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Original Article

ORIGINAL ARTICLE

Management of anaemia in French dialysis patients: results from a large epidemiological retrospective study

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ABSTRACT

Background. Limited real-world data are available in Europe, especially France, regarding the therapeutic management of anaemia in patients with dialysis-dependent chronic kidney disease (DD CKD).

Methods. This retrospective, longitudinal, observational study was based on medical records from the MEDIAL database of not-for-profit dialysis units in France. From January to December 2016, we included eligible patients (≥18 years), with a diagnosis of CKD and receiving maintenance dialysis. Patients with anaemia were followed up for 2 years after inclusion. Patient demographic data, anaemia status, CKD-related anaemia treatments, and treatment outcomes including laboratory test results were evaluated.

Results. Of 1632 DD CKD patients identified from the MEDIAL database, 1286 had anaemia; 98.2% of patients with anaemia were receiving haemodialysis at index date (ID). Of patients with anaemia, 29.9% had haemoglobin (Hb) levels of 10–11 g/dL and 36.2% had levels of 11–12 g/dL at ID. Furthermore, 21.3% had functional iron deficiency and 11.7% had absolute iron deficiency. The most commonly prescribed treatments at ID for patients with DD CKD–related anaemia were intravenous (IV) iron with erythropoietin-stimulating agents (ESAs) (65.1%). Among patients initiating ESA treatment at ID or during follow-up, 347 (95.3%) reached the Hb target of 10–13 g/dL and maintained response within the target Hb range for a median duration of 113 days.

Conclusions. Despite combined use of ESAs and IV iron, duration within the Hb target range was short, suggesting that anaemia management can be further improved.

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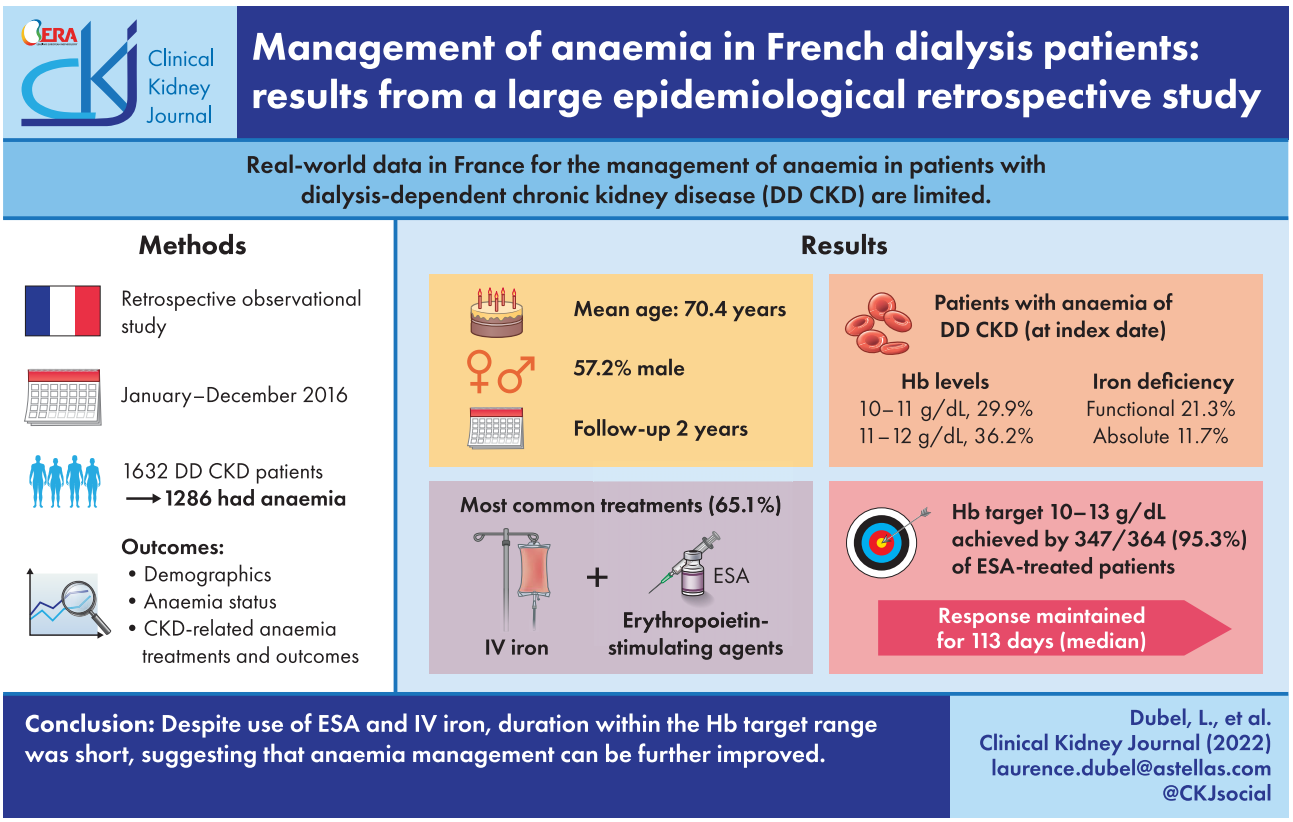
LAY SUMMARY

Anaemia is common among patients with chronic kidney disease (CKD). For patients receiving dialysis, clinical guidelines recommend treatment with intravenous iron supplementation combined with erythropoietin-stimulating agents (ESAs); however, despite wide use of this treatment combination, about one in five patients still has functional iron deficiency. We studied the medical records of 1286 adults with CKD-related anaemia who were receiving maintenance dialysis. One-third of these patients had an iron deficiency at the time of their first anaemia record in 2016. Across all patients, the most commonly prescribed anaemia treatment was intravenous iron plus ESAs. After starting ESAs, 95% of patients reached the haemoglobin target level of 10–13 g/dL; 13 g/dL is higher than the recommended target range, but was used to record patients whose haemoglobin was briefly above 12 g/dL. Haemoglobin levels stayed in this range for 113 days on average. Although patients were treated according to clinical guidelines, haemoglobin levels remained within the target range for only a short time, suggesting that anaemia treatment could be further improved.

GRAPHICAL ABSTRACT



Keywords: anaemia, CKD, ESA, France, haemodialysis

INTRODUCTION

Chronic kidney disease (CKD) has an estimated prevalence of over half a billion patients worldwide [1]. In France, the prevalence of CKD in 2017 was estimated at approximately 6 million patients [1]. Anaemia is a frequent complication of CKD that contributes to morbidity and mortality in the CKD patient population [2], and the current standard of care for CKD-related anaemia is erythropoietin-stimulating agents (ESAs) combined with iron therapy [3]. Based on data from a Swedish study, CKD-related anaemia is present in up to 90% of dialysis-dependent (DD) patients, and approximately 80% of DD patients receive ESAs [4].

Iron storage deficiency leads not only to anaemia, but also to a reduced response to ESA treatment [5]. Several risk factors contribute to absolute and functional iron deficiency in CKD, including blood losses, impaired iron absorption and chronic inflammation [6]. Consequently, Kidney Disease: Improving Global Outcomes (KDIGO) and European Renal Best Practice (ERBP) guidelines recommend supplemental iron therapy to increase haemoglobin (Hb) levels prior to and during ESA treatment [3, 7].

Furthermore, maintenance of Hb levels in the range 10–11.5 g/dL (KDIGO [3]) or 10–12 g/dL (ERBP [7]) is recommended.

There are minimal real-world data available regarding the management of patients with DD CKD–related anaemia in Europe, and specifically in France. We investigated the real-world clinical management of patients with DD CKD–related anaemia in France.

MATERIALS AND METHODS

Study design

This was a retrospective, longitudinal, observational study of medical records from the MEDIAL database in France. The database included 71 not-for-profit dialysis units from the Pays de la Loire, Morbihan and Rhônes Alpes regions. Database records included patient demographic data, anaemia status, CKD-related anaemia treatments, concomitant treatments, and treatment outcomes including laboratory test results. The study inclusion period was from 1 January 2016 to 31 December 2016.

Patients

Eligible patients were aged ≥18 years, diagnosed with CKD and receiving maintenance dialysis (haemodialysis or peritoneal dialysis) during 2016, with or without a formal diagnosis of anaemia. Patients with at least one of the following criteria for anaemia were included in the DD CKD–related anaemia cohort: Hb <13 g/dL for males or <12 g/dL for females; a record of any anaemia treatment (ESAs, iron therapy or both); or prior anaemia diagnosis (International Classification of Diseases-10 code D63.8). Patients were required to have 1 year of medical history prior to index date (ID; date of first anaemic marker recorded during the study inclusion period), and up to 2 years of follow-up data after ID (follow-up period). Eligible patients with DD CKD–related anaemia must also have had data from at least one post-ID visit.

Patients were further categorized based on Hb level at ID (<10, ≥10–<11, ≥11–<12, ≥12 g/dL) for several pre-defined subgroups of interest: Hb level; inflammation status [C-reactive protein (CRP) ≤5, >5 mg/L]; diabetes status (yes, no); hypertension status (yes, no); ESA dosage range (<8000, ≥8000–≤16 000, and >16 000 units/week); ESA resistance status (ERS; yes, no) and ESA resistance index (ERI) for ESA-treated patients (<5, ≥5–<15, ≥15–≤30 and >30 IU/kg/week/g/dL) [8]; and dialysis vintage (length of time receiving dialysis before ID; <1, ≥1–≤5 and >5 years). ERS was defined as Hb level <11 g/dL over 4–6 months despite weekly doses of epoetin alfa (EPO) of >500 IU/kg or >30 000 IU/week (or ≥1.5 µg/kg per month for darbepoetin [9]) for each ESA treatment initiation. Dosage/unit conversion ratios used for ESA dosages ranges were 1 µg = 200 units for darbepoetin and 1 µg/month = 70–80 units/week for methoxy polyethylene glycol (PEG)-epoetin beta. ERI was calculated as weekly ESA dose per kilogram of body weight divided by Hb level over a 6-month period. Patient iron storage status was defined as adequate [transferrin saturation (TSAT) ≥20% and ferritin ≥100 ng/mL], functional iron deficiency (TSAT <20% and ferritin ≥100 ng/mL) or absolute iron deficiency (TSAT <20%, ferritin <100 ng/mL [5]).

Exclusion criteria included participation in a clinical trial at ID, objection to medical data collection and analysis, current or prior organ transplantation (unless explanted), active cancer or undergoing chemotherapy, or a history of cancer within the 5 years preceding 2016.

Endpoints

Key endpoints included an evaluation of the proportion of patients with DD CKD and DD CKD–related anaemia in 2016; a description of the DD CKD–related anaemia population, including demographic and clinical characteristics, proportions of patients in each subgroup of interest, and dialysis regimen at ID; clinical history and laboratory characteristics of patients with DD CKD–related anaemia at ID; anaemia management at ID and over the follow-up period, including annual frequency of red blood cell (RBC) transfusions and changes in anaemia treatment; Hb level evolution over the follow-up period for each treatment combination, and the duration of response to ESA treatment; and deaths in patients with DD CKD–related anaemia.

Therapeutic management and changes in Hb levels of patients with DD CKD–related anaemia (by Hb level at ID) were recorded at ID and every 2 months up to 2 years of follow-up from the ID.

Statistical analyses

Data were analysed descriptively for all variables in the overall DD CKD and DD CKD–related anaemia cohorts, and in the subgroups of interest with a minimum of 30 patients (sufficient for statistical estimation). Missing data were not imputed or replaced. Assuming 5% missing data, a minimum precision of 2.5% and 2.8% was calculated when describing DD CKD and DD CKD–related anaemia management, respectively, at ID, and modifications over the follow-up period (e.g. RBC transfusions, treatment changes).

Numbers of treatment changes during follow-up were analysed for all patients, whilst the sequence of treatment regimens during follow-up was analysed for all regimens with a duration of ≥45 days. Although KDIGO 2012 and ERBP guidelines recommend target Hb ranges for ESA therapy of 10–11.5 g/dL and 10–12 g/dL, respectively, to maximize improvements in patient quality of life [3, 7], our target range was 10–13 g/dL to capture patients for whom Hb briefly exceeds 12 g/dL without being considered as true ‘off target’, and to more accurately reflect clinical practice. However, this was applied only when analysing Hb levels following treatment initiation.

Duration of response to ESAs, for patients who initiated ESA treatment and had one or more value within the target Hb range, was defined as the time in days from the first date after ESA initiation when Hb was in the target range (start date) to the first post-start date when Hb was outside the target range (event of interest). Response duration was estimated using the Kaplan–Meier method accounting for censored outcomes (death, loss to follow-up, treatment response to end of follow-up, and treatment change). Loss to follow-up was defined as no data collected for ≥6 months.

Additional *ad hoc* analyses were conducted to assess whether inflammation and ESA resistance components (Hb and dosage) are correlated. A chi-squared test examined the association between Hb level (<10 or ≥10 g/dL) and CRP class at ID (≤5 or >5 mg/L), and a Pearson correlation test explored the correlation between darbepoetin dosage at ID (µg/kg/month) and CRP in the CKD anaemia population. The relationship between CRP class and darbepoetin dosage at ID in the CKD anaemia population was tested by Student’s *t*-test with a threshold of error of 5% for equality of variances and equality of means, and equality of means calculated using the Satterthwaite method.

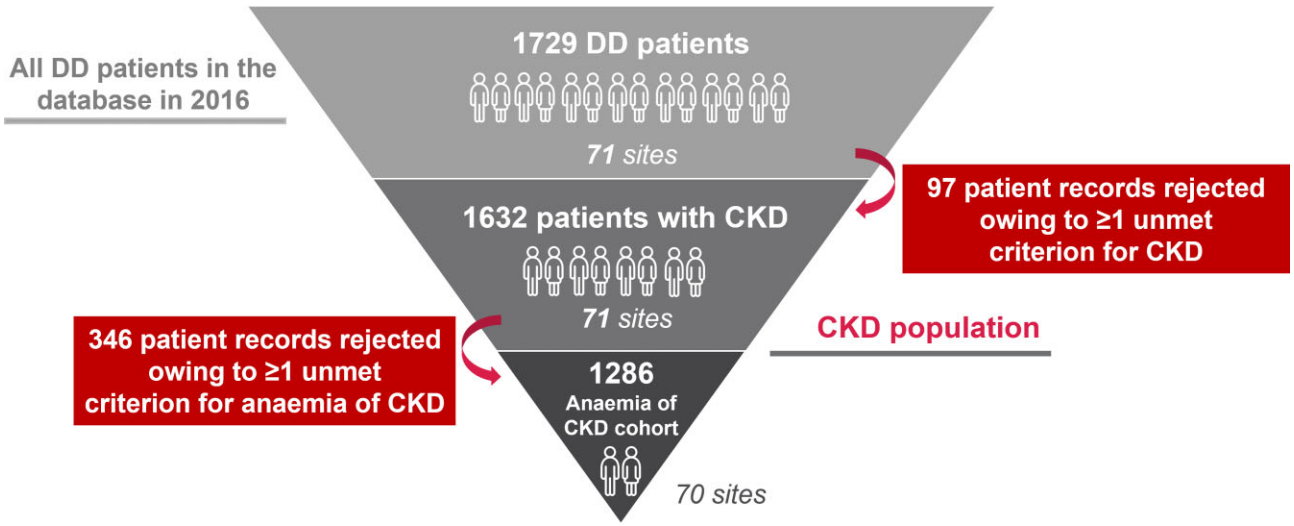


Figure 1: Study population flow diagram of patient records extracted from the MEDIAL database.

RESULTS

Patient demographics and baseline characteristics

From the MEDIAL database, 1729 medical records for DD patients were abstracted; 1632 met the criteria for CKD (DD CKD cohort) and 1286 (79% of the DD CKD cohort) met the definition for anaemia (DD CKD–related anaemia cohort) (Fig. 1). Patients with DD CKD–related anaemia had a mean [standard deviation (SD)] age of 70.4 (14.6) years and 57.2% (736/1286) were male (Table 1).

Patient subgroups of interest

Most ESA-treated patients in the DD CKD–related anaemia cohort (69.5%, 743/1069) received dosages of <8000 units/week; only 7.3% (78/1069) received >16 000 units/week. Almost all patients (99.6%, 898/902) were considered non-resistant to ESAs. Only 11.4% (97/851) of patients had ERI of >15 IU/kg/week/g/dL, and 2.1% (18/851) had ERI >30 IU/kg/week/g/dL. Most patients had midrange (5–15 IU/kg/week/g/dL; 39.8%, 339/851) or lower (<5 IU/kg/week/g/dL; 48.8%, 415/851) ERIs.

Dialysis regimen and vintage

Most patients with DD CKD (99.3%, 1621/1632) were on maintenance haemodialysis and 0.8% (13/1632) received peritoneal dialysis. The mean (SD) duration of all dialysis sessions was 3.82 (0.45) h and session frequency was 2.52 (1.11) per week.

Almost half of patients with DD CKD (47.0%, 730/1552) had a dialysis vintage of ≥1–≤5 years, while 37.2% (577/1552) and 15.8% (245/1552) had received dialysis for <1 year and >5 years, respectively. Among patients with DD CKD–related anaemia, 58.0% (730/1259) had a dialysis vintage ≥1–≤5 years, while 22.6% (284/1259) and 19.5% (245/1259) had received dialysis for <1 year and >5 years, respectively.

Clinical history and laboratory characteristics at ID

Clinical history and laboratory characteristics of patients with DD CKD–related anaemia were categorized according to Hb levels at ID (Table 1). Of those with available Hb data at ID, patients predominantly had Hb levels of 10–11 g/dL (29.9%, 359/1200) and 11–12 g/dL (36.2%, 434/1200), with fewer patients having Hb levels of <10 g/dL (15.6%, 187/1200) and >12 g/dL (18.3%, 220/1200). A similar distribution by age group was observed for each Hb level category, but the proportion of males increased with increasing Hb level (Table 1). The majority of patients with DD CKD–related anaemia had a Charlson Comorbidity Index (CCI) of [11–12] (47.1%, 606/1286). Minimal differences were observed for CCI per Hb category level (Table 1).

Of patients with DD CKD–related anaemia, 35.5% (457/1286) received statins, 11.0% (141/1286) received angiotensin-converting enzyme inhibitors, 12.8% (165/1286) received angiotensin II receptor antagonists and 4.6% (59/1286) received immunosuppressive treatments. The proportion of patients receiving concomitant treatments was similar across Hb categories.

Overall, patient laboratory data at ID were heterogeneous between Hb level categories, with few clear trends observed (Table 2). However, mean CRP and ferritin levels were numerically higher in patients in the <10 g/dL Hb category versus those with higher Hb concentrations. Among patients with available data, 46.5% (511/1099) of patients had a CRP level outside the normal range (>5 mg/L), 33.1% (259/783) had a TSAT <20% and 14.6% (114/781) had a ferritin level <100 ng/mL. Furthermore, 21.3% (164/769) of patients had functional iron deficiency (combined TSAT <20% and ferritin ≥100 ng/mL), and 11.7% (90/769) had absolute iron deficiency (combined TSAT <20% and ferritin <100 ng/mL).

Anaemia management at ID

At ID, 83.1% (1069/1286) of patients with DD CKD–related anaemia received at least one dose of ESA (with or without iron) and 77.4% (995/1286) received at least one dose of intravenous (IV) iron (with or without an ESA); 4.6% (59/1286) of patients did not receive anaemia treatment.

The most frequently reported combination therapy at ID was ESA plus IV iron (65.1%, 837/1286). Of patients receiving at least one dose of ESA, the most commonly used ESAs at ID were darbepoetin and PEG epoetin beta [57.9% (619/1069) and 27.5%

Table 1: Patient demographics and baseline characteristics in the DD CKD–related anaemia cohort.

	Hb levels				
	<10 g/dL (*N* = 187)	≥10–<11 g/dL (*N* = 359)	≥11–<12 g/dL (*N* = 434)	≥12 g/dL (*N* = 220)	Total[a] (*N* = 1286)
Age at ID					
Mean (SD)	70.42 (13.93)	71.38 (15.03)	70.23 (14.68)	70.59 (14.04)	70.43 (14.56)
Min–Max	26.00–94.00	20.00–96.00	25.00–95.00	24.00–95.00	20.00–96.00
Age at ID categories, *n* (%)					
18–45 years	12 (6.4)	24 (6.7)	32 (7.4)	12 (5.5)	87 (6.8)
45–65 years	49 (26.2)	73 (20.3)	96 (22.1)	49 (22.3)	296 (23.0)
65–75 years	37 (19.8)	70 (19.5)	112 (25.8)	52 (23.6)	295 (22.9)
≥75 years	89 (47.6)	192 (53.5)	194 (44.7)	107 (48.6)	608 (47.3)
Sex, *n* (%)					
Male	94 (50.3)	194 (54.0)	257 (59.2)	147 (66.8)	736 (57.2)
BMI (kg/m²)					
N	176	343	418	216	1167
Mean (SD)	26.05 (5.92)	27.01 (5.81)	27.24 (6.55)	27.45 (5.77)	26.98 (6.10)
Min–Max	15.54–50.59	14.15–51.93	13.79–71.21	16.62–48.48	13.79–71.21
Hb (g/dL)					
N	187	359	434	220	1200
Mean (SD)	9.22 (0.67)	10.49 (0.29)	11.46 (0.32)	12.76 (0.71)	11.06 (1.20)[b]
Min–Max	6.10–9.90	10.00–10.90	11.00–12.00	12.10–15.90	6.10–15.90
Hypertension, *n* (%)					
N	187	359	434	220	1286
Yes	59 (31.6)	114 (31.8)	122 (28.1)	60 (27.3)	375 (29.2)
CRP categories (mg/L), *n* (%)[c]					
N	169	328	398	203	1099
≤5 mg/L	73 (43.2)	177 (54.0)	229 (57.5)	109 (53.7)	588 (53.5)[d]
>5 mg/L	96 (56.8)	151 (46.0)	169 (42.5)	94 (46.3)	511 (46.5)[d]
Diabetes, *n* (%)					
N	187	359	434	220	1286
Yes	56 (29.9)	102 (28.4)	131 (30.2)	71 (32.3)	383 (29.8)
CCI					
N	187	359	434	220	1286
Mean (SD)	10.41 (2.26)	10.43 (2.46)	10.25 (2.42)	10.34 (2.27)	10.31 (2.39)
CCI categories, *n* (%)					
N	187	359	434	220	1286
<8	12 (6.4)	26 (7.2)	34 (7.8)	13 (5.9)	92 (7.2)
8–10	63 (33.7)	115 (32.0)	156 (35.9)	79 (35.9)	459 (35.7)
11–12	97 (51.9)	173 (48.2)	204 (47.0)	106 (48.2)	606 (47.1)
>12	15 (8.0)	45 (12.5)	40 (9.2)	22 (10.0)	129 (10.0)

[a]Total number of patients from the DD CKD–related anaemia cohort, including 86 patients with missing data for Hb levels.
[b]Mean (SD) calculated based on total number of patients with available data (excluding missing patients).
[c]Defined by CRP in class (mg/L), *n* (%).
[d]Percentages calculated based on total number of patients with available data (excluding missing patients).
BMI, body mass index.

(294/1069) of patients, respectively]. The mean (SD) dose of darbepoetin was 2.22 (1.97) µg/kg/month for patients on ESA plus IV iron combination therapy, and 1.84 (1.44) µg/kg/month for those on ESA monotherapy. Mean administration dose of darbepoetin was 0.63 µg/kg for patients on ESA monotherapy and ESA plus IV iron combination therapy (Supplementary data, Tables S1 and S2).

Treatment regimens at ID by Hb level

For patients with Hb levels of <10, ≥10–<11 and ≥11–<12 g/dL, the most common anaemia treatment received at ID was ESA plus IV iron, followed by ESA only. The most common treatment for patients with Hb level ≥12 g/dL was ESA plus IV iron, followed by IV iron monotherapy (Supplementary data, Table S3).

Anaemia management over the follow-up period

Use of RBC transfusions

During follow-up, 17.3% (222/1286) of patients with DD CKD–related anaemia received at least one RBC transfusion, ranging from 8.9% (14/157) treated only with IV iron to 20.3% (47/231) treated only with ESAs. Of the patients receiving RBC transfusions during follow-up, 59.9% (133/222) received exactly one RBC transfusion, with similar proportions (57.1%–66.0%) between patients receiving each therapy type. The proportion of patients receiving either one or multiple transfusions was 18.2% (152/837) for patients receiving IV iron plus ESA, 20.3% (47/231) for ESA only, 8.9% (14/157) for IV iron only and 15.3% (9/59) for no anaemia treatment at ID. However, the total annual number of RBC transfusions was heterogeneous between patients receiving each treatment scheme, with a high mean (SD) observed for

Table 2: Laboratory characteristics at ID by Hb level.

	Hb levels				
	<10 g/dL (N = 187)	≥10–<11 g/dL (N = 359)	≥11–<12 g/dL (N = 434)	≥12 g/dL (N = 220)	Total[a] (N = 1286)
Albumin (g/L)					
N	129	265	314	164	872
Mean (SD)	35.9 (5.6)	37.4 (4.5)	38.5 (3.9)	38.6 (3.7)	37.8 (4.4)
CRP (mg/L)					
N	169	328	398	203	1099
Mean (SD)	16.8 (29.0)	10.2 (15.4)	8.6 (15.1)	9.9 (20.0)	10.6 (19.1)
TSAT (%)					
N	119	226	290	147	783
Mean (SD)	24.6 (13.3)	24.3 (9.3)	25.6 (9.8)	24.5 (9.9)	24.9 (10.3)
Ferritin (ng/mL)					
N	115	226	289	150	781
Mean (SD)	503.4 (467.1)	395.1 (335.3)	366.9 (265.4)	306.1 (271.1)	384.6 (329.7)
TSAT categories (%), n (%)					
N	119	226	290	147	783
<20%	43 (36.1)	81 (35.8)	85 (29.3)	50 (34.0)	259 (33.1)
≥20%	76 (63.9)	145 (64.2)	205 (70.7)	97 (66.0)	524 (66.9)
Ferritin categories (ng/mL), *n* (%)					
N	115	226	289	150	781
<100 ng/mL	16 (13.9)	27 (11.9)	36 (12.5)	35 (23.3)	114 (14.6)
≥100 ng/mL	99 (86.1)	199 (88.1)	253 (87.5)	115 (76.7)	667 (85.4)

[a]Total number of patients from the DD CKD–related anaemia cohort, including 86 patients with missing data for Hb levels.

IV iron-treated patients [2.5 (6.7)], and low mean (SD) observed for ESA-treated patients [0.9 (1.0)].

Treatment changes over the follow-up period

Of patients with DD CKD–related anaemia, 55.9% (719/1286) had one or more treatment change during follow-up. Most of these patients (85.8%, 617/719) only had a single treatment change, while 13.9% (100/719) had two changes. Initial treatment change after ID primarily consisted of either discontinuation (50.3%, 362/719) or treatment add-on (49.4%, 355/719).

Almost all patients who received ESAs only (96.1%, 222/231) or no anaemia treatment (98.3%, 58/59) at ID had one or more treatment change during follow-up. In contrast, 79.6% (125/157) of IV iron and 37.4% (313/837) of ESA plus IV iron patients at ID had one or more treatment change during follow-up. Of all patients with treatment changes, those receiving ESAs plus IV iron at ID exclusively had discontinuations (100%, 313/313), whereas a majority of those receiving ESAs only (90.5%, 201/222) or IV iron only (76%, 95/125) at ID had treatment add-ons.

Treatment regimen sequences

When treatment regimens lasting ≥45 days were considered, at ID, 37.8% (486/1286) of patients received darbepoetin plus IV iron treatment, 16.3% (209/1286) of patients received PEG epoetin beta plus IV iron, and 13.5% (173/1286) of patients received IV iron monotherapy (Fig. 2). Using the same criterion over the follow-up period, the most common treatment sequences were darbepoetin plus IV iron from ID to end of follow-up (36.9%, 475/1286); PEG epoetin beta plus IV iron at ID, switching to darbepoetin plus IV iron for the first treatment change and remaining on darbepoetin plus IV iron to end of follow-up (8.9%, 115/1286); and darbepoetin at ID, switching to darbepoetin plus IV iron for the first treatment change and remaining on darbepoetin plus IV iron until the end of follow-up (7.7%, 99/1286) (Fig. 2). Of the 62 patients with no treatment at ID, the majority went on to receive other treatments during the follow-up period—at the first treatment change, these treatments were predominantly IV iron only (2.2%, 28/1286) and darbepoetin only (1.2%, 15/1286) (Fig. 2).

Changes in Hb level over the follow-up period

Over the follow-up period, Hb values were maintained at 10–12 g/dL, with a similar mean number of Hb level evaluations over the follow-up period, regardless of anaemia severity at ID (Table 3). For patients receiving either treatment add-ons or discontinuations, the coefficient of variation (CV) in mean Hb level was low (<10.3%) at each timepoint in the 3–6 months preceding the change (Fig. 3).

Duration of ESA treatment response

Of patients with DD CKD–related anaemia who initiated ESA treatment either at ID or during the follow-up period, 95.3% (347/364) had at least one Hb measure within the target range (10–13 g/dL) during follow-up (Supplementary data, Table S4). Overall, the median (95% confidence interval) response duration was 113.0 (98.0–125.0) days; a numerically shorter response duration [98.0 (98.0–125.0) days] was observed for patients with dialysis vintage of <1 year, compared with patients with dialysis vintage of ≥1–≤5 years [120.0 (92.0–169.0) days] and >5 years [106.0 (85.0–211.0) days] (Fig. 4). Additionally, the proportion of patients with Hb determinations outside the target range decreased with increasing dialysis vintage, with a corresponding increase in proportions of censored patients (Supplementary data, Table S4). Approximately one-third of patients were censored during follow-up (34.3%, 119/347), and the main reason for censoring was a change in treatment (71.4%, 85/119, of all censored events) (Supplementary data, Table S4).

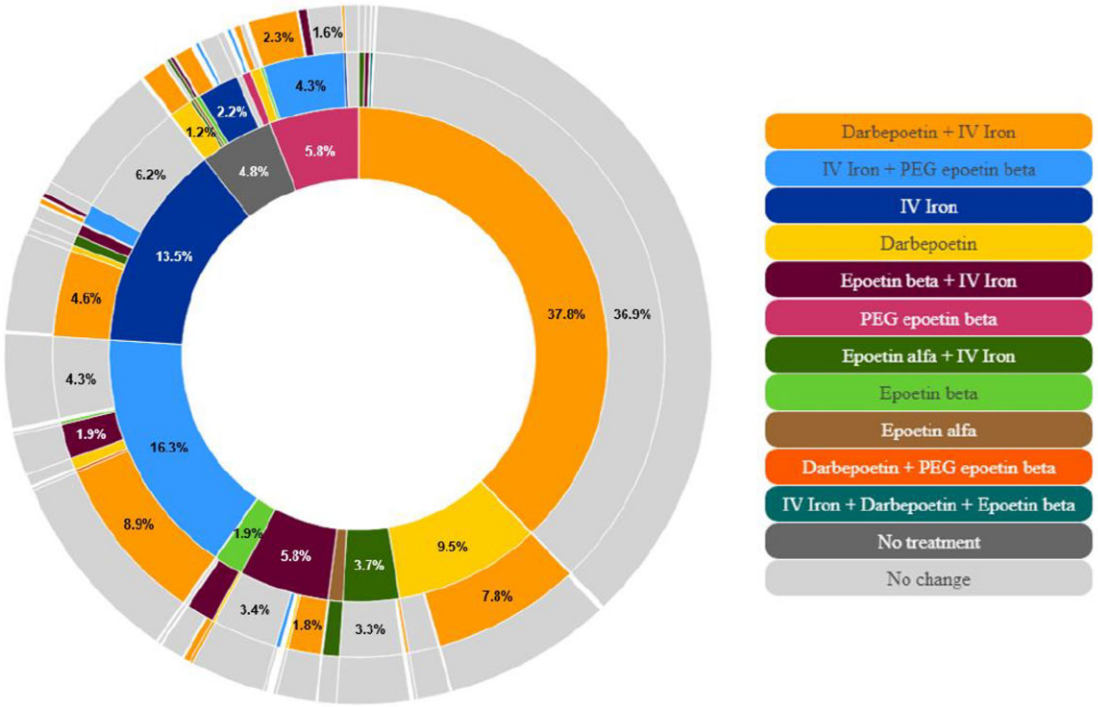


Figure 2: Significant[†] treatment sequences during the follow-up period. [†]Treatments administered for <45 days were not considered as a significant new regimen and were excluded from this diagram. The innermost sequence of the sunburst corresponds to the treatment administered during the ID period (−1/+1 month from ID). Only treatments or combinations received by more than one patient are displayed and only the first three sequences are presented (1% of patients had more than three sequences). Percentages are calculated based on the proportions of the overall patient population within each ring.

Table 3: Hb evaluation frequency over the follow-up period.

	Hb levels				
	<10 g/dL (*N* = 187)	≥10–<11 g/dL (*N* = 359)	≥11–<12 g/dL (*N* = 434)	≥12 g/dL (*N* = 220)	Total[a] (*N* = 1286)
Mean Hb level over the follow-up period, *n*					
N	187	359	434	220	1249
Missing	0	0	0	0	37
Mean (SD)	10.57 (0.79)	10.80 (0.54)	11.04 (0.61)	11.52 (0.95)	10.99 (0.78)
Annual number of evaluations[b], *n*					
N	187	359	434	220	1249
Missing	0	0	0	0	37
Mean (SD)	19.83 (9.59)	19.35 (8.99)	17.74 (7.58)	17.61 (8.56)	18.22 (8.75)

[a]Total number of patients from the DD CKD–related anaemia cohort, including 86 patients with missing data for Hb levels.
[b]Total number of evaluations during the whole follow-up × 365/duration of follow-up in days.

Deaths

During follow-up, the mortality rate of patients with DD CKD–related anaemia was 12.1% (156/1286); 4% (51/1286) were lost to follow-up (primarily due to transfer to other dialysis centres). The primary single cause of patient death was cardiovascular events (23.9%, 33/138; Supplementary data, Fig. S1). Among patients receiving ESAs at ID and with more than one Hb value in the target range, there were two deaths (1.7%, 2/119); one due to aortic valve disease and the other to myocardial infarction.

Ad hoc analysis of CRP, Hb levels and ESA dosage

In total, 56.8% of patients with Hb level <10 g/dL had a CRP >5 mg/L compared with 44.6% of patients with Hb level ≥10 g/dL (Table 1). The mean (SD) CRP in all patients was 10.7 (19.1) mg/L compared with 16.8 (29.0) mg/L in patients with Hb level <10 g/dL (Table 2). This difference is statistically significant ($P = .0033$), indicating a relationship between Hb level and CRP class at ID in the CKD anaemia population.

CRP and darbepoetin dosage had a statistically significant linear relationship ($P = .0373$), with a correlation coefficient of $r = 0.09$. The average darbepoetin dosage at ID was 1.95 µg/kg/month for patients with CRP ≤5 mg/L and 2.20 µg/kg/month for patients with CRP >5 mg/L. For CRP class and darbepoetin dosage, there was a statistically significant difference in variances ($P < .0001$) but no significant difference in means ($P = .1104$).

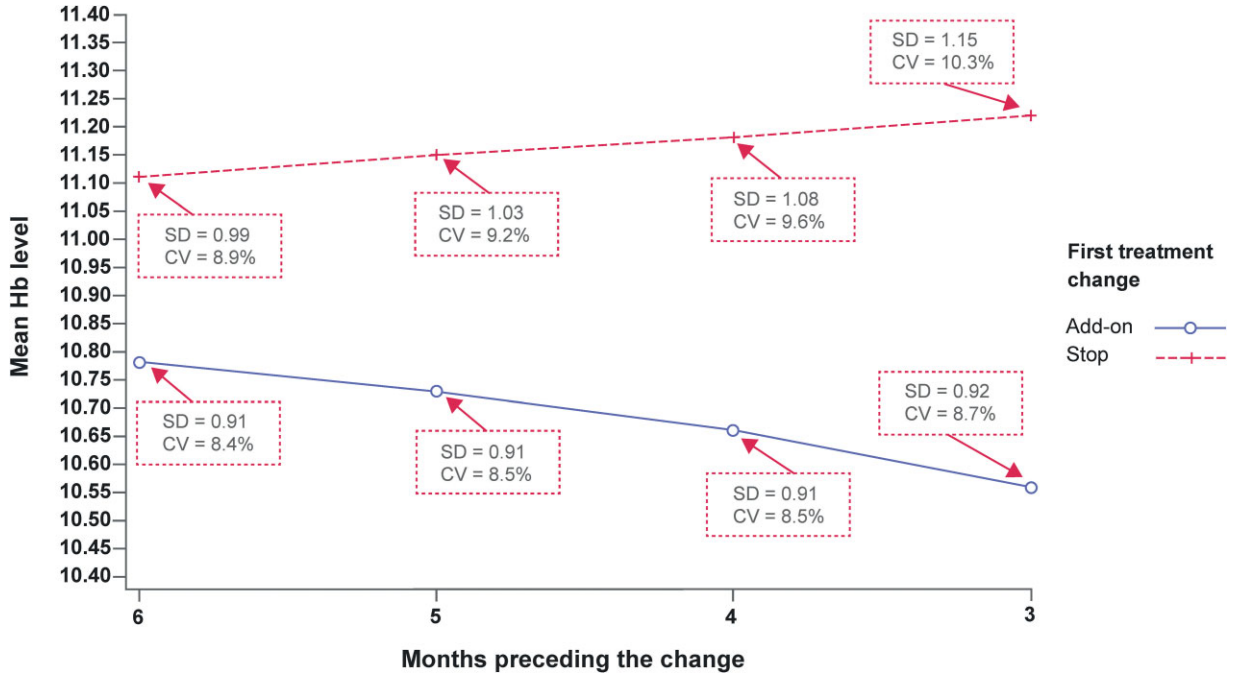


Figure 3: Hb levels prior to treatment change in the DD CKD–related anaemia patient population.

DISCUSSION

This study investigated the real-world therapeutic management of CKD-related anaemia, in 1286 DD patients in France from 71 non-profit units, over a 2-year follow-up period. This is the first study of its kind for patients with DD CKD–related anaemia in France, and adds to a limited pool of data for this patient cohort in Europe. In particular, analysis of the median response duration for ESA therapy had not previously been investigated in this patient population. Our study also included analysis by Hb level to provide detailed insights into therapeutic anaemia management for patient subgroups.

We found that patients with DD CKD–related anaemia most frequently received a combination of IV iron and ESA therapy, with few receiving oral iron therapy, in line with Haute Autorité de Santé 2017 guidelines [10]. IV iron therapy has been shown to improve patient response to ESA treatment and reduce ESA dosage requirements in patients with DD CKD–related anaemia [11]. The KDIGO 2012 guidelines for patients with DD or non-dialysis-dependent CKD–related anaemia also recommend the use of supplemental IV iron in combination with ESAs to increase patient Hb levels or reduce ESA dosage [3].

Although more than two-thirds of patients with DD CKD–related anaemia had adequate iron stores at ID, 21.3% of patients had functional iron deficiency, which is usually indicative of an underlying inflammatory state [12], and 11.7% had absolute iron deficiency.

At ID, darbepoetin was the most common ESA treatment administered in this study population. For all ESA and IV iron treatment modalities at ID, higher mean and maximum doses were observed for ESA + iron combinations compared with ESA-only therapy. The mean dose of darbepoetin was also greater for patients on ESA plus IV iron combination therapy than for those on ESA monotherapy. Mean doses per administration observed in our study for ESA monotherapy and ESAs combined with IV iron were consistent with clinical trial data [13, 14], indicating that 0.45–0.75 µg/kg is the optimal weekly starting dose for darbepoetin treatment.

The median duration of ESA response was 113.0 days, and a numerically shorter response duration was observed for patients with dialysis vintage of <1 year versus ≥1 year. This is a relatively short duration given the chronic nature of CKD-related anaemia and likely contributes to the high proportion of treatment changes observed over the 2-year follow-up period. There are few studies focusing on ESA response duration in patients with DD CKD–related anaemia. However, it has previously been demonstrated that the initial increase in Hb level occurs within the first 4 weeks following initiation of ESA therapy in CKD-related anaemia patients [15], which is consistent with our findings. The rate of Hb increase in response to ESA therapy may vary depending on patient characteristics such as history of cardiovascular disease, or study methodology such as initial dose and dose frequency [16].

DD CKD anaemia patients with lower Hb levels experienced greater inflammation than those with higher levels; more patients with Hb level <10 g/dL had a CRP >5 mg/L compared with patients with Hb level ≥10 g/dL, and the mean CRP in the total patient population was lower compared with patients with Hb level <10 g/dL. Moreover, *ad hoc* analysis provided strong evidence of an association between Hb level (<10 or ≥10 g/dL) and CRP class at ID (≤5 or >5 mg/L). The findings of the present study also indicated a relationship between CRP and darbepoetin dosage, with higher levels of inflammation experienced by patients receiving higher doses of darbepoetin. The average darbepoetin dosage at ID was greater for patients with CRP >5 mg/L, and CRP and darbepoetin dosage had a statistically significant linear relationship. Moreover, for CRP class and darbepoetin dosage, there was a significant difference in variances. However, the correlation between darbepoetin dosage and CRP was weak with no significant difference in means for CRP class and darbepoetin dosage. As ESA molecules have different dosage systems

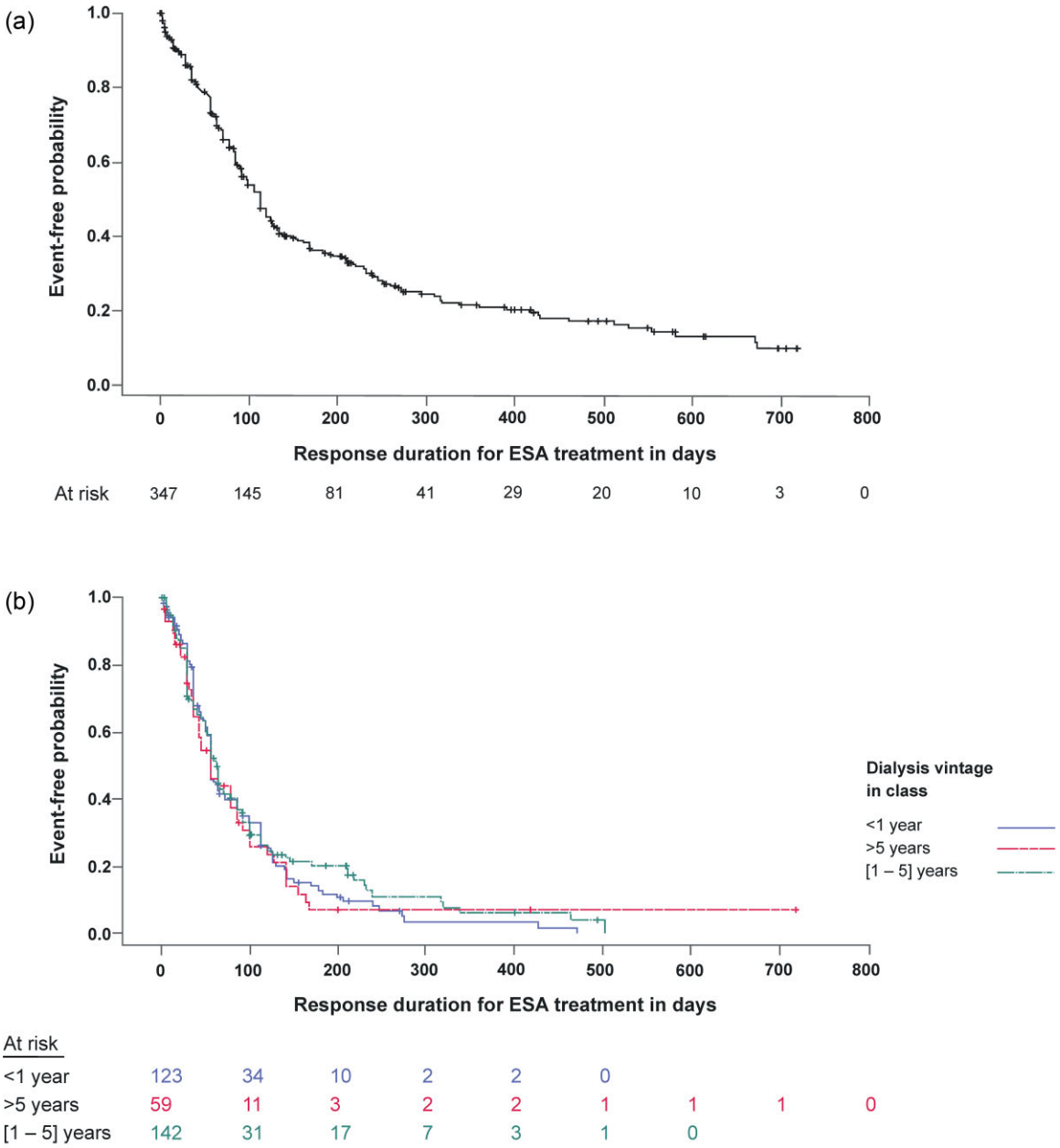


Figure 4: ESA treatment response duration over the follow-up period (**a**) overall and (**b**) by dialysis vintage.

and units, the correlation between CRP and ESA could only be assessed for patients taking darbepoetin as this represented a homogeneous subgroup that consisted of >50% of included patients.

Limitations of our study include those typical of observational studies. While MEDIAL is one of the largest French databases available for DD patients, only three geographical regions of France were covered, which may affect the generalizability of the findings. ERI data are inherently biased since ESA doses are not typically administered above 500 IU/kg for extended periods owing to deleterious effects on the patient [17]; instead, patients with long-term ESA resistance and substantial comorbidities are reverted to conventional dosages of ≤500 IU/kg. Additionally, not-for-profit health units in France typically do not treat patients with severe comorbidities, who are primarily referred to larger public hospitals, general hospitals and university hospitals with more extensive facilities; this would reduce the number of patients with elevated ERIs (>15 IU/kg/week/g/dL) in the MEDIAL database. A relatively low proportion (less than two-thirds) of patients with iron biomarker results was also reported in this study; this may be related to the lack of data sharing between external biological laboratories in some dialysis centres within the MEDIAL database. In general, patient records of scheduled RBC transfusions were not evenly distributed over the follow-up period. Annual numbers of RBC transfusions are derived from the total number of RBC transfusions received during the follow-up period and the duration of follow-up in days. Since all patients are included and have variable follow-up durations, this annualization calculation may lead to increased heterogeneity in results observed. Lastly, there

were relatively few major cardiovascular events recorded from DD CKD anaemia patients over the follow-up period. As such, further statistical analysis on this small subset of data was considered unnecessary.

To conclude, we describe the real-life therapeutic management of patients with DD CKD–related anaemia in France. Results and outcomes from this study are consistent with the current literature and clinical guidelines on the use of ESA plus IV iron combination therapy in the DD CKD–related anaemia patient population. Despite this, duration within the Hb target range was short, indicating that management of anaemia can be further improved.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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CONFLICT OF INTEREST STATEMENT

G.R. received funding from Astellas and consulting fees from Astellas-France. G.C. received honoraria from Astellas Pharma, Amgen, AstraZeneca, GSK, Takeda and Vifor Pharma, and support for attendance travel costs from Vifor Pharma and Sanofi. M.L. is an employee of Astellas Pharma Europe Ltd. L.D. is an employee of Astellas Pharma France. S.H. is an employee of IQVIA, HEOR vendors contracted to generate data on behalf of Astellas. P.Z. received honoraria and consulting fees from Vifor Pharma and Astellas. C.C. and V.M.C. have no conflicts of interest to disclose.

AUTHORS' CONTRIBUTIONS

Study design and conduct was carried out by G.C., C.C., G.R., P.Z., L.D. and M.L. Data acquisition was done by V.M.C. and S.H. Analysis of study data was by G.C., C.C., G.R., P.Z., L.D., M.L. and S.H. Interpretation of study data was performed by G.C., C.C., G.R., P.Z., L.D., M.L. and V.M.C.

DATA AVAILABILITY STATEMENT

Researchers may request access to anonymized participant level data, trial level data, and protocols from Astellas-sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing see: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx.

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