OP0165

LONG-TERM OUTCOME OF A RANDOMIZED CONTROLLED TRIAL COMPARING TACROLIMUS WITH MYCOPHENOLATE MOFETIL AS INDUCTION THERAPY OF SEVERE LUPUS NEPHRITIS

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Background:

Objectives: To report the 10-year outcome of a cohort of patients with lupus nephritis (LN) treated with combined glucocorticoids with either mycophenolate mofetil (MMF) or tacrolimus (TAC) as induction in a randomized controlled trial (RCT).

Methods: 150 patients with active lupus nephritis were randomized to receive either MMF (2-3g/day) (N=76) or TAC (0.1-0.06mg/kg/day) (N=74) in combination with high-dose prednisolone (0.6mg/kg/day for 6-8 weeks and tapered) as induction therapy between 2005 and 2012. Complete renal (CR) or good partial renal responders were switched to azathioprine (AZA) (2mg/kg/day) for maintenance. We hereby report the 10-year outcomes of the patients in terms of renal flares (proteinuric/nephritic), renal function decline (drop in eGFR by $\geq 30\%$ from baseline), development of chronic kidney disease (CKD) stage 4/5 (eGFR $< 30\text{ml/min}$) and mortality. Factors affecting renal prognosis were studied by Cox regression analysis. Renal parameters (urine P/Cr ratio [uPCR], eGFR) at different time points from 6 to 24 months were studied for their predictive value of a poor renal prognosis by ROC analysis.

Results: 150 patients (92% women) with active LN were studied (ISN/RPS class III+V 36%; IVG/S+V 46%; pure V 19%). The mean age was 35.5 ± 12.8 years and SLE duration was 50.2 ± 62 months. The mean histological activity and chronicity score was 8.2 ± 3.4 and 2.6 ± 1.6 , respectively. At baseline, 59(39%) patients were hypertensive, 62(41%) had active urinary casts, 112(75%) had microscopic hematuria and 67% patients had eGFR $< 90\text{ml/min}$. As reported previously, the rate of complete renal response (CR) was 59% in the MMF and 62% in the TAC group ($p=0.71$). Maintenance therapy with AZA was given to 79% patients. After a follow-up of 118.2 ± 42 months, proteinuric and nephritic renal flares occurred in 34% and 37% of patients treated initially with MMF and 53% and 30% in those treated with TAC, respectively. There was a total of 77 renal flares in 43 (57%) patients treated with MMF (0.11/patient-year) and 92 renal flares in 46 (62%) of patients treated with TAC (0.12/patient-year; $p=0.44$). The cumulative risk of having a renal flare of patients treated with MMF/AZA was 28% at 3 years, 42% at 5 years and 58% at 10 years, whereas the corresponding figures for patients treated with TAC/AZA was 32% at 3 years, 53% in 5 years and 66% in 10 years ($p=0.43$). For those who achieved CR after induction therapy, the mean time to first renal flare was 70.4 ± 47.1 months in the MMF group and 65.2 ± 50 months in the TAC group ($p=0.61$). The cumulative incidence of a composite outcome of decline of eGFR by $\geq 30\%$, development of CKD stage 4/5 or death at 5 and 10 years was 24% and 33%, respectively, in patients treated with MMF, and 17% and 33%, respectively, in those treated with TAC ($p=0.90$). Factors significantly associated with this outcome were first time lupus nephritis (HR 0.26[0.11-0.59]; $p=0.001$), uPCR at 6 months (HR 1.33[1.02-1.76]; $p=0.04$) and eGFR at 6 months (HR 0.98[0.97-0.997]; $p=0.02$). Exploratory ROC analysis demonstrated that an eGFR cut-off of 80ml/min (AUC 0.70; sensitivity 0.64, specificity 0.66) and uPCR cut-off of 0.75 (AUC 0.73; sensitivity 0.69, specificity 0.74) at month 18 best predicted CKD stage 4/5 or decline of eGFR by $\geq 30\%$.

Conclusion: Long-term data of our RCT showed that TAC remained non-inferior to MMF as induction therapy of LN in terms of renal flares, renal function decline and mortality. Relapsed renal disease, lower eGFR and more proteinuria post-induction therapy were associated with a poorer outcome. An uPCR ≤ 0.75 and eGFR of $> 80\text{ml/min}$ at 18 months best predicted a better outcome at 10 years, and should be considered as a target for induction/consolidation therapy.

Acknowledgments: NIL

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2020-eular.2568

OP0166

ALTERNATIVE RENAL RESPONSE DEFINITIONS IN A RANDOMIZED, CONTROLLED TRIAL OF OBINUTUZUMAB FOR PROLIFERATIVE LUPUS NEPHRITIS

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Background: Obinutuzumab, a type II anti-CD20 mAb, resulted in rapid and complete B-cell depletion and improved renal responses in proliferative lupus nephritis (LN) in the Phase 2 NOBILITY trial and will be further evaluated in the Phase 3 REGENCY trial. Recent analyses suggest alternative urinary sediment, serum creatinine (SCr), and urine protein/creatinine ratio (UPCR) requirements may be better measures of response in LN than those used in NOBILITY [1,2].

Objectives: To evaluate the NOBILITY response definitions and to report the results of NOBILITY using alternative definitions of renal response.

Methods: 126 patients with active Class III/IV LN were randomized to obinutuzumab or placebo in combination with mycophenolate and glucocorticoids. NOBILITY complete renal response (CRR) required UPCR < 0.5 , SCr $\leq$ the upper limit of normal (ULN) of the reference laboratory and not increased $> 15\%$ from baseline SCr, and inactive urinary sediment. Exploratory analyses were conducted, and alternative response definitions were evaluated post hoc.

Results: NOBILITY CRR was increased with obinutuzumab over placebo at Week 52 (35% vs. 23%, $P = 0.11$) and Week 76 (40% vs. 18%, $P = 0.007$). Response rates were low among patients with baseline SCr $< 0.65\text{mg/dL}$ ($n = 45$) due to the requirement that SCr not increase $> 15\%$ from baseline; increasing this threshold to 25% increased the response rate to a level similar to other groups (Figure). Alternative response definitions demonstrated increased rates of response in both treatment groups and similar benefits of obinutuzumab over placebo at Weeks 52 and 76 (Table).

Conclusion: Obinutuzumab resulted in consistent treatment benefits across a range of renal response definitions in NOBILITY and will be further evaluated in REGENCY. A requirement that SCr not increase $> 15\%$ from baseline may be overly restrictive in patients with low baseline SCr ($< 0.65\text{mg/dL}$), where a change of 15% represents $< 0.1\text{mg/dL}$ and is of questionable clinical relevance. These findings may inform LN clinical trial design and more accurately reflect clinical practice.

References:

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Figure. Week 76 response in NOBILITY by baseline serum creatinine level

UPCR, urine protein/creatinine ratio; SCr, serum creatinine; ULN, upper limit of normal.

Acknowledgments: This study was funded by F. Hoffmann-La Roche.

Disclosure of Interests: Zahir Amoura Grant/research support from: GSK, Roche, Consultant of: GSK, Astra Zeneca, Amgen, Philippe Rémy: None declared, Luis Fernando Quintana Porras: None declared, Laurent Chiche: None declared, Dominique Chauveau: None declared, Dario Roccatoello: None declared, Richard Furie Grant/research support from: AstraZeneca, Biogen, Consultant of: AstraZeneca, Biogen, Thomas Schindler Employee of: F. Hoffmann-La Roche, Jay Garg Employee of: Genentech, Matthew D. Cascino Employee of: Genentech, Brad H. Rovin Grant/research support from: GSK, Consultant of: GSK, Andrea Doria Consultant of: GSK, Pfizer, Abbvie, Novartis, Ely Lilly, Speakers bureau: UCB pharma, GSK, Pfizer, Janssen, Abbvie, Novartis, Ely Lilly, BMS

DOI: 10.1136/annrheumdis-2020-eular.2983