

cyclophosphamide as initial induction therapy whereby the benefit of adding biologics such as belimumab is not clear. Of course, people argue that the use of belimumab in such cases may allow faster tapering of glucocorticoids and decrease the risk for renal flares with an added benefit for extrarenal lupus. Another argument often being cited is that even in complete renal responses repeat renal biopsy after therapy shows residual histologic activity.

Still most patients will not flare and identification of those at risk for flare can be done better after initial therapy. Moreover, the clinical significance of histologic activity in complete responders is not clear with only a few of these patients eventually showing evidence of clinical flare. Consistently reported risk factors for a higher disease flare rate include younger age at disease onset, no use of antimalarials, persistent generalized disease activity and serological activity (anti-dsDNA, low complement). Accordingly, in stable patients with improving proteinuria I would consider adding novel therapies after the first year if there is residual proteinuria at the 1–2 gm/day range especially in the presence of risk-factors for flares as defined above.

What do we do for patients with refractory or partial responding disease? According to the 2019 EULAR EDTA recommendations<sup>1</sup> following failure of first line therapy, all remaining first-line therapies including mycophenolate mofetil (MMF)/mycophenolic acid (MPA) (2–3 g/day), cyclophosphamide (CY) and calcineurin inhibition (CNI) (especially tacrolimus) as monotherapy or ‘multitarget’ therapy, are recommended. B-cell depleting therapies such as rituximab, although off-label, are also indicated either as monotherapy or as add-on therapy to MMF/MPA or CY; complete depletion of circulating B-cells predicted clinical remission at 76 weeks. This has recently been supported by a successful trial of obinutuzumab.<sup>2</sup> Following a response to rituximab, relapses are not uncommon, but occur after a variable length of time. Repeat dose can be considered to prevent or treat a relapse. Finally, belimumab, when added to standard-of-care (including MMF or CY), may gradually reduce proteinuria and the risk for kidney flares.

#### Learning Objectives

- Explain the treatment goals in lupus nephritis and their rationale
- Describe initial therapy and define refractory or residual disease
- Discuss the pros and cons of early vs late introduction of novel agents as add-on regimens in standard therapy

#### REFERENCES

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## Plenary I: Novel strategies for optimizing outcomes in SLE

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### PREVENTING DAMAGE AND REDUCING MORTALITY IN LUPUS: HOW ARE WE DOING?

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10.1136/lupus-2021-la.14

Damage accrual in patients with lupus is due to both the disease itself and the medications used to treat the disease, especially corticosteroids. The disease courses in patients with lupus vary, with most patients running a relapsing remitting course (RR), a smaller number pursue a permanently active (PA) course, and another minority running a monophasic (M) prolonged remission course.<sup>1</sup> In an inception cohort of 232 patients followed for 10 years we found that 76% followed a RR course, 10.8% a PA course and 11.6% a M prolonged remission course. Despite disease activity over time being better controlled in the modern era, patients with RR lupus will spend almost half of their course with active disease, resulting in significant damage accrual over time. In an inception cohort of 73 patients followed for 15 years, with a mean duration on corticosteroids of 117 months, there was a progressive increase in damage and at 15 years with 80% of the damage items recorded being definitely or possibly corticosteroid related.<sup>2</sup> Furthermore, it has been shown that early damage is a predictor of mortality. In 263 inception patients followed for 10 years, 190 (72%) had no early damage and 73 (28%) had early damage. In patients with early damage, 25% died within 10 years as compared to only 7.3% with no early damage ( $p = 0.0002$ ).<sup>3</sup> Thus, prevention of damage accrual is a key objective in the management of patients with lupus.

We examined whether damage accrual over a 5-year period is reduced with the prior use of antimalarials. Of an inception cohort of 354 patients who had a first ACR/SLICC score of 0, 75 developed damage over the first 5 years and these were matched with 150 controls with no damage. Antimalarials were protective for damage accrual in the first 5 years supporting their use at diagnosis.<sup>4</sup> Finally belimumab, the first biologic approved for the treatment of lupus, has been assessed for the prevention of long term damage accrual. Patients followed long term from the original belimumab trials, compared with propensity score matched patients from the University of Toronto Lupus cohort matching for 17 clinical variables, showed that belimumab reduced organ damage progression, slowed the rate of organ damage progression and reduced the magnitude of year-to-year organ damage.<sup>5</sup>

#### Learning Objectives

- Describe damage accrual and the nature of the damage
- Describe how damage accrual is associated with mortality
- Demonstrate that hydroxychloroquine protects against damage accrual
- Demonstrate that belimumab protects against damage accrual

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