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Editorial Comment

EDITORIAL COMMENT

Timing of eculizumab therapy for C3 glomerulonephritis

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Abstract

Eculizumab is an anti-C5 antibody that inhibits C5 cleavage and prevents the generation of the terminal complement complex C5b-9. Eculizumab is licensed to treat paroxysmal nocturnal haemoglobinuria or atypical haemolytic uraemic syndrome (aHUS). Clinical trials are ongoing for C3 glomerulopathy. Given the unfamiliarity of physicians with these rare diseases and the variability of clinical presentation, a delayed initiation of eculizumab therapy is common. Thus, the question arises as to what extent improvement of kidney function may be expected when patients have been dialysis dependent for weeks or months already when eculizumab is initiated. Furthermore, given the high cost and potential adverse effects of eculizumab, the question arises of when to stop therapy because of futility when patients with kidney-only manifestations remain dialysis dependent. In literature reports, eculizumab was stopped as early as after 3 weeks because the patient remained dialysis dependent. In this issue of *CKJ*, Inman *et al.* report on eculizumab-induced reversal of dialysis-dependent kidney failure from C3 glomerulonephritis, illustrating both the potential benefit of eculizumab for this complement-mediated disease and the need for lengthy therapy—dialysis independency was reached after 5 months of eculizumab. Indeed, there are reports of renal function recovery when eculizumab was initiated after 4 months on dialysis and of recovery of renal function 2.0–3.5 months after initiation of eculizumab in dialysis-dependent patients with C3 glomerulopathy or aHUS.

Key words: complement, dialysis, eculizumab, glomerulonephritis, haemolytic uraemic syndrome

The report by Inman *et al.* [1] on eculizumab-induced reversal of dialysis-dependent kidney failure from C3 glomerulonephritis illustrates some of the complexities associated with the prescription of eculizumab, including the expanding spectrum of indications and the timing of administration.

Eculizumab is a recombinant humanized monoclonal IgG2/4k antibody that binds to the human C5 complement protein, inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9 [2, 3]. In Europe, eculizumab is licensed to treat paroxysmal nocturnal haemoglobinuria or atypical haemolytic uraemic syndrome (aHUS). For both diseases, eculizumab is initially administered weekly, 600–900 mg i.v. in adults, followed by a maintenance phase of 900–1200 mg/2 weeks. The higher dose corresponds to therapy of aHUS. Each 300 mg vial of eculizumab costs €3887.52 in Spain. Thus, the annual cost may range from €322 000 to 435 000 per year. The main adverse effects are infusion reactions and infections, especially meningococcal infections. Meningococcal vaccination is required prior to initiation of eculizumab and prophylactic treatment with appropriate antibiotics should be maintained until 2 weeks after vaccination. In aHUS, thrombotic microangiopathy (TMA) may recur from 4 to 127 weeks following discontinuation of eculizumab. Thus, this is an expensive, potentially life-saving drug, not devoid of potentially severe adverse effects, which is

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used for the chronic therapy of rare diseases that have a wide spectrum of clinical manifestations [4]. Furthermore, case series and reports suggest that eculizumab may be beneficial in at least some patients with another rare disease, C3 glomerulopathy, as illustrated by Inman *et al.* [1, 5, 6]. A number of issues are derived for these facts: the rareness and variable clinical presentation often lead to a delayed diagnosis and therapy. The availability of alternative, more traditional therapeutic approaches (plasma exchange, immune suppressants) may further delay the start of therapy with eculizumab. Finally, being an expensive drug that requires long-term or chronic therapy negatively affects the physician's decision to start therapy. It is conceivable that third-party payers may pressure physicians not to start therapy until alternative diagnostic possibilities have been ruled out and alternative therapies have failed, further delaying or even impeding therapy or to stop therapy in the absence of improvement. Physicians may feel tempted to initiate a therapeutic trial of the drug, with the aim of maintaining therapy if an improvement is observed or stopping treatment in the absence of improvement. Thus, the question nephrologists may be asked is when is it too late to initiate therapy for a patient already on dialysis and in the absence of extrarenal symptoms, or how long should therapy be maintained in dialysis-dependent patients? Case reports and series are providing some insights that support a wide variability, with recovery of renal function observed when eculizumab was initiated after up to 4 months on dialysis and recovery of renal function up to 5 months after initiating eculizumab for a patient on dialysis, as illustrated by Inman *et al.* (Table 1 and Figure 1) [1, 7–18].

Unsurprisingly, prescription of eculizumab is frequently delayed in the course of complement-mediated diseases, sometimes for decades, even when kidney biopsies are available. In a recent case report, diagnosis of aHUS was made 25 years after the first episode of anaemia, thrombocytopenia and acute kidney injury [7]. In this particular case, a first renal biopsy for proteinuric kidney disease at age 15 years showed focal proliferative glomerulonephritis. This led to a misdiagnosis of TMA secondary to hypertensive emergency in the context of uncontrolled glomerulopathy when at age 26 years acute kidney injury required haemodialysis. Three months after initiating dialysis, the diagnosis of aHUS was made based on the development of neurological symptoms and reassessment of family history, leading to prescription of eculizumab 4 months after the start of dialysis. After 2 months of eculizumab, the patient remained dialysis dependent, but neurological symptoms improved. Unfortunately, the patient's sister was diagnosed with membranoproliferative glomerulonephritis at age 14 years and went on to develop encephalopathy and end-stage renal disease, followed by death at

Table 1. Representative cases of eculizumab for dialysis-dependent renal failure

Reference	Disease	Patient characteristics (age in years/sex)	Time initiation dialysis-initiation eculizumab	Time initiation eculizumab-stop dialysis	Total time on dialysis (months)
[7]	aHUS	27/female	4 months	Dialysis ongoing 2 months after initiating eculizumab[a]	>6 (non-recovery)
[8]	aHUS	0.6/female	4 months	1 month	5
[9, 10]	aHUS	21/female	2–3 months[b]	0.5 months	2.5–3.5[b]
[11]	aHUS	32/female	1.7 months	2 months	3.75
[12]	aHUS	0.3/male	1.6 months	2.3 months	3.9
[13]	aHUS	64 /female	1.5 months	0.75 months	2.25
[1]	C3GN	38/female	0.75 months	5 months	5.75
[14]	DDD	8/male	6 days	1 day	0.25
[15]	aHUS	51/male	4 days	2.5 months	2.55
[16]	aHUS	50/female	2 days	1 month	1
[17]	aHUS	32/male	0	3.5 months	3.5
[18][c]	aHUS	$n = 5$; 2–12.5	0.5–1.4 months[d]	All recovered: 0.5–1.0 months	

aHUS, atypical haemolytic uraemic syndrome; C3GN, C3 glomerulonephritis; DDD, dense-deposits disease.
[a]Never recovered renal function and received renal trasplantation (Ana Avila, personal communication).
[b]Different numbers provided in abstract and full text versions.
[c]Case series, plasma exchange-resistant aHUS.
[d]After diagnosis of aHUS.

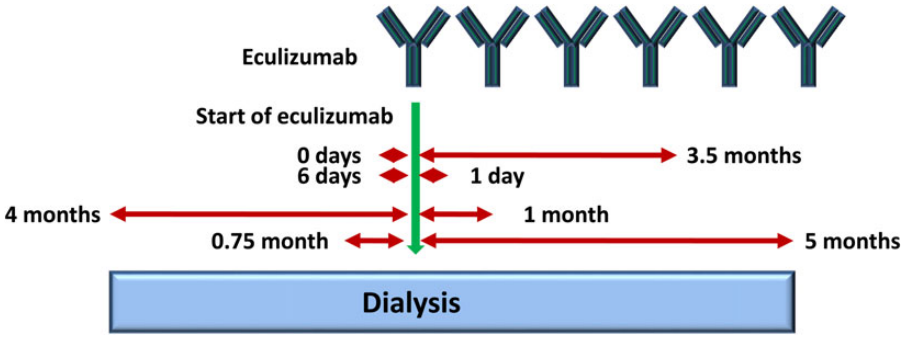

Fig. 1. Range of reported time on dialysis before the initiation of eculizumab therapy for complement-related kidney failure (atypical haemolytic uraemic syndrome of C3 glomerulopathy) in patients who eventually became dialysis independent and range of time until stopping dialysis. Four patients are depicted: those with the shortest and longest periods of dialysis prior to and following eculizumab.

a young age [3]. In another report, treatment with eculizumab led to almost full renal recovery following months of dialysis in a 21-year-old woman with aHUS [9, 10]. Again, typical HUS was diagnosed at age 3 years, kidney impairment at age 14 years and a diagnosis of aHUS was made 18 years after the first symptoms of the disease, when she presented with TMA progressing to anuria despite intensive plasma exchange. Two to three months into dialysis (it is unclear since the abstract and full text report provide different data) severe encephalopathy developed and prompted the institution of eculizumab therapy. After the second eculizumab dose, renal function recovered and dialysis was discontinued, for a total of 2.5–3.5 months on dialysis [9, 10]. These and other case reports as well as clinical trials have now established that eculizumab may be life-saving in dialysis-dependent patients with aHUS, in whom it may restore renal function even after prolonged periods of dialysis (Table 1) [1, 7–18, 19], it may improve life-threatening extrarenal manifestations of aHUS [7] and is required to prevent recurrence in the kidney graft for most forms of aHUS [20]. As might be expected, in a series of 12 off-trial patients, the extent of renal function recovery within 6 months correlated inversely with the time interval between the onset of the episode of aHUS and the initiation of eculizumab: all patients starting eculizumab within 28 days of the current aHUS episode recovered some renal function, while only four out of seven patients starting eculizumab after 28 days displayed improved renal function and two could not be weaned from dialysis [21]. However, details were not provided for length of pre-eculizumab dialysis for those two patients [21]. Recovery of dialysis-dependent renal failure was more frequent among eculizumab-treated patients than among plasma exchange-treated historical controls. Among 12 patients requiring haemodialysis at the start of eculizumab, at 3 months, four patients were still receiving dialysis. At last follow-up, one further patient was dialysis independent, implying that recovery of renal function took longer than 3 months. However, in this report, the median time on dialysis before the start of eculizumab treatment was similar in patients who became dialysis independent ($n = 9$) compared with those who still required dialysis ($n = 3$) at last follow-up (16 versus 12.8 days; $P = 0.8$), suggesting that we are still missing pieces of the puzzle [22]. In two patients who were on haemodialysis for 3 weeks and 5 months, respectively, eculizumab therapy was stopped due to the absence of an improvement in kidney function. In contrast, one patient was maintained with eculizumab despite having received dialysis for 5 months and, in the absence of extrarenal manifestations, in the expectation of potential kidney function improvement. The authors suggested that eculizumab treatment of 3–6 months' duration is required before establishing eculizumab resistance in a patient with aHUS [22]. In a phase 2 trial of eculizumab for aHUS dialysis were discontinued in four of five patients [19]; however, details were not provided as to the duration of dialysis before the start of therapy or the time to stop dialysis after starting eculizumab. These details are, however, reported in case reports or case series.

C3 glomerulopathy is a recently introduced pathological entity, defined as a disease process due to abnormal control of complement activation, deposition or degradation and characterized by predominant glomerular C3 deposition with electron-dense deposits [23, 24]. C3 glomerulopathy may be classified into dense-deposit disease and C3 glomerulonephritis. However, the morphological or clinical distinction from post-infectious glomerulonephritis may not be evident at the time of renal biopsy. Thus, it is suggested that in renal biopsy diagnosis, the use of the descriptive morphological term 'glomerulonephritis with dominant C3' indicates the likelihood that the case represents the disease process of C3 glomerulopathy. Given the involvement of abnormal complement regulation, eculizumab has been used to treat C3 glomerulopathy. A flurry of case reports and case series, including the report by Inman *et al.*, suggest that at least for some patients with C3 glomerulopathy, eculizumab may beneficial, although failures have also been reported [1, 5, 6, 25–27]. Factors affecting response to therapy are poorly understood, although acute lesions and high circulating membrane attack complex levels have been proposed to indicate higher chances of response to therapy [6]. Interestingly, response of rapidly progressive or crescentic C3 glomerulopathy to eculizumab has been reported in the past 12 months, including by Inman *et al.* [1, 5, 27]. Two pilot, open label, single-arm, efficacy and safety studies of eculizumab for glomerulonephritis are currently ongoing, testing the dose currently in use of aHUS for 52–74 weeks [28]. A Columbia University Phase 1 study in patients with biopsy-proven dense deposits disease or C3 nephropathy was started in 2010 and is expected to recruit six patients and be completed by the 1end of 2015 (ClinicalTrials.gov identifier: NCT01221181). An Italian, Phase 2 study in primary membranoproliferative glomerulonephritis will recruit 10 patients and the estimated study completion date is June 2016 (ClinicalTrials.gov identifier: NCT02093533). Neither of these trials is expected to settle the issue. For rare disease, case reports and case series continue to provide valuable information that advance the field.

In conclusion, while case reports may be biased by selective reporting of positive results, there is increasing evidence that eculizumab may be beneficial for at least some patients with C3 glomerulopathy and that both in these patients and in patients with aHUS, recovery of renal function can occur after months on dialysis if eculizumab therapy is maintained.

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Conflict of interest statement

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(See related article by Inman *et al.* Eculizumab-induced reversal of dialysis-dependent kidney failure from C3 glomerulonephritis. *Clin Kidney J* (2015) 8: 445–448.)

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