Treatment of Lupus Nephritis Rituximab in LN

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Treatment of diffuse or focal proliferative LN

- Immunosuppressive therapy in class III, IV
- Even with aggressive therapy, some patients progressing to ESRD

Risk factors during therapy

- Frequency and severity of renal flares
- Complete or partial response

Risk factors for progression at the onset of disease

- Elevated serum creatinine
- Hypertension
- Nephrotic range proteinuria
- Hematocrit below 26 percent
- Black and Hispanic race
- Severity of acute and chronic tubulointerstitial disease
- Cellular crescents
- Male gender?
- Delayed therapy

Contreras G et al. Lupus 2005; 14:890.
Faurschou M et al. J Rheumatol 2006; 33:1563.

Complete response

- Inactive urine sediment
- Serum creatinine ≤1.4 mg/dL
- Protein excretion ≤330 mg/d

- 5-year renal survival: 94 vs 46%
- 10-year renal survival: 94 vs 31%
- 10-year pt. survival: 95 vs 60%

Partial response

- 50% reduction in proteinuria to < 1.5 g/day
- Stable serum creatinine

- 10-year renal survival: 45 vs 19%
- 10-year pt. survival: 76 vs 46%

Lupus Nephritis Collaborative Study Group. Am J Kidney Dis 2000; 35:904

PRINCIPLES OF IMMUNOSUPPRESSIVE THERAPY

Duration of initial therapy

- As short as 3 months
- As long as one year
- Averages about 6 months
- Indications: class III and IV with or without class V
- Based on KDIGO and ACR guidelines

Goal of immunosuppressive therapy

- Resolution of inflammatory and immunologic activity
- Achievement of a complete response
- Histologic "remission
- Clinical "response:
  - SCr
  - Upro
  - U sediment

Hahn BH et al. ACR guidelines..... Arthritis Care Res (Hoboken) 2012; 64:797.
Bertsias GK et al. EULAR/ERA-EDTA recommendations.... Ann Rheum Dis 2012; 71:1771.

Complete clinical response

Urine protein:

- Lupus Nephritis Collaborative Study Group: < 330 mg/d
- ALMS, LUNAR, ACCESS: < 500
- ELNT: < 1000 mg/d

Serum creatinine:

- Normal
- < 1.2 mg/dl
- ≤ 1.4 mg/dl
- 15 to 25 percent of baseline

Urine sedimant:

- RBC to ≤ 10 hpf
- RBC to ≤ 5 hpf
- Absence of RBC cast

Induction therapy

KDIGO, ACR, EULAR/ERA-EDTA:

- Gluco. + MMF or Cyclo.
- No response in 3 months: Cyclo. to MMF or MMF to Cyclo.
- MMF: Black and Hispanic, childbearing age women
- Methylprednisolone pulses: AKI, crescentic GN, severe extrarenal disease

- Oral prednisolone 60 mg/d, tapered every 2 weeks by 10 mg/d until 40 mg/day, then tapered 5 mg/d every 2 weeks until 7.5-10 mg/d
- ELNT: 500 mg IV every 2 weeks for a total of six doses (results same as higher doses NIH but mostly white pt)
- Euro-Lupus cyclo. regimen was effective in minor ethnicity in ACCESS trial

ELNT study. Arthritis Rheum 2002; 46:2121.

Cyclophosphamide (NIH)

- longer, higher-dose regimen
- 0.5 to 1 g/m² monthly 6-7 m
- WBC< 4000 or ANC< 1500 on day 10-14: dose reduced by 0.25 g/m²
- Not good response: dose increased by 0.25 g/ m², max dose 1 g/m²
- Contrast to NIH: maintenance on MMF or Aza
- Oral Cyclo.: 1.0 mg/kg/d titrating up to 1.5, for 2-4 m

Gourley MF et al. Ann Intern Med 1996; 125:549.

MMF (ALMS)

- 0.5 g twice daily in week 1, 1 g twice daily in week 2, and a target of 1.5 g twice daily thereafter or, if not tolerated, 1 g three to two times daily
- Equal to Cyclo (NIH dose), but better in minor ethnicity
- meta-analysis included 45 trials and 2846 patients: MMF similar to Cyclo in terms of mortality, incidence of ESRD, and relapse during induction, and side effect except ovarian failure and alopecia

Appel GB et al. ALMS study. J Am Soc Nephrol 2009;20:1103.

Monitoring of patients

- Visits every 2- 4 weeks for first 3 months, then every 2- 3 months:
  - Clinical response (cr,Upro, U/A)
  - Immunologic response (C3, C4, anti-DNA Ab)
  - Monitoring toxicity (CBC, LFT)

Preventing toxicity

- Prevention of PCP
- Prevention of cyclo-induced bladder and gonadal toxicity
- Minimizing glucocorticoid-induced bone loss and other adverse effects

Less preferred therapies (CNIs, Rituximab,Abatacept)

Tacrolimus

- Chinese patients:
  - Multi-target regimen (Tac 4 mg, MMF 1 g, pred)
  - Result better or same, but
    - Short-term follow up
    - Higher adverse effect, dropout
    - Hemodynamic, podocyte stabilizing effect Tac
- Good in Cyclo or MMF intolerance, pregnancy

Liu Z et al. Ann Intern Med 2015; 162:18.

Rituximab

- LUNAR (Ritux Vs placebo):
  - Ritux 1 g 0, 15 d and 24, 26 wks plus MMF 1 g tid plus pred pulse
  - No significant difference in R
  - Side effects almost same
- No use of rituximab as initial induction therapy (add-on therapy)

LUNAR study. Arthritis Rheum 2012; 64:1215

Less preferred therapies (CNIs, Rituximab,Abatacept)

Abatacept (CTLA4-Ig)

- Fusion protein binds CD80 (B7-1) and CD86 (B7-2) on APCs, competitive inhibitor of the CD28-B7 T cell costimulation
- Add-on therapy in ACCESS:
  - Euro-lupus Cyclo, pred, 500-750 mg monthly Abatacept for 24 to 52 wks
  - No difference compa. to placebo
  - Same adverse effect
- In other trail (with MMF)higher rate of herpes Z, GE

Class IV or III+V

- Worse prognosis
- More aggressive therapy
- MMF+ Tac+ Pred

ACCESS Trial Group. Arthritis Rheumatol 2014;66:3096.

Maintenance therapy

Relapse when

- No approp. maintenance ther.
- Partial remission more than complete
- 5 to 15 per 100 patient-years

Maintenance therapy

- MMF preferred
- AZA for pregnancy, non-tolerant to MMF
- CNIs in non-tolerant to MMF, AZA

- Meta-analysis 6 trials , 514 pts:
  - Mortality risk, ESRD the same
  - Lower renal relapse with MMF (16.4 versus 30.2%)
  - Similar adverse effects

- Maintain trial: no difference
- ALMS maintenance trial: renal relapse less in MMF (16 versus 32%)
- A third trial: MMF much better than Cyclo, AZA near to MMF
- In summary: MMF>AZA>Cyclo

Houssiau FA et al. MAINTAIN Nephritis Trial. Ann Rheum Dis 2010; 69:2083.
Dooley MA et al. N Engl J Med 2011; 365:1886. (ALMS Maintenance trial)

Approach to extended (maintenance) therapy

Cyclo induction

- 2-4 wks after last dose IV Cyclo
- Immediately after PO Cyclo
- If WBC> 3000 and ANC> 1500

- MMF 1 g/bid, tapering to 0.5-1 g/d in third year
- AZA 2 mg/kg/d, max 150-200
- For 3 years or longer
- Pred 0.05 to 0.2 mg/kg/d, tapering off or ≤ 5 mg/d
- Every 3-4 months follow-up

Therapy of resistant or relapsing class III, IV LN

Resistant

- Unresponsive to induction
- True resistant uncommon:
  - Noncompliance
  - Inadequacy of regimen
- MMF to Cyclo
- Cyclo to MMF
- Rituximab in resistant to both, long-term efficacy and safety?
- MMF+Tac
- Belimumab (BAFF, BLyS, B cell survival factor inhibitor, SLE)

Cortés-Hernández J et al. Nephrol Dial Transplant 2010; 25:3939.

Relapsing LN

- Nearly ½ renal flare following reduction or cessation of ther
- 5- 15 per 100 patient-years
- Risk factors:
  - More severe disease at baseline
  - A delay in reaching a CR
  - Attainment of a PR Vs. CR
- Worse prognosis particularly those with a nephritic sediment (RBC and /or WBC casts)
- Proteinuria, increase Cr in glomerulosclerosis
- Kidney biopsy

Moroni G et al. Kidney Int 1996; 50:2047.

Therapy of resistant or relapsing class III, IV LN

Relapsing LN

- No treatment for solely serologic activity (increase anti-ds DNA, decrease C3, C4)
- In one report, 75% subsequent clinical relapse in 8- 10 wks, only 40% was renal relapse

Treatment of Relapse

- Initial immunosuppressive type
- Severity of relapse
- Timing of relapse
- Potential toxicity of drugs

Mild Relapse

- Active urine, < 50% inc.prot., stable SCr
- Increase Pred, MMF or AZA

Moderate to severe relapse

- Active urine, > 50% inc.prot., sometimes increase SCr
- Mainly increase proteinuria, doing kidney biopsy for MGN or MGN+ III or IV
- High dose pred+ MMF
- Cyclo if intolerant of MMF, or already on enough dose of MMF
- Rituximab: frequent relapse or resistant

Nephrol Dial Transplant (2013) 28: 106–111
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Beyond the LUNAR trial. Efficacy of rituximab in refractory lupus nephritis

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Abstract

Background. The treatment of lupus nephritis (LN) remains problematic because the current treatment regimen based on unspecific immunosuppressants such as steroids, cyclophosphamide and mycophenolate has significant side effects and is often inefficient. B-cell ablation with the chimeric anti-CD20 antibody rituximab (RTX) has been considered as an alternative treatment option but the randomized controlled LUNAR trial failed to show any additive effect of RTX beyond a steroid–mycophenolate mofetil (MMF) combination for LN type III/IV/V in incident patients. At present, no such trial is available for the use of RTX in refractory LN.

Methods. We analysed existing evidence on this topic by performing a systematic analysis of reports that document outcomes of RTX treatment for refractory LN.

Results. Out of 233 reports, we selected 26 for analysis, which described 300 patients with a mean follow-up of 60 weeks. The complete or partial response criteria were met by 87% of patients with LN class III, 76% with class IV and 67% with class V, respectively. Mixed classes responded in 76% of patients. RTX induced complete responses in 60% (type III), 45% (type IV), 40% (type V) and 24% (mixed types), respectively.

Conclusions. Our systematic review of existing evidence suggests that RTX effectively induces remission of LN in patients who have not achieved remission with standard therapies. Another randomized controlled trial should be conducted to test the efficacy of RTX in refractory LN.

Rituximab in Severe Lupus Nephritis: Early B-Cell Depletion Affects Long-Term Renal Outcome

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Background and objectives: Standard treatment for lupus nephritis, including corticosteroids and cyclophosphamide, is efficient but is still associated with refractory or relapsing disease, or severe deleterious effects. Rituximab, a monoclonal chimeric anti-B cell antibody, is increasingly used in patients with lupus nephritis, but reported series were small and had a short follow-up.

Design, setting, participants, & measurements: The authors analyzed clinical and histologic data of 20 patients who were treated with rituximab for lupus nephritis and followed up for at least 12 mo.

Results: Nineteen women and one man received rituximab as induction treatment for an active class IV (15 cases) or class V (5 cases) lupus nephritis. Rituximab was given for lupus nephritis refractory to standard treatment (12 cases), for relapsing disease (6 cases), or as first-line treatment (2 cases). Three patients received cyclophosphamide concomitantly with rituximab. Ten received new injections of rituximab as maintenance therapy. Side effects included mainly five infections and four moderate neutropenias. After a median follow-up of 22 mo, complete or partial renal remission was obtained in 12 patients (60%). Lupus nephritis relapsed in one patient, who responded to a new course of rituximab. The achievement of B cell depletion 1 mo after rituximab, which negatively correlated with black ethnicity and hypoalbuminemia, was strongly associated with renal response. Rapidly progressive glomerulonephritis did not respond to rituximab.

Conclusion: Rituximab is an interesting therapeutic option in relapsing or refractory lupus nephritis when early B cell depletion is obtained.

Clin J Am Soc Nephrol 4: 579–587, 2009. doi: 10.2215/CJN.04030808

Combined III or IV+ V

- More resistant to standard treatment
- Worse outcome:
  - CR 27% Vs 60%
  - Renal survival 50% Vs 75% at 10 years

Membranous LN

- 10-20% LN
- Treatment for:
  - Severe (symptomatic) NS,
  - Elevated or rising SCr,
  - Concomitant III or IV
- In one study 79 with LN MGN:
  - 36 pure
  - 15 + III
  - 28 + IV
- At presentation, with or without extrarenal or serologic manifest.

Membranous LN

- LN MGN:
  - Glomerular deposition of IgG, IgM, IgA, C3, and C1q (full house)
  - Electron-dense subendo. or mesangial deposits on EM
  - Endoth. tubuloreticular structures on EM
  - Immune deposits along TBM and small blood vessels
- Negative glomerular capillary stain for anti-PLA2R Ag

- 10-year renal survival of 72-98%
- Probability of transition from pure V to V+III or IV 35% at 10 yr

- NONIMMUNOSUPPRESSIVE THERAPY:
  - ACIs-ARBs
  - Blood pressure control
  - Lipid control
  - Anti coagulation: thromboembolic events (23%), hypoalb., APS

Immunosupp. Therapy MGN

- No RCT
- Ther. for poor prognostic factors:
  - NS or persistent protein.> 3.5 g
  - Progressive rise in Scr
  - Mixed membranous and prolifer.

- Many rheumatologists and some nephrologists suggest treatment for all class V patients (protein.> 1g)(no spontaneous remission unlike primary MGN)

Pure MGN

- MMF (2.5-3 g)+ pred is preferred
- IV Cyclo or CNIs in case of MMF intolerance or contraind.
- Pregnancy test for women, and pred, CNIs, AZA
- No CNIs in GFR <40 mL/min/1.73
- On CNIs, if incr. cr >30% or >0.3, then decrease CNIs by 25%
- NIH trial: no difference in Cyclo Vs CNIs, less relapse with Cyclo
- No difference in Cyclo Vs MMF

Rituximab

- Observational study of 50 patients with class III, IV, or V LN:
  - Glucocorticoid-free regimen:
    - Rituximab: 1 g on days 1, 15
    - Methylprednisolone: 500 mg IV on days 1 and 15
    - Plus MMF
  - CR or PR 90% of patients by a median of 37 weeks

Proteinuria response in LN

- Slow response of proteinuria (<0.5 g) in different class of LN even with different drugs:
  - 28% at one year
  - 52% at two years
  - The higher the level of baseline proteinuria, the longer the time to response
- No early change in immuno. in stable patients:
  - No meaningful response in 6 months, so change or add
  - Worsening in 3 months, so change or add

Prospective observational single-centre cohort study to evaluate the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but no oral steroids

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Ann Rheum Dis 2013;**72**:1280–1286.

ABSTRACT

Objectives Lupus nephritis (LN) is a serious complication of systemic lupus erythematosus (SLE). All current treatment regimens include oral steroids, which are associated with severe adverse events and long-term damage. We have piloted a steroid-avoiding protocol (rituxilup) for the treatment of biopsy-proven active International Society of Nephrology/Renal Pathology Society (ISN/RPS) class III, IV, or class V LN.

Methods We report the findings from the first 50 consecutive patients, treated with 2 doses of rituximab (1 g) and methyl prednisolone (500 mg) on days 1 and 15, and maintenance treatment of mycophenolate mofetil. Patients on maintenance steroids or with life-threatening SLE or requiring dialysis were excluded. Renal remission was defined as serum creatinine no greater than 15% above baseline; complete biochemical remission (CR) was defined as urine protein : creatinine ratio (PCR)<50 mg/mmol or partial remission (PR) if PCR>50 mg/mmol but non-nephrotic and >50% reduction.

Results A total of 45 (90%) patients achieved CR or PR by a median time of 37 weeks (range 4–200). Overall, 72% (n=36) achieved CR (median time 36 weeks (11–58)) and a further 18% (n=9) achieved persistent PR (median time 32 weeks (19–58)). By 52 weeks, CR and PR had been achieved in 52% (n=26) and 34% (n=17) respectively. In all, 12 relapses occurred in 11 patients, at a median time of 65.1 weeks (20–112) from remission. A total of 6/50 patients had systemic flares. Of the 45 responders, only 2 required >2 weeks of oral steroids. Adverse events were infrequent; 18% were admitted, 10% for an infective episode.

Conclusions The rituxilup cohort demonstrates that oral steroids can be safely avoided in the treatment of LN. If findings are confirmed, it could mark a step change in the approach to the treatment of LN.

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The use of rituximab in newly diagnosed patients with systemic lupus erythematosus: long-term steroid saving capacity and clinical effectiveness

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ABSTRACT

Background: Previous reports indicate that treating patients with lupus (SLE) at or close to the time of diagnosis successfully without using any, or minimal, corticosteroids by using B-cell depletion (BCD) is possible in the short-term. It is not however known whether using BCD is as effective or reduces corticosteroid use in the long-term. We report the long-term (up to 7 years) use of BCD with respect to its steroid-saving capacity and clinical effectiveness in newly diagnosed SLE.

Methods: Sixteen female patients with SLE were treated at, or shortly after diagnosis, with BCD therapy (BCDT) minimising the routine use of oral steroids. Post-treatment, most patients were given hydroxychloroquine (n=14) and azathioprine (n=10). The British Isles Lupus Assessment Group (BILAG) disease activity index was used for clinical assessment. Serum antidouble-stranded DNA (dsDNA) antibodies, complement (C3), erythrocyte sedimentation rate (ESR), circulating B lymphocytes ($CD19^+$) and total inmmunoglobulins were tested every 2–6 months (average of 4.5 years) (SD 2) post-treatment. Disease activity and steroid requirement were compared with three patients with SLE treated conventionally, each matched for ethnicity, sex, age, clinical features, disease duration at diagnosis and follow-up period.

Results: All patients given rituximab achieved BCD. The mean number of flares during follow-up (new BILAG A or B) was 2.63 (SD 3) in the BCDT group and 4 (SD 3.6) in the controls (NS, p=0.14). Post-BCDT, mean anti-dsDNA antibody level fell from 1114 U/mL (SD 1699.3) to 194 (SD 346.7) at 18 months (p=0.043), mean serum ESR fell by >70% at 6 months maintained during follow-up and serum C3 level normalised in 8 patients. The mean cumulative prednisolone dose at 60 months for the patients who underwent BCDT (n=11) was 4745.67 mg (SD 6090 mg) vs 12 553.92 mg (SD 12 672 mg) for the controls (p=0.01).

Conclusions: Early treatment of patients with SLE with BCDT is safe, effective and enables a reduction in steroid use.

nephron Clinical Practice

Review

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Rituximab in Systemic Lupus Erythematosus and Lupus Nephritis

Hannah Beckwith Liz Lightstone

Abstract

Treatment options for systemic lupus erythematosus (SLE) and lupus nephritis (LN) have high associated morbidity and mortality. Side effects, particularly from long-term corticosteroid usage, limit patient adherence, with subsequent impacts on treatment efficacy. In addition, a subset of patients with SLE/LN fails to respond to current standard immunotherapy. There is an urgent need to develop steroid-sparing treatment regimens as well as novel therapies for the management of refractory disease. Rituximab is a chimeric mouse/human monoclonal antibody directed against the B cell CD20 receptor. It has been used in the treatment of non-Hodgkin's lymphoma for over 30 years and has an excellent safety profile. Recent work has demonstrated a role for B cell depletion therapy in the management of autoimmune disease, and the efficacy of rituximab in many observational studies in SLE and LN has been noted. Unfortunately, two large randomised controlled trials evaluating rituximab for the treatment of renal and non-renal lupus failed to meet their primary endpoints. Reasons for this have been discussed extensively within the medical community with a general consensus that trial design (steroid use, trial size and endpoints used) was the principal reason for the failures. Despite the lack of trial evidence, clinical experience means many physicians firmly believe in the value of rituximab in SLE/LN treatment and have continued to use it in their clinical practice. Recent work has demonstrated the efficacy of rituximab as a steroid-sparing agent and as an alternative therapeutic option for refractory SLE/LN. There are two further rituximab randomised controlled trials planned/started in LN – one using a steroid-minimising regimen with rituximab for induction and one evaluating rituximab for LN refractory to 6 months standard of care treatment. Rituximab remains a problematic drug in lupus and LN – it is a biologically plausible agent with a huge amount of supportive anecdotal clinical data. Yet the completed trials have been negative to date despite clinical experience strongly suggesting efficacy. It is hoped that the two new trials will determine the role for rituximab, at least in LN.

Rituximab alone as induction therapy for membranous lupus nephritis

A multicenter retrospective study

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Abstract

The optimal treatment for pure membranous lupus nephritis (MLN) remains undetermined. Rituximab constitutes a promising therapeutic option for lupus nephritis and is currently being evaluated for use in idiopathic membranous nephritis. We retrospectively analysed the efficacy and tolerance of rituximab as a monotherapy in the induction treatment of pure MLN.

We retrospectively investigated SLE patients with biopsy-proven pure class V lupus nephritis presenting with a protein-to-creatinine ratio of at least 2 g/g and treated with rituximab as monotherapy. A background low dose of corticosteroids (≤20 mg/day) was allowed, as was hydroxychloroquine; higher doses of steroids and/or immunosuppressive drugs fell under the exclusion criteria. Remission status was evaluated at baseline and 6, 12, and 24 months after rituximab.

The study included 15 patients (13 women, median age 37 years, 27% with extra-renal manifestations, median SLE duration 1.5 years). The median protein-to-creatinine ratio was 4.9 g/g, 80% of the patients had nephrotic-range proteinuria, the median serum albumin was 24 g/L, the median serum creatinine was 0.7 mg/dL, and the median eGFR was 122 mL/min/1.73 m^2. The median follow-up was 29 months (6–112 months). Treatment failure occurred in 2 patients. However, remission was recorded in the remaining 13 (87%, complete remission in 8 patients) with a median time to remission of 5 months. Median proteinuria decreased from 4.9 g/g to 0.16 g/g at month 12 and to 0.11 g/g at month 24. Median serum albumin increased to 36.5 g/L at month 24, and all patients had serum albumin levels greater than 30 g/L at month 12. Renal function remained stable in all patients. Relapse of proteinuria was recorded in 3 patients (at 12, 29, and 34 months). No patients experienced serious adverse events.

Rituximab as monotherapy may represent an effective treatment for pure MLN with an excellent tolerance profile.

Abbreviations: ACR = American College of Rheumatology, CKD = chronic kidney disease, CR = complete remission, ESRD = end-stage kidney disease, EULAR/ERA-EDTA = European Renal Association–European Dialysis and Transplant Association, HCQ = hydroxychloroquine, MLN = pure membranous lupus nephritis, NRs = nonresponders, PR = partial response, SLE = systemic lupus erythematosus, UPCR = urine protein to creatinine ratio.

Keywords: induction therapy, lupus nephritis, monotherapy, pure class V lupus nephritis, rituximab, systemic lupus erythematosus

Complete Remission of Lupus Nephritis With Rituximab and Steroids for Induction and Rituximab Alone for Maintenance Therapy

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Lupus nephritis (LN) is a severe and frequent complication of systemic lupus erythematosus. For decades, cyclophosphamide-based regimens have been the gold standard in treating patients with LN. However, cyclophosphamide use is associated with increased morbidity and mortality, and thus alternative treatments are needed. We report 3 cases of severe class IV LN successfully treated with rituximab as an induction, as well as a long-term maintenance, treatment. Complete remission of LN, documented by means of a control kidney biopsy, occurred in all patients and was maintained during follow-up using rituximab as sole maintenance treatment. No severe infectious complications were observed during treatment with rituximab. Our data suggest that rituximab may prove to be an optimal maintenance treatment in patients with severe LN.

Am J Kidney Dis 52:346-352.

American Journal of Kidney Diseases, Vol 52, No 2 (August), 2008: pp 346-352

Nephrology (Carlton). 2017 Jan;22(1):49-57. doi: 10.1111/nep.12737.

Rituximab protects podocytes and exerts anti-proteinuric effects in rat adriamycin-induced nephropathy independent of B-lymphocytes.

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Author information

Abstract

AIM: This study was aimed at examining the effects of treatment with rituximab, a chimeric monoclonal antibody against the protein CD20, in a B-lymphocyte independent adriamycin-induced rat model of nephrotic syndrome. Rituximab is an emerging rescue therapy used in patients with complicated nephrotic syndrome and, therefore, we sought to elucidate the apparent B-lymphocyte independent mechanism underlying its anti-proteinuric effect.

METHODS: Adriamycin-induced nephropathy was established in Wistar rats by intravenously injecting 10 mg/kg of adriamycin, which were then treated with rituximab or purified human IgG weekly and euthanized on day 28. Proteinuria, glomerular expression of sphingomyelin phosphodiesterase acid-like 3b protein, and podocyte-related proteins were examined using immunofluorescence staining and a reverse transcription-polymerase chain reaction.

RESULTS: Rituximab treatment of rats with adriamycin-induced nephropathy significantly reduced urinary protein excretion 14 to 28 days after induction of disease, compared with those treated with purified normal human IgG. Furthermore, rituximab treatment also prevented the reduction of glomerular nephrin and podocin expression on day 28. Double-immunofluorescence staining revealed that after in vivo administration, rituximab was bound to the glomeruli, which also expressed synaptopodin or sphingomyelin phosphodiesterase, acid-like 3b. Moreover, sphingomyelin phosphodiesterase, acid-like 3b expression was significantly decreased on day 28 of adriamycin-induced nephropathy, which was also prevented by rituximab.

CONCLUSIONS: This study demonstrated that rituximab directly affected glomerular podocytes and ameliorated proteinuria in adriamycin-induced nephropathy in rats. Furthermore, protection of podocyte function by rituximab may be mediated by direct modulation of a sphingomyelin phosphodiesterase, acid-like 3b-dependent mechanism.

Thank You
for Your Attention