ARP Rheumatology 2024;1:2-3
https://doi.org/10.63032/DHPZ2410

EDITORIAL

Lupus nephritis outcomes – is the picture changing?

Farinha F[1], Rahman A[2]

Lupus nephritis (LN) is one of the most severe manifestations of Systemic Lupus Erythematosus (SLE) and LN patients have worse outcomes and comorbidity rates compared to non-LN SLE patients[1]. Notably, LN is associated with progression to end-stage renal disease (ESRD) and death[2].

The prognosis of LN improved considerably during the second half of the twentieth century. In more recent years, however, while some studies continued to show an improvement over time[3], others have showed that mortality and ESRD rates have reached a plateau[1,4,5], suggesting that available treatments have limited effectiveness and cannot further improve the outcomes.

The study of a multicentre Italian cohort of 499 patients diagnosed with LN from 1970 to 2016 suggested that clinical presentation of LN has become less severe in the last years, leading to a better long-term renal survival. According to the authors, reasons for improvement include a prompt diagnosis of renal involvement, a wider indication to renal biopsy, treatment based on renal biopsy and increased clinical experience in the management of LN[3].

Slightly different results were suggested by a single-centre study in the UK that also analysed the outcomes of 219 LN patients over four decades, from 1975 to 2015. The 5-year mortality rates decreased from the first decade (24%) to the second (4%) but then remained stable. Main causes of death were infections (31%), cardiovascular disease (31%) and malignancies (16.7%). The 5-year progression to ESRD was stable over the four decades (5% overall)[4].

Furthermore, a recently published population-wide study in Western Australia analysed ESRD and mortality rates for 366 patients with LN, in the period between 1985 and 2015. The authors found no improvement in the mortality and ESRD rates for LN patients over time[1].

A systematic review and meta-analysis published in 2016 aimed to investigate changes in ESRD risk amongst adults with LN from 1971 to 2015 and included 187 studies reporting on 18,309 patients. In developed countries, the estimated risk of ESRD at 5 years of LN decreased gradually from 16% (95%CI: 14–17%) in 1970–1979 to 11% (95%CI: 10–12%) in the mid-1990s, when it plateaued. ESRD risks at 10 and 15 years showed steeper declines in the 1970s and 1980s, but also plateaued in the mid-1990s at 17% (95%CI: 16–18%) and 22% (95%CI: 20–23%), respectively[5].

Since 2020, two drugs have been approved for LN by both the Food and Drug Administration and the European Medicines Agency - belimumab and voclosporin. Other drugs have shown promising results in phase 2 clinical trials, and there are a few currently being tested in phase 3 trials, notably obinutuzumab (NCT04702256), anifrolumab (NCT05138133) and secukinumab (NCT04181762).

The use of high-dose corticosteroids is associated with an increased risk of serious infections[6], and infection is one of the main causes of death in LN patients. In the successful phase 3 trial of voclosporin, this drug was used in combination with mycophenolate mofetil and low-dose steroids[7], bringing hope that it will be possible to treat LN effectively with lower doses of corticosteroids than the ones traditionally used, and subsequently less damage accrual and improved survival.

The response to treatment, including the levels of proteinuria and estimated glomerular filtration rate at 12 months, has been one of the major factors associated with renal outcome and survival in patients with LN[8-10]. However, renal flares are frequent and have been associated with a higher risk of progression to ESRD[11,12]. By contrast, achieving a sustained renal remission is associated with a lower risk of flares[13] and a predictor of reduced mortality, chronic kidney disease and ESRD[14,15].

A recent review on factors associated with a reduced risk of renal flares included: attaining a low level of proteinuria (< 700–800 mg/24h) by 12 months, using mycophenolate over azathioprine, adding belimumab to standard therapy, maintaining immunosuppressive / biological treatment for at least 3 to 5 years, and using hydroxychloroquine[12].

In fact, a recently published post-hoc analysis of four phase 3 randomized controlled trials of belimumab investigated the effect of antimalarial agents (AMA), different doses of belimumab, and their combination on preventing renal flares in SLE patients treated for extra-renal manifestations. All participants received standard of care plus either belimumab or placebo. Compared

[1] ULS Lezíria EPE, Santarém, Portugal; Centre for Rheumatology, University College of London, London, UK; [2] Centre for Rheumatology, University College of London, London, UK
Submitted: 15/03/2024
Accepted: 16/03/2024
Correspondence to: Filipa Farinha
E-mail: filipa.mcfarinha@gmail.com

with placebo, the risk of renal flares was lower for intravenous belimumab 10 mg/kg (HR: 0.62; 95%CI: 0.41-0.92; P=0.018) and intravenous belimumab 1 mg/kg (HR: 0.42; 95%CI: 0.22-0.79; P=0.007), while no significant association was found for subcutaneous belimumab 200 mg. AMA use also yielded a lower hazard of renal flares (HR: 0.66; 95%CI: 0.55-0.78; P<0.001). The lowest flare rate was observed for the combination of intravenous belimumab 1 mg/kg and AMA (HR: 0.31; 95%CI: 0.18-0.54; P<0.001)[16].

In conclusion, recent advances in the management of patients with LN have the potential of improving the prognosis of this serious condition. Hopefully, the picture is changing and a brighter future awaits.

REFERENCES

1. Nossent JC, Keen HI, Preen DB, Inderjeeth CA. Population-wide long-term study of incidence, renal failure, and mortality rates for lupus nephritis. Int J Rheum Dis. 2024;27(2):e15079. https://doi.org/10.1111/1756-185X.15079
2. Hanly JG, O'Keeffe AG, Su L, Urowitz MB, Romero-Diaz J, Gordon C, et al. The frequency and outcome of lupus nephritis: results from an international inception cohort study. Rheumatology (Oxford). 2016;55(2):252-62. https://doi.org/10.1093/rheumatology/kev311
3. Moroni G, Vercelloni PG, Quaglini S, Gatto M, Gianfreda D, Sacchi L, et al. Changing patterns in clinical-histological presentation and renal outcome over the last five decades in a cohort of 499 patients with lupus nephritis. Ann Rheum Dis. 2018;77(9):1318-25. https://doi.org/10.1136/annrheumdis-2017-212732
4. Gisca E, Duarte L, Farinha F, Isenberg DA. Assessing outcomes in a lupus nephritis cohort over a 40-year period. Rheumatology (Oxford). 2021;60(4):1814-22. https://doi.org/10.1093/rheumatology/keaa491
5. Tektonidou MG, Dasgupta A, Ward MM. Risk of End-Stage Renal Disease in Patients With Lupus Nephritis, 1971-2015: A Systematic Review and Bayesian Meta-Analysis. Arthritis Rheumatol. 2016;68(6):1432-41. https://doi.org/10.1002/art.39594
6. Singh JA, Hossain A, Kotb A, Wells G. Risk of serious infections with immunosuppressive drugs and glucocorticoids for lupus nephritis: a systematic review and network meta-analysis. BMC Medicine. 2016;14(1):137. https://doi.org/10.1186/s12916-016-0673-8
7. Rovin BH, Teng YKO, Ginzler EM, Arriens C, Caster DJ, Romero-Diaz J, et al. Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2021;397(10289):2070-80. https://doi.org/10.1016/S0140-6736(21)00578-X
8. Dall'Era M, Cisternas MG, Smilek DE, Straub L, Houssiau FA, Cervera R, et al. Predictors of long-term renal outcome in lupus nephritis trials: lessons learned from the Euro-Lupus Nephritis cohort. Arthritis Rheumatol. 2015;67(5):1305-13. https://doi.org/10.1002/art.39026
9. Tamirou F, Lauwerys BR, Dall'Era M, Mackay M, Rovin B, Cervera R, et al. A proteinuria cut-off level of 0.7 g/day after 12 months of treatment best predicts long-term renal outcome in lupus nephritis: data from the MAINTAIN Nephritis Trial. Lupus Sci Med. 2015;2(1):e000123. https://doi.org/10.1136/lupus-2015-000123
10. Moroni G, Gatto M, Tamborini F, Quaglini S, Radice F, Saccon F, et al. Lack of EULAR/ERA-EDTA response at 1 year predicts poor long-term renal outcome in patients with lupus nephritis. Annals of the Rheumatic Diseases. 2020;79(8):1077-83. https://doi.org/10.1136/annrheumdis-2020-216965
11. Sidiropoulos PI, Kritikos HD, Boumpas DT. Lupus nephritis flares. Lupus. 2005;14(1):49-52. https://doi.org/10.1191/0961203305lu2059oa
12. Banos A, Bertsias G. Flares in Lupus Nephritis: Risk Factors and Strategies for Their Prevention. Curr Rheumatol Rep. 2023;25(10):183-91. https://doi.org/10.1007/s11926-023-01109-6
13. Gatto M, Frontini G, Calatroni M, Reggiani F, Depascale R, Cruciani C, et al. Effect of Sustained Clinical Remission on the Risk of Lupus Flares and Impaired Kidney Function in Patients With Lupus Nephritis. Kidney International Reports. Published online 18/01/2024. DOI:https://doi.org/10.1016/j.ekir.2024.01.016. https://doi.org/10.1016/j.ekir.2024.01.016
14. Pakchotanon R, Gladman DD, Su J, Urowitz MB. Sustained complete renal remission is a predictor of reduced mortality, chronic kidney disease and end-stage renal disease in lupus nephritis. Lupus. 2017:961203317726376. https://doi.org/10.1177/0961203317726376
15. Fernandes das Neves M, Irlapati RV, Isenberg D. Assessment of long-term remission in lupus nephritis patients: a retrospective analysis over 30 years. Rheumatology (Oxford). 2015;54(8):1403-7. https://doi.org/10.1093/rheumatology/kev003
16. Gomez A, Jägerback S, Sjöwall C, Parodis I. Belimumab and antimalarials combined against renal flares in patients treated for extra-renal systemic lupus erythematosus: results from 4 phase III clinical trials. Rheumatology (Oxford). 2024;63(2):338-48. https://doi.org/10.1093/rheumatology/kead253