Expanding the therapeutic options for renal involvement in lupus: eculizumab, available evidence

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Expanding the therapeutic options for renal involvement in lupus: Eculizumab, available evidence

AIM: To systematically review available literature on the efficacy of eculizumab for the treatment of renal involvement in patients with systemic lupus erythematosus (SLE)

METHODS: We conducted a literature search developed *a priori,* to identify articles reporting clinical experience with the use of eculizumab in SLE patients, focusing on renal involvement. The search strategy was applied to Ovid MEDLINE, In-Process and Other Non-Indexed Citation, EMBASE, Cochrane Central Register of Controlled Trials and Scopus from 2002 (year of the first publication retrieved ever indexed in Pubmed using "eculizumab" as search term) to present. Abstracts from EULAR and ACR congresses were also screened.

RESULTS: We included 6 publications describing the renal outcome in SLE patients receiving eculizumab. Five out of six cases described the occurrence of thrombotic microangiopathy (TMA) in renal biopsies of patients with known SLE;3 cases with biopsy-proven lupus nephritis (LN) and 2 patients with SLE-related antiphospholipid syndrome without histologic evidence of LN. One study reported the outcome of a patient with severe refractory LN successfully treated with eculizumab. All patients, regardless of the presence of concomitant LN, presented with severe hypocomplementemia and renal function impairment. All patients showed a sustained improvement of renal function and normalization of complement parameters after treatment with eculizumab[median follow-up 9 months (1-17)].

CONCLUSION: Despite the limitations of the currently available evidence, existing data are promising and provide preliminary support for the use of eculizumab in selected cases of SLE with renal involvement, especially in the presence of TMA, or in patients with refractory LN.

Keywords: lupus nephritis, eculizumab, complement, systemic lupus erythematosus, antiphospholipid antibody

Introduction

Systemic lupus erythematosus (SLE) pathogenesis is rooted in dysregulation of the immune system [1][2][3]. Reduced thresholds of B and T cell activation induce loss of self tolerance and production of autoantibodies [4][5][6] while impaired clearance of apoptotic cells and immune complexes is responsible for their deposition and consequent activation of inflammatory pathways resulting in tissue damage [7][3][8].

Complement is a fundamental component of the innate immune system and plays a crucial rolein modulating the adaptive immune response [9],influencing T-cell activation [10], natural antibody development [11] and auto-reactive B-cell regulation [12].

Alternative pathways (e.g. formation of the C3 convertase complex) and terminal components of complement activation (C5-C9) are believed to play a relevant role in the pathogenesis of lupus nephritis (LN) [9][12][13][14]. Additionally, genetic or acquired deficiencies of certain components of the classical complement pathways (C1q, C2 or C4) [8][15] or of lectin pathway (mannose-binding lectin) [16] are responsible for rare forms of SLE. Similarly, mutations in complement inhibitor factors such as complement factor H have been associated with SLE, in particular with LN[17].

Eculizumab is a recombinant fully humanized IgG2/IgG4 monoclonal antibody that blocks the formation of the terminal complex sC5b-9 and C5a by binding to the C5 complement component and consequently blocking the activation pathway [18]. Eculizumab has been approved for patients with paroxysmal nocturnal hemoglobinuria(PNH) and atypical hemolytic uremic syndrome (aHUS) [18][19].Growing evidence from *in vitro* and *in vivo* studies suggest a promising role for eculizumab for the treatment of other autoimmune [20][21][22][23][24][25]and primary renal diseases.

Treatment with eculizumab has been shown to significantly reduce proteinuria and renal dysfunction and prolong survival in a lupus-prone New Zealand Black/New Zealand White (NZB/W) murine model[14]. In addition, eculizumab has been successfully used to prevent recurrences of catastrophic antiphospholipid antibody syndrome (CAPS) in a kidney recipient [26] and to induce remission in a patient with type II membranoproliferative glomerulonephritis.[27]. Recently, a pilot randomized controlled trial showed that eculizumab treatment may stabilize renal function in chronic antibody mediated injury in kidney transplant recipients [28].

Against this background, in addition to aHUS and PNH, this drug may prove to be efficacious for patients with certain types of glomerulopathies. However, the efficacy of eculizumab for the treatment of LN remains to be demonstrated.

Methods

We performed a detailed literature search, developed *a priori,* to identify and include in our study articles that reported clinical experience with the use of eculizumab in SLE patients with renal involvement. Key words and subject terms used in the search included: ("eculizumab"[Supplementary Concept] OR "eculizumab"[All Fields]) AND ("lupus erythematosus, systemic"[MeSH Terms] OR ("lupus"[All Fields] AND "erythematosus"[All Fields] AND "systemic"[All Fields]) OR "systemic lupus erythematosus"[All Fields] OR ("systemic"[All Fields] AND "lupus"[All Fields] AND "erythematosus"[All Fields]).

The search strategy was applied to Ovid MEDLINE, In-Process and Other Non-Indexed Citation, EMBASE, Cochrane Central Register of Controlled Trials and Scopus from 2002 (year of the first publication retrieved ever indexed in Pubmed using "eculizumab" as search term) to present; abstracts from EULAR and ACR were also screened. Studies that met the above mentioned criteria were systematically analyzed by two independent reviewers (MR and SS).

Disagreements were resolved by consensus; if consensus could not be achieved, a third party (IC) provided an assessment of eligibility. As the data on eligibility were dichotomous (eligible: yes/no), inter-rater agreement at both the title and abstract review and the full article review stages was determined by calculation of Cohen's kappa coefficient (k=0.89).

Results

Characteristics of retrieved studies are summarized in *Table 1*. Five out of six cases described the occurrence of thrombotic microangiopathy (TMA) in the renal biopsies of patients with an underlying diagnosis of SLE. Of those, 3 patients had TMA lesions in association with LN histological characteristics in the absence ofanti-phospholipid antibodies (aPL)[29][30][31] and 2 patients had SLE-related antiphospholipid syndrome without histologic evidence of LN[32][33]. Finally, one study reported the outcome of a patient with severe refractory LN successfully treated with eculizumab[34].

All patients underwent previous immunosuppressive treatments as listed in *Table 1*and five out of six (all those with TMA) had received plasmapheresis. Eculizumab was introduced either because of lack of efficacy or due to adverse reactions to immunosuppressive agents.[31][32][33][34][30][29][29].

All patients, regardless of the presence of concomitant LN, presented with severe hypocomplementemia and renal function impairment. Histological findings on renal biopsy are shown in *Table 1*. Patients showed a sustained improvement of renal function and normalization of complement parameters after treatment with eculizumab. In 3 cases, renal flares were observed after eculizumab discontinuation and improvement in renal parameters was observed after re-initiation of eculizumab. Normalization of platelets counts and haptoglobulin were also reported. Response to eculizumab seems to be sustained during the follow-up period [median 9 months (1-17)].

None of the studies reported adverse events attributed to eculizumab. One patient developed retrocardiac pneumonia with moderate pleural effusion due to Streptococcus pneumoniae. Meropenem was introduced and eculizumab temporarily stopped[29].

Discussion

Conventional treatments for SLE are usually directed against the adaptive immune response by limiting T and B cell activation, and/or lowering auto-antibody production. Targeting the complement pathway and consequently limiting the inflammatory response unleashed by tissue deposition of auto-antibodies and immune complexes may represent an alternative treatment strategy in SLE in some clinical manifestations of SLE. In our literature search we found an overall successful response to eculizumab in patients with TMA and SLE. Thrombotic microangiopathy has been significantly associated with antiphospholipid antibodies (aPL) and represents the hallmark histologic lesion of the aPL-associated nephropathy detected in both primary APS and SLE patients[35][36]. Canaud et al. also reported a successful use of eculizumab in three consecutive kidney transplant recipients with post-transplant TMA due to aPL-associated nephropathy recurrence that was resistant to plasmaphereisis [37]. Lonze et al. [26], also described the case of a patient with TMA in the context of primary Catastrophic APS (CAPS)who was successfully treated with eculizumab to prevent CAPS relapses before a renal transplantation.

However, besides the successful use of complement inhibition to prevent or reverse TMA, in two cases[29][34]improvement in renal function was also observed after eculizumab use in the context of active LN. Of note, in one of those patients, improvement in renal function was seen in the absence of TMA on renal biopsy [34].

Eculizumab has been shown to inhibit complement-mediated TMA in aHUS patients (resolving thrombocytopenia and TMA) and to improve renal transplantation outcomes by allowing plasma exchange-dependent patients to stop this treatment [19]. It has been also

used off-label in TTP patients refractory to treatment with plasma exchange. In the light of these observations, eculizumab may be a potential treatment option in refractory SLE patients with TMA (with or without aPL).It is biologically plausible that targeting different pathogenic mechanisms (with steroids/standard immunosuppression, anticoagulation, plasmapheresis and complement inhibition) may improve the prognosis and the management of SLE. The treatment of patients with features of renal thrombotic microvascular involvement coexisting with LN can be challenging and often requiresan aggressive approach. In fact, TMA in patients with SLE is frequently associated with poor renal outcomes [38] and, in the presenceof aPL, may lead to irreversible end-stage renal failure[38].As eculizumab has already been used to control PNH and aHUS during pregnancy[39,40], it could represent a further tool to manage renal flares in the setting of pregnancy, when many immunosuppressive agents are contraindicated. Indeed, renal flares (including new onset of TMA) are not uncommon during pregnancy [41]and negatively impact pregnancy outcomes[42].

However, despite these promising observations, some considerations are warranted.

The efficacy of eculizumab for the treatment of SLE remains to be determined. Furie et al. [43] enrolled 24 SLE patients in a single center, randomized, placebo-controlled, double-blind, dose ranging phase I study. This trial failed to demonstrate significant efficacy of eculizumab, as determined by laboratory and clinical parameters or SLEDAI scores. It is important to note that phase I studies are not powered to determine efficacy of new experimental therapies. In addition, the majority of patients had low disease activity. However, in this trial, no adverse events were observed related to eculizumab and there was no significant human antibody response.

In conclusion, despite the limitations of the currently available evidence presented here (low number of patients, potential publication bias with studies reporting only positive outcomes, heterogeneity in clinical presentation, renal histologic findings, and applied protocols),

available data are promising and provide preliminary support for targeting complement pathways in SLE. Future studies should evaluate whether eculizumab represents an additional therapeutic option in the treatment of selected cases of SLE with renal involvement, especially in the presence of TMA, or in patients with refractory LN.

Key messages.

- Renal involvement occurs in 40% of SLE patients, with ESKD developing in 15% of them
- Therapeutic options are needed for SLE patients intolerant/resistant to conventional therapy or during gestation
- Complement plays a crucial role in modulating the adaptive immune response in patients with SLE
- Eculizumab may be considered in selected cases of SLE with renal involvement, TMA, refractory LN

Compliance with Ethical standard

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest statement

The authors declare no conflict of interest and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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