	NR

CNS, central nervous system; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; NR, not reported; PE, pulmonary embolism; PF, purpura fulminans.
[a]Adult patients were defined as those ≥18 years old; pediatric patients were defined as those <18 years old.
[b]This publication does not report any authors.
[c]Efficacy data were reported for 22 patients treated with Ceprotin and 10 patients treated with Protexel. Safety data were reported for 79 patients who received Ceprotin.
[d]Only 2 out of the 6 patients received treatment with protein C concentrate. The sex of these 2 patients was not specified.
[e]It is unclear which patients received treatment with protein C concentrate.
[f]Patients from the studies by de Kort et al. [7], Mathias et al. [8], and Sanz-Rodriguez et al. [23] were included in the study by Minford et al. [9].
[g]Sex was not reported for 12 of the 14 patients.
[h]Patient subsequently experienced 5 miscarriages.

regimens apart from mentioning a pediatric patient who received long-term treatment with 1 or 2 infusions of 60 IU/kg Protexel per week in combination with an unspecified vitamin K antagonist [19]. The third publication was a multicenter retrospective study that evaluated the efficacy and safety of Protexel in 9 patients with SCPCD [21]. In the study, 30 replacement therapy courses were recorded with a mean dose ranging between 24 and 90 IU/kg/d for prophylactic courses and 51 and 209 IU/kg/d for treatment courses [21].

Although Ceprotin is only currently approved for i.v. administration [5,6], a number of publications reported on patients who switched from i.v. to s.c. administration [7–9,20,22–24]. The International Society on Thrombosis and Haemostasis recommendations and guidelines for the diagnosis and management of SCPCD recommend s.c. administration as the preferred administration route for protein C concentrate owing to problems associated with central venous line devices [3]. Consistent with this recommendation, the decision to switch to s.c. administration was associated with challenges encountered with i.v. administration [7–9,20,22–24].

Treatment outcomes for Ceprotin were generally favorable. Three AEs in 1 publication were identified as being possibly related to Ceprotin administration [15]. Two other publications mentioned adverse effects/complications, but whether these events were related to Ceprotin was not clearly established [9,19]. None of the 3 publications reporting on Protexel mentioned any adverse effects/complications associated with this replacement therapy [14,19,21].

Since the literature review was conducted, 2 case studies detailing the use of protein C concentrate for the treatment of patients with SCPCD have been published [30,31]. One case study

TABLE 3 Protein C concentrate dosing regimens.

Author and year of publication	Patient age at which protein C concentrate started	Protein C concentrate via i.v. administration (Any concomitant treatment)	Protein C activity levels prior to treatment	Protein C activity levels after i.v. administration of protein C concentrate	Protein C concentrate via s.c. administration (Any concomitant treatment)	Protein C activity levels after s.c. administration of protein C concentrate
Ceprotin						
Aytac et al. [12], 2018	≥13 y old	25 IU/kg twice weekly (2 × 150 mg daily oral dabigatran etexilate)	6% (normal range, 70%-130%)	Around 10% after 42 h	NR	NR
Tcheng et al. [25], 2008 Patient 1	NR	550 IU/dose daily decreased to 85 IU/kg 3 times per week (LMWH; treatment details NR)	8%	21% (24 h after 85 U/kg dose)	NR	NR
Tcheng et al. [25], 2008 Patient 2	~1 d old	156 IU/kg every 12 h switched to 90 U/kg/dose 3 times per week	5%	31% (24 h after 45 U/kg dose)	NR	NR
Boey et al. [20], 2016	≥18 y old	100 U/kg/wk (6000 units) (warfarin; INR target, 2.5-3.5) 100 U/kg/wk (6000 units) (rivaroxaban; treatment details NR) 5000 U/wk (rivaroxaban; treatment details NR)	3% (normal range, 65%-130%) Chromogenic assay	Trough levels of 2%-3% Trough levels of 12%-18%	5000 units administered in 2 weekly doses	C_{max} of 25% at 24 h
de Kort et al. [7],[a] 2011	5 d old	500 IU (180 IU/kg) 3 times daily; dose changed to 250 IU (90 IU/kg) 4 times daily	0.02 IU/mL (normal, 0.42 IU/mL)	Between 0.14 and 0.31 U/mL	750 IU once daily	Between 0.14 and 0.31 U/mL
Mathias et al. [8],[a,b] 2004 Patient 1	~21 d old	50 IU/kg 3 times daily, increased to 200 IU/kg twice daily	5 IU/dL (normal range, 37-81 IU/dL)	Dose increased to achieve trough levels >25 IU/mL	500 IU (~70 IU/kg), increased to 2000 IU (290 IU/kg) every 48 h	Trough levels of 25 IU/mL achieved with 2000 IU every 48 h
Mathias et al. [8],[a,b] 2004 Patient 2	10 d old	50 IU/kg 3 times daily, increased to 100 IU/kg	5 IU/dL	Dose increase to 100 IU/kg achieved trough levels of 40-50 IU/dL	2000 IU every 48 h	Trough levels <25 IU/dL
Sanz-Rodriguez et al. [23],[a] 1999	9 d old	20 IU/kg every 6 h, increased to 80 IU/kg twice daily 80 IU/kg every 12 h, lowered to 80 IU/kg twice weekly (acenocoumarol; INR target, 3.0-4.2)	<0.01 IU/mL Chromogenic assay	Dose increased to maintain protein C chromogenic activity >0.80 IU/mL	350 IU/kg every 48 h	C_{max} for a 350 IU/kg dose: 0.59 IU/mL

(Continues)

TABLE 3 (Continued)

Author and year of publication	Patient age at which protein C concentrate started	Protein C concentrate via i.v. administration (Any concomitant treatment)	Protein C activity levels prior to treatment	Protein C activity levels after i.v. administration of protein C concentrate	Protein C concentrate via s.c. administration (Any concomitant treatment)	Protein C activity levels after s.c. administration of protein C concentrate
Shah et al. [24], 2016	3 d old	100 IU/kg every 6 h (UFH; treatment details NR) 100 IU/kg every 12 h (enoxaparin 1 mg/kg every 12 h)	<10% (age-specific reference range, 24%-44%)	Dose titrated to achieve trough protein C levels of 25% (chromogenic)	100 IU/kg every 12 h, increasing to every 48 h (enoxaparin 1 mg/kg every 12 h increasing to every 48 h) 80-120 IU/kg every 48 h (enoxaparin 1 mg/kg every 48 h alternating with Ceprotin; enoxaparin eventually stopped)	Protein C activity target ≥15%
Minford et al. [9],[a] 2014	3 wk to 4.5 y[c]	Doses varied from 30-50 IU/kg twice weekly to 90 IU/kg 4 times daily (oral anticoagulant; treatment details NR)	Undetectable: *n* = 4 ≤0.1 IU/mL *n* = 9 0.12 IU/mL *n* = 1	Trough levels between 0.1 and 0.61 (*n* = 10)	Doses varied from 330 IU/kg daily to 34 IU/kg every 5 d[d] (oral anticoagulant; treatment details NR)	Trough levels between 0.1 and 1.14 (*n* = 6)
Dreyfus et al. [22],[e] 1995	~2 d to 3 mo	Mean initial dose: 46.7 ± 25 IU/kg (oral anticoagulant; treatment details NR)	0.01-0.12 IU/mL (*n* = 9)	0.08-0.38 IU/mL (*n* = 9)	3000 IU every 3 d (*n* = 1)	NR
Unspecified						
Veron et al. [17], 2019	5 d old	Initial dose: 80 IU/kg 4 times per day Current dose: 80 IU/kg/d (warfarin; treatment details NR)	16%, chromogenic assay	NR	Attempts to switch to s.c. administration failed	NR
Williams et al. [18], 2009	7 y old[f]	50 U/kg twice weekly	NR	NR	NR	NR

C_{max}, maximum concentration; INR, international normalized ratio; i.v., intravenous; LMWH, low-molecular-weight heparin; NR, not reported; s.c., subcutaneous; UFH, unfractionated heparin.

[a]Patients from the studies by de Kort et al. [7], Mathias et al. [8], and Sanz-Rodriguez et al. [23] were included in the study by Minford et al. [9].

[b]Ceprotin is described as a protein C concentrate (Baxter Biosciences) in the publication.

[c]Age at which treatment with protein C concentrate via s.c. administration started.

[d]Most recent dose administered subcutaneously reported.

[e]Ceprotin is described as protein C concentrate (Immuno) in the publication.

[f]Patient received protein C concentrate prophylaxis at ~3 weeks old; however, treatment was discontinued due to numerous central-line infections. At 7 years old, the patient resumed protein C concentrate prophylaxis via i.v. administration.

TABLE 4 Reported outcomes following treatment with protein C concentrate.

Author and year of publication	Patients, *n*	Outcomes
Ceprotin		
Aytac et al. [12], 2018	1	Ceprotin with dabigatran etexilate: no AEs; no recurrence
Boey et al. [20], 2016	1	Ceprotin with warfarin: splenic infarction after omitting a single dose of Ceprotin Ceprotin with rivaroxaban: rapidly progressing upper limb DVT after missing 2 doses of rivaroxaban Ceprotin s.c.: no breakthrough thrombosis over 12 mo following initiation of s.c. prophylaxis; infusions well tolerated with no skin complications
de Kort et al. [7],[a] 2011	1	Ceprotin i.v.: initial skin lesions healed slowly but completely; the patient developed a central venous catheter infection necessitating treatment with antibiotics and catheter replacement; the patient showed normal neurologic development, apart from blindness[b] Ceprotin s.c.: during 1 y of follow-up, no new episodes of PF or thrombosis; laboratory investigations revealed no signs of DIC and normal D-dimer
Dreyfus et al. [22],[c] 1995	9	Resolution of skin lesions; no signs of neurologic impairment (n = 5); no signs of renal impairment (n = 4); no neutralizing antibodies against protein C; no product-related side effects
Manco-Johnson et al. [15],[d] 2016	25	7 patients experienced 25 acute events: 22 events recovered, 2 showed improvement, and 1 was unchanged Effective in preventing coagulopathy and thrombosis in 23 cases of short-term protein C replacement for surgery 83 AEs occurred in 17 patients during treatment with Ceprotin, of which 3 events experienced by 1 patient were considered possibly related to treatment administration: abdominal pain and pain in the extremity, both serious AEs, and PF
Mathias et al. [8],[a,e] 2004	2	Patient 1, Ceprotin i.v.: during the 9-mo period, the patient required prolonged hospital admissions for i.v. antibiotics and 2 line replacements due to line-related sepsis Ceprotin s.c.: infusions were well tolerated Patient 2, Ceprotin i.v.: the patient experienced recurrent problems related to line infections Ceprotin s.c.: infusions were well tolerated
Minford et al. [9],[a] 2014	14	Considered safe and effective in the maintenance therapy of children with SCPCD Thirteen patients switched from i.v. administration owing to difficulties with central venous access; 6 of these patients had recurrent central-line sepsis Three patients experienced adverse effects: 1 patient experienced induration at the injection site; 1 patient developed a hematoma; 1 patient developed an infection at the injection site
Richards et al. [26],[c] 1997	1	Successful delivery via cesarean section of a healthy baby at gestational week 38. No thrombotic or hemorrhagic complications during pregnancy
Sanz-Rodriguez et al. [23],[a] 1999	1	Ceprotin i.v.: at the age of 2.5 mo, the patient was blind and had hemiparesis on the left side and all cutaneous lesions completely healed Ceprotin i.v. with acenocoumarol: 2 thrombotic episodes occurred during treatment; owing to recurrent phlebitis, the use of peripheral venous access devices was abandoned in favor of a central catheter connected to a s.c. reservoir. Later, the central line was replaced due to a fungal infection. No catheter-related thrombosis Ceprotin s.c.: no thromboembolic episodes; no local or general complications; no protein C inhibitors detected
Shah et al. [24], 2016	1	Ceprotin i.v.: owing to difficult peripheral i.v. access, i.v. administration was changed to s.c. administration on day 11 Ceprotin s.c.: complete resolution of skin lesions by 5 wk (correlated with gradual fall and normalization of D-dimer); protein C activity ≥15% since the age of 1 y; no thrombosis recurrence; growth and development were normal; s.c. infusions were well tolerated without any problems/side effects
Tcheng et al. [25], 2008	2	Patient 1, Ceprotin i.v.: no thrombotic complications. The patient developed purpuric skin lesions and increased irritability after 1 wk of switching from Ceprotin to LMWH; after resumption of Ceprotin prophylaxis, no further thrombotic events were reported Patient 2, Ceprotin i.v.: resolution of DIC and skin lesions; no thrombotic complications. The patient experienced a thrombotic event with purpuric lesions within days of stopping Ceprotin and switching to LMWH; the patient did well after resumption of Ceprotin prophylaxis A PK study revealed that dosing should be based on individual PK parameters rather than protein C trough level only

(Continues)

TABLE 4 (Continued)

Author and year of publication	Patients, *n*	Outcomes
Protexel		
Dreyfus et al. [21], 2007	9	Considered safe and effective for the treatment and prevention of PF and thrombotic events; no untoward side effects
Chambost et al. [14], 1997	1	Protexel and heparin: necrotic skin lesion healed within 3 wk. No evidence of neurologic[f] or renal impairment Protexel and oral anticoagulant therapy: 6 recurrent episodes of necrotic hematoma occurred when Protexel treatment was stopped; the patient was hospitalized and received Protexel with 3 batches of FFP. The patient resumed treatment with Protexel and oral anticoagulant therapy at 18 mo old; during 1 y, no further thrombosis occurred, no hospitalization occurred, no neutralizing antibodies were observed, no product side effects were observed, and oral anticoagulant therapy was reduced
Ceprotin and Protexel		
Prescrire Editorial Board [19],[g] 2003	Unclear[h]	Short-term prophylaxis (Ceprotin or Protexel) No cases of thrombosis were reported Ceprotin long-term prophylaxis Nine patients received treatment (combined with an oral anticoagulant in 8 patients). Thrombotic episodes were reported in 4 patients; episodes were considered probably related to withdrawal of protein C in 3 patients Protexel long-term prophylaxis One patient received treatment in combination with a vitamin K antagonist: 3 episodes of lower-limb thrombosis occurred in the first year of treatment (possibly related to underdosing of protein C); no cases of thrombosis were reported after the first year Among 79 patients treated with Ceprotin, there were 10 cases of moderate allergic reaction and 12 cases of hemorrhage (unclear whether bleeding events were treatment-related); no antihuman protein C antibodies in patients who were tested (*n* = 15)
Unspecified		
Boz et al. [13], 2019	2[i]	NR
Özdemir et al. [16], 2017	1	Skin lesions improved. The intracranial bleeding with which the patient presented also improved following treatment
Veron et al. [17], 2019	1	Ceprotin with warfarin: attempts to decrease dose or increase dosing interval led to a rapid increase in D-dimer and complications with the catheter
Williams et al. [18], 2009	1	Ceprotin i.v.: no breakthrough lesions[j]

AE, adverse event; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; FFP, fresh frozen plasma; i.v., intravenous; LMWH, low-molecular-weight heparin; PF, purpura fulminans; PK, pharmacokinetic; NR, not reported; s.c., subcutaneous; SCPCD, severe congenital protein C deficiency.

[a]Patients from the studies by de Kort et al. [7], Mathias et al. [8], and Sanz-Rodriguez et al. [23] were included in the study by Minford et al. [9].

[b]At 5 weeks old, bilateral retinal detachment resulted in complete blindness.

[c]Ceprotin is described as protein C concentrate Immuno in the publication.

[d]Ceprotin is not mentioned in this publication; however, data from this noninterventional registry are also reported in another abstract [27], which states that patients received treatment with Ceprotin.

[e]Ceprotin is described as protein C concentrate (Baxter Biosciences) in the publication.

[f]Retinal damage resulted in total blindness.

[g]This publication does not report any authors.

[h]Efficacy data were reported for 22 patients treated with Ceprotin and 10 patients treated with Protexel. Safety data were reported for 79 patients who received Ceprotin.

[i]This publication included 6 patients; however, only 2 patients received treatment with protein C concentrate.

[j]At 3 weeks old, the patient received protein C concentrate (unspecified) and anticoagulation, which successfully treated the patient's PF; however, protein C concentrate prophylaxis was discontinued due to numerous central-line infections. Treatment with protein C concentrate (unspecified) was later resumed when the patient was 7 years old and is described here.

reported the treatment of a male patient with s.c. administration of Ceprotin over 12.5 years without complications [30]. Immediately after birth, the patient received 120 IU/kg of Ceprotin via i.v. administration followed by 60 IU/kg via i.v. administration every 6 hours [30]. The patient was discharged from hospital on day 73 and was receiving 1000 IU/d (243 IU/kg) Ceprotin maintenance therapy via s.c. administration [30]. At 12.5 years old, the patient switched treatment to a direct oral anticoagulant (apixaban) [30].

The other case study reported the treatment of a male neonatal patient with homozygous protein C deficiency who presented with

purpura fulminans, intracranial hemorrhage, and bilateral retinal detachments [31]. Replacement therapy with an unspecified protein C concentrate was started on day 11 with an initial dose of 100 IU/kg, followed by 50 IU/kg every 8 hours [31]. Dose adjustments were made so that the patient received up to 80 IU/kg every 8 hours [31]. On day 17, the patient switched treatment to warfarin instead of protein C concentrate [31]. After 2 months of treatment, the patient's skin lesions were healed, and no new hemorrhagic brain infarctions were observed, although there was ongoing ischemic tissue loss [31].

When considering therapeutic approaches for the treatment of patients with SCPCD, it is important to distinguish protein C concentrate replacement therapies from recombinant human-activated protein C products. In contrast with recombinant human-activated protein C products, protein C concentrate replacement therapies are activated through the endogenous hemostatic process of the patient. Drotrecogin alfa (activated; Xigris, Eli Lilly) was a human-activated protein C product indicated for the treatment of high-risk septic patients that was withdrawn owing to the occurrence of serious bleeding events during treatment [32,33]. In the case of Ceprotin, several bleeding episodes have been observed during treatment; however, the administration of concurrent anticoagulant medication and/or tissue plasminogen activator may have caused these bleeding episodes or increased the bleeding risk [5,6]. AnactC (KM Biologics) is another activated human protein C concentrate that is only available in Japan [4]. Two case studies report the treatment of patients with SCPCD using AnactC [34,35]. In both cases, treatment with AnactC seemed effective and no adverse effects were observed; further details are provided in Appendix S1.

The main limitation of this review was the small number of publications that met the eligibility criteria for inclusion. This is, however, a reflection of the limited number of publications that focus on SCPCD. Additionally, it was difficult to make comparisons across publications owing to a wide variation in treatment regimens and follow-up times between patients and changes in the management of patients with SCPCD over time.

5 | CONCLUSION

Despite these limitations, this review provides valuable insights into the treatment of patients with SCPCD in clinical practice, including protein C concentrate dosing regimens, administration routes, and associated clinical outcomes.

ACKNOWLEDGMENTS

Under the direction of the authors, medical writing support was provided by Sarah Morgan, PhD, employee of Excel Scientific Solutions, Inc (Fairfield, Connecticut), and was funded by Takeda Development Center Americas, Inc, Cambridge, Massachusetts. Robert Petermann contributed to the conception and design of the work and contributed to reviewing the findings. Neera Sinha-Frazer contributed to the verification of extracted data and assisted in the interpretation of the data.

FUNDING

This study was funded by Takeda Development Center Americas, Inc, Cambridge, Massachusetts.

AUTHOR CONTRIBUTIONS

C.S., A.W., V.T., and M.K.O. contributed to the analysis and interpretation of the data. H.T.G. reviewed the literature and contributed to the interpretation of the data. P.L.T. and H.S. contributed to the interpretation of the data. All authors revised the manuscript critically for intellectual content. All authors gave their final approval for the manuscript to be published and agree to take responsibility for the integrity of all aspects of the work.

RELATIONSHIP DISCLOSURE

C.S. is an employee of Takeda Development Center Americas, Inc, a Takeda company, and a Takeda shareholder. At the time the targeted literature review and data analysis were conducted, A.W. was an employee of ICON Plc. A.W. is now an employee of Takeda Pharmaceuticals, Canada. V.T. is an employee of ICON Plc. At the time the targeted literature review and data analysis were conducted, M.K.O. was an employee of ICON Plc. M.K.O. is currently an employee of the American Cancer Society. H.S. is an employee of Baxalta Innovations GmbH, a Takeda company, and a Takeda shareholder. H.T.G. is an employee of Takeda Development Center Americas, Inc, a Takeda company, and a Takeda shareholder. P.L.T. is an employee of Baxalta Innovations GmbH, a Takeda company, and a Takeda shareholder.

DATA AVAILABILITY

The datasets, including the template data extraction form and data extracted from the included studies, are available upon request from the corresponding author.

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SUPPLEMENTARY MATERIAL

The online version contains supplementary material available at https://doi.org/10.1016/j.rpth.2024.102542