AperTO - Archivio Istituzionale Open Access dell'Università di Torino

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

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1634220> since 2019-02-13T14:33:27Z

Published version:

DOI:10.1007/s00296-017-3686-5

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

This is the author's final version of the contribution published as:

Sciascia, Savino; Radin, Massimo; Yazdany, Jinoos; Tektonidou, Maria; Cecchi, Irene; Roccatello, Dario; Dall'Era, Maria. Expanding the therapeutic options for renal involvement in lupus: eculizumab, available evidence. RHEUMATOLOGY INTERNATIONAL. None pp: 1-7.
DOI: 10.1007/s00296-017-3686-5

The publisher's version is available at:
<http://link.springer.com/10.1007/s00296-017-3686-5>

When citing, please refer to the published version.

Link to this full text:
<http://hdl.handle.net/2318/1634220>

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 role in 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 of anti-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 haptoglobin 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 plasmapheresis [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 requires an aggressive approach. In fact, TMA in patients with SLE is frequently associated with poor renal outcomes [38] and, in the presence of 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.

REFERENCES

- [1] Wu H, Zhao M, Tan L, Lu Q. The key culprit in the pathogenesis of systemic lupus erythematosus: Aberrant DNA methylation. *Autoimmun Rev* 2016;15:684–9. doi:10.1016/j.autrev.2016.03.002.
- [2] Lipsky PE. Systemic lupus erythematosus: an autoimmune disease of B cell hyperactivity. *Nat Immunol* 2001;2:764–6. doi:10.1038/ni0901-764.
- [3] Mak A, Kow NY. The pathology of T cells in systemic lupus erythematosus. *J Immunol Res* 2014;2014:419029. doi:10.1155/2014/419029.
- [4] Schneider M. Pitfalls in lupus. *Autoimmun Rev* 2016. doi:10.1016/j.autrev.2016.07.033.
- [5] Arbuckle MR, McClain MT, Rubertone M V, Scofield RH, Dennis GJ, James JA, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. *N Engl J Med* 2003;349:1526–33. doi:10.1056/NEJMoa021933.
- [6] Pisetsky DS. Anti-DNA antibodies — quintessential biomarkers of SLE. *Nat Rev Rheumatol* 2015;12:102–10. doi:10.1038/nrrheum.2015.151.
- [7] Frieri M, Stampfl H. Systemic lupus erythematosus and atherosclerosis: Review of the literature. *Autoimmun Rev* 2016;15:16–21. doi:10.1016/j.autrev.2015.08.007.
- [8] Elkon KB, Santer DM. Complement, interferon and lupus. *Curr Opin Immunol* 2012;24:665–70. doi:10.1016/j.coi.2012.08.004.
- [9] Carroll MC. A protective role for innate immunity in autoimmune disease. *Clin Immunol* 2000;95:S30–8. doi:10.1006/clim.1999.4813.
- [10] Kaya Z, Afanasyeva M, Wang Y, Dohmen KM, Schlichting J, Tretter T, et al. Contribution of the innate immune system to autoimmune myocarditis: a role for complement. *Nat Immunol* 2001;2:739–45. doi:10.1038/90686.
- [11] Fleming SD, Shea-Donohue T, Guthridge JM, Kulik L, Waldschmidt TJ, Gipson MG, et al. Mice deficient in complement receptors 1 and 2 lack a tissue injury-inducing subset of

the natural antibody repertoire. *J Immunol* 2002;169:2126–33.

- [12] Carroll MC. The role of complement in B cell activation and tolerance. *Adv Immunol* 2000;74:61–88.
- [13] Barilla-LaBarca ML, Toder K, Furie R. Targeting the complement system in systemic lupus erythematosus and other diseases. *Clin Immunol* 2013;148:313–21.
doi:10.1016/j.clim.2013.02.014.
- [14] Wang Y, Hu Q, Madri JA, Rollins SA, Chodera A, Matis LA. Amelioration of lupus-like autoimmune disease in NZB/WF1 mice after treatment with a blocking monoclonal antibody specific for complement component C5. *Proc Natl Acad Sci U S A* 1996;93:8563–8.
- [15] Belot A, Cimaz R. Monogenic forms of systemic lupus erythematosus: new insights into SLE pathogenesis. *Pediatr Rheumatol Online J* 2012;10:21. doi:10.1186/1546-0096-10-21.
- [16] Lee YH, Witte T, Momot T, Schmidt RE, Kaufman KM, Harley JB, et al. The mannose-binding lectin gene polymorphisms and systemic lupus erythematosus: two case-control studies and a meta-analysis. *Arthritis Rheum* 2005;52:3966–74.
doi:10.1002/art.21484.
- [17] Jönsen A, Nilsson SC, Ahlqvist E, Svenungsson E, Gunnarsson I, Eriksson KG, et al. Mutations in genes encoding complement inhibitors CD46 and CFH affect the age at nephritis onset in patients with systemic lupus erythematosus. *Arthritis Res Ther* 2011;13:R206. doi:10.1186/ar3539.
- [18] Hillmen P, Hall C, Marsh JCW, Elebute M, Bombara MP, Petro BE, et al. Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria. *N Engl J Med* 2004;350:552–9.
doi:10.1056/NEJMoa031688.

- [19] Legendre CM, Licht C, Muus P, Greenbaum LA, Babu S, Bedrosian C, et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. *N Engl J Med* 2013;368:2169–81. doi:10.1056/NEJMoa1208981.
- [20] Oku K, Nakamura H, Kono M, Ohmura K, Kato M, Bohgaki T, et al. Complement and thrombosis in the antiphospholipid syndrome. *Autoimmun Rev* 2016. doi:10.1016/j.autrev.2016.07.020.
- [21] Huda R, Tüzün E, Christadoss P. Targeting complement system to treat myasthenia gravis. *Rev Neurosci* 2014;25:575–83. doi:10.1515/revneuro-2014-0021.
- [22] Reis ES, Mastellos DC, Yancopoulou D, Risitano AM, Ricklin D, Lambris JD. Applying complement therapeutics to rare diseases. *Clin Immunol* 2015;161:225–40. doi:10.1016/j.clim.2015.08.009.
- [23] Kessler RA, Mealy MA, Levy M. Treatment of Neuromyelitis Optica Spectrum Disorder: Acute, Preventive, and Symptomatic. *Curr Treat Options Neurol* 2016;18:2. doi:10.1007/s11940-015-0387-9.
- [24] Shapiro R, Chin-Yee I, Lam S. Eculizumab as a bridge to immunosuppressive therapy in severe cold agglutinin disease of anti-Pr specificity. *Clin Case Reports* 2015;3:942–4. doi:10.1002/ccr3.399.
- [25] Manrique J, Cravedi P. Role of monoclonal antibodies in the treatment of immune-mediated glomerular diseases. *Nefrol Publicación Of La Soc Española Nefrol* 2014;34:388–97. doi:10.3265/Nefrologia.pre2014.Feb.12506.
- [26] Lonze BE, Singer AL, Montgomery RA. Eculizumab and renal transplantation in a patient with CAPS. *N Engl J Med* 2010;362:1744–5. doi:10.1056/NEJMc0910965.
- [27] Vivarelli M, Pasini A, Emma F. Eculizumab for the treatment of dense-deposit disease. *N Engl J Med* 2012;366:1163–5. doi:10.1056/NEJMc1111953.
- [28] Kulkarni S, Kirkiles-Smith NC, Deng YH, Formica RN, Moeckel G, Broecker V, et al.

Ecilizumab Therapy for Chronic Antibody-Mediated Injury in Kidney Transplant Recipients: A Pilot, Randomized-Controlled Trial. *Am J Transplant* 2016.
doi:10.1111/ajt.14001.

- [29] Coppo R, Peruzzi L, Amore A, Martino S, Vergano L, Lastauka I, et al. Dramatic effects of ecilizumab in a child with diffuse proliferative lupus nephritis resistant to conventional therapy. *Pediatr Nephrol* 2015;30:167–72. doi:10.1007/s00467-014-2944-y.
- [30] El-Husseini A, Hannan S, Awad A, Jennings S, Cornea V, Sawaya BP. Thrombotic microangiopathy in systemic lupus erythematosus: Efficacy of ecilizumab. *Am J Kidney Dis* 2014;65:127–30. doi:10.1053/j.ajkd.2014.07.031.
- [31] Boneparth A, Moorthy LN, Weiss L, Rajasekhar H, Murphy S, Drachtman RA. Complement Inhibition in the Treatment of SLE-Associated Thrombotic Thrombocytopenic Purpura. *Glob Pediatr Heal* 2015;2:2015–7.
doi:10.1177/2333794X15570150.
- [32] Hadaya K, Ferrari-Lacraz S, Fumeaux D, Boehlen F, Toso C, Moll S, et al. Ecilizumab in acute recurrence of thrombotic microangiopathy after renal transplantation. *Am J Transplant* 2011;11:2523–7. doi:10.1111/j.1600-6143.2011.03696.x.
- [33] Kronbichler A, Frank R, Kirschfink M, Szilágyi Á, Csuka D, Prohászka Z, et al. Efficacy of ecilizumab in a patient with immunoadsorption-dependent catastrophic antiphospholipid syndrome: a case report. *Medicine (Baltimore)* 2014;93:e143.
doi:10.1097/MD.0000000000000143.
- [34] Pickering MC, Ismajli M, Condon MB, McKenna N, Hall AE, Lightstone L, et al. Ecilizumab as rescue therapy in severe resistant lupus nephritis. *Rheumatol (United Kingdom)* 2015;54:2286–8. doi:10.1093/rheumatology/kev307.
- [35] Tektonidou MG, Sotsiou F, Moutsopoulos HM. Antiphospholipid syndrome (APS) nephropathy in catastrophic, primary, and systemic lupus erythematosus-related APS. *J*

Rheumatol 2008;35:1983–8.

- [36] Tektonidou MG, Sotsiou F, Nakopoulou L, Vlachoyiannopoulos PG, Moutsopoulos HM. Antiphospholipid syndrome nephropathy in patients with systemic lupus erythematosus and antiphospholipid antibodies: prevalence, clinical associations, and long-term outcome. *Arthritis Rheum* 2004;50:2569–79. doi:10.1002/art.20433.
- [37] Canaud G, Kamar N, Anglicheau D, Esposito L, Rabant M, Noël L-H, et al. Eculizumab improves posttransplant thrombotic microangiopathy due to antiphospholipid syndrome recurrence but fails to prevent chronic vascular changes. *Am J Transplant* 2013;13:2179–85. doi:10.1111/ajt.12319.
- [38] Sciascia S, Cuadrado MJ, Khamashta M, Roccatello D. Renal involvement in antiphospholipid syndrome. *Nat Rev Nephrol* 2014;10:279–89. doi:10.1038/nrneph.2014.38.
- [39] Miyasaka N, Miura O, Kawaguchi T, Arima N, Morishita E, Usuki K, et al. Pregnancy outcomes of patients with paroxysmal nocturnal hemoglobinuria treated with eculizumab: a Japanese experience and updated review. *Int J Hematol* 2016;103:703–12. doi:10.1007/s12185-016-1946-x.
- [40] De Sousa Amorim E, Blasco M, Quintana L, Sole M, de Cordoba SR, Campistol JM. Eculizumab in pregnancy-associated atypical hemolytic uremic syndrome: insights for optimizing management. *J Nephrol* 2015;28:641–5. doi:10.1007/s40620-015-0173-5.
- [41] Sciascia S, Baldovino S, Schreiber K, Solfietti L, Roccatello D. Antiphospholipid Syndrome and the Kidney. *Semin Nephrol* 2015;35:478–86. doi:10.1016/j.semnephrol.2015.08.009.
- [42] Moroni G, Doria A, Giglio E et al. Maternal outcome in pregnant women with lupus nephritis. A prospective multicenter study. - PubMed - NCBI 2016:S0896–8411(16)30090–7.

- [43] Furie R, Matis L, Rollins S et al. A single dose, placebocontrolled, double blind, phase I study of the humanized anti-C5 antibody h5G1.1 in patients with systemic lupus erythematosus. *Arthritis Rheum* 2004;50:S35–747.